LEVERAGING MULTISENSORY NEURONS, CIRCUITS, BRAINS, AND BODIES TO STUDY CONSCIOUSNESS: FROM THE OUTSIDE-IN AND INSIDE-OUT

By

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY
in
Neuroscience

September 30, 2018
Nashville, Tennessee

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DEDICATION

Dedicated to my chosen family – many of whom are colleagues, but above all family.

ACKNOWLEDGMENTS

I am incredibly indebted to a great number of colleagues and friends. In my young career, being part of the scientific endeavor has allowed me to not only pose and attempt to answer interesting questions, but has also given me the opportunity to meet dozens and dozens of curious minds, people who think and engage with the world at a global scale, and who truly aim to make a positive impact. Above all, I feel incredibly fortunate to be surrounded by people who make me better, and who allow me to be a minuscule part of their world.

Chronologically, I first have to thank Lauren, Tim, Dick, Janine and Mike, for sparking my interest and encouraging me to start a career in research. Next, I would like to express my deep gratitude toward Andrea, Olaf, Bruno, Roy, Nathan, Fosco, Javier, Silvia, Giulio, Roberto, Christian, Petr, Mariia, and Polona, for showing me the ropes and so gracefully including me in your lives. It has been four years since I left Switzerland, yet today I feel as connected with *y'all* as ever. Finally, I have to thank those who have colored my doctorate experience.

First and foremost, I want to thank my advisor and mentor, Mark, for giving me the freedom to grow (and make mistakes) while always being incredibly supportive. I am sorry for all the nagging – though I will continue to do so – and cannot thank you enough for all your hard work over the years. Sincerely, thank you.

Next, I have to thank my dissertation committee; Randolph, Frank, and Geoff. Thank you for always providing constructive feedback and a fresh view on scientific questions and problems. I am grateful for your invaluable time, and I want to re-assure you, I truly believe our conversations have made me a better scientist.

Of course, I would be remiss not to thank my labmates, fellow students, and undergraduate students whom have truly made a difference. Gabby, Aaron, Collins, David S., David T., Jacob, Lauren, Iliza, LeAnne, Antonia, Mohit, Matt, Justin, and Juli, thank you for stimulating scientific discussions, but most importantly for keeping me sane and enabling my beer drinking. Randy, Carlos, Danielle, Melissa, Katherine, Robin, and Corey, thank you for walking this path with me, sharing close enough experiences to empathize, yet also being removed enough to always be a breath of fresh air. Marissa, Kahan, Nick, Emily, Sydney, and Lane, thank you for giving me the opportunity to grow as a mentor, and quite frankly, for at times taking off my plate tasks I did not want to do.

Lastly regarding my time as a Ph.D. student, I want to thank a whole host of collaborators, both at Vanderbilt and beyond. Elisa, thank you for sharing your insight regarding neural networks, your attention to detail, and for truly being an exceptional collaborator. Max, Majed, Femke, and Elia, thank you for an incredible summer in Redmond and teaching me all I know about Bayesian models. Nathan, it was incredible having you in Nashville over a summer. Thank you for your endless advice, kindness, and positive outlook. Yumiko and Shaun, thank you for trusting me with your data and for your infinite patience. Ryan, thank you for always sharing data, and John, thank you for helping me interpret Ryan's data. Carissa and Tiffany, thank you for teaching me what I know with regard to clinical research and always having such a positive and can-do attitude. Ram, thank you for thinking as an engineer and pretending that what I had to say at journal club made sense. Joseph and Michael, thank you for showing me that there are different approaches to science, and for so quickly making me feel as "one of the guys". Marcie, Sam, and Ian, thank you for so gracefully welcoming Andrea and I into your team, and for allowing us to do some crazy experiments.

Finally, Whitney. Thank you for your endless love and support. Thank you for listening to my unwarranted complaints and for making life so fun. I couldn't ask for a better partner and I can't wait for the next chapter of our lives together.

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CHAPTER I

GENERAL INTRODUCTION

The Outside-In and The Inside-Out

The role of the central nervous system is to guide organism-environment interactions. These interactions by necessity must occur via the medium of the body and be informed by sensory input. Importantly, the brain does not have direct access to the outside world. It is locked inside a dark and silent skull. In turn, the brain must infer the occurrence of events and the presence of objects in the environment given electrico-chemical impulses that are generated at our sensory periphery, and then transduced and relayed up the neuroaxis. In principle, therefore, our perceptual experiences may have very little to do with what is out there – and more fundamentally, there is nothing that is intrinsically "out there". Each organism creates its own *Umwelt*, its sensory surrounding, given the constraints of the biological sensors it possess (Helmholtz, 1867; Knill & Richards, 1996; Kersten et al., 2004).

The fact that subjective perception is built by (and putatively, for) the brain has naturally led to a panoply of cognitive and neurobiological theories of perceptual awareness (used interchangeably with consciousness). It is not the goal of the current work to discuss in detail consciousness theories that are not currently at the forefront of scientific thought. Similarly, a detailed distinction between access and phenomenal consciousness (Block, 1995), an ontological and epistemological treatise of consciousness (Dennett, 1991), discussion of the hard vs. easy problems (Chalmers, 1995), zombie (Chalmers, 1996) and Chinese room (Searle, 1980) thought-experiments, Cartesian theaters (Dennett, 1991), and what is it like to be a bat (Nagel, 1974) will be left aside. On the other hand, in the section that follows I will briefly describe some of the most prominent contemporary scientific approaches to conscious perception. Then, I will argue that these theories can be placed on a continuum; from models tackling the science of consciousness from the "outside-in" to models taking an "inside-out" approach.

By "outside-in" I refer to adopting the stance (either implicitly or explicitly) that the organism within which the brain is housed is primarily a passive entity. Photons hit the retina and sound waves perturbate the cochlear membrane, these environmental energies are transduced into neural signals, and eventually – through a series of hierarchically organized manipulations in the neocortical mantle - are perceived as visual and auditory objects. On the other hand, by "inside-out" I refer to theories that ascribe a more active role to either the flesh that houses the central nervous system, or to top-down neural processes, in encoding exteroceptive signals. Namely, while perceptual awareness is largely determined by features of stimuli and the neural patterns they evoke in "outside-in" models, conscious experience is primarily driven by already-existing neural or corporeal states (e.g., Bayesian priors) in "inside-out" theories. Within these latter theories, perceptual awareness is imposed onto the external world, as opposed to being driven by it.

Lastly, I will argue that while current theories of consciousness are derived almost exclusively from findings within the visual neurosciences (Crick & Koch, 1990, 1998), they by and large posit neural integration as a central tenet in engendering perceptual awareness (see Mudrik et al., 2014 for a similar argument). Further, and critically, our experience of the world is multisensory (see Deroy et al., 2014, 2016; O'Callaghan, 2017; Spence & Bayne, 2014). In turn, the dissertation will focus on developing a science of multisensory awareness; a science of consciousness that is in line with our multisensory perceptual experience and which may afford significant mechanistic insight, as neural integration is a *de facto* component of multisensory integration. In other words; there are not audio-visual receptors in sensory periphery.

More specifically, in a first step I will query whether observations resulting from visual neuroscience may be directly translated to the study of multisensory perceptual awareness? Or alternatively, can the study of multisensory perceptual awareness further inform consciousness models originally derived from visual neuroscience? Next, by probing different theories at the extreme of the "inside-out"/"outside-in" spectrum (see below) and evaluating them against a common criterion - whether the postulated role they ascribe to integration holds – I will illustrate how the study of multisensory integration can inform consciousness approaches throughout the entire "outside-in"/"inside-out" continuum.

Approaches to Consciousness

Global (Neuronal) Workspace Theory

Bernard Baars' Global Workspace Theory (GWT; Baars, 1988, 2002) is a cognitive model that conceives of the brain as a distributed set of specialized networks. There are hubs for sensory processing, for language, attention, and decision-making, among other computations (Baars, 1988, 2002). This distributed architecture allows for efficient processing, yet it also poses a problem – namely; how is information exchanged and pooled between modules (Dennett, 2001)? Further, conscious contents are i) singular and ii) fleeting within our stream of consciousness. In turn, we must ask ourselves how do distributed networks result in a unitary experience? A possible solution for this binding problem is that the modules that compose the brain compete for access into a global workspace (Baars, 1988, 2002). The content of the global workspace are consciously experienced, are only momentarily active, and are broadcasted to a multitude of unconscious cognitive processes. Thus, consciousness has an integrative function by coordinating processing in distributed networks (Baars, 1988, 2002).

While this original postulation of the GWT may in principle account for aspects of our subjective experience and reconcile the fact that the brain is a distributed network that has to nonetheless work together, due to its qualitative approach it is also a theory that is hard to falsify. Hence, Dehaene and colleagues (Dehaene et al., 2006; Dehaene & Changeux, 2011) proposed a neuronal implementation of the global workspace architecture, the so-called Global Neuronal Workspace theory (GNW; Dehaene & Naccache, 2001). This version of the GWT is conceptually similar to Baars' formulation – most importantly for the current purposes, by proposing that consciousness has an integrative function. More specifically, the GNW theory states that as the global workspace must be engaged for there to be a conscious experience, neural activity associated with a particular experience has to be sustained for long enough as to index a particular state within a dynamical system; a particular constitution of the workspace (Dehaene & Changeux, 2011, see Joglekar et al., 2018 for computational evidence). This sustained brain activity originates from inputs ascending from sensory periphery and becomes essentially decoupled from stimuli presentation if the initial input drives activity beyond a threshold of no return. Alternatively, the sustained neural activity indexing a perceptual state may be propelled into existence by top-down attentional signals amplifying bottom-up sensory signals and generating a "neuronal avalanche" or the occurrence of "neuronal ignition" (Dehaene & Changeux, 2011, Joglekar et al., 2018). Mechanistically, neural signals that are consciously experienced recruit fronto-parietal cortices with long-distance excitatory cortio-cortical connections forming a reverberating neuronal assembly with distant perceptual areas (van Vugt et al., 2018; Joglekar et al., 2018; see Edelman, 1978 and Edelman & Tononi, 2000, for early discussions of the role of reentrant motifs in neural circuits in consciousness). Indeed, computational simulations (Dehaene et al., 2003, 2005; Joglekar et al., 2018) suggest that once stimulus-evoked activation has reached highly interconnected fronto-parietal areas, two important changes occur: first, the activation can reverberate, thus holding information online for a long duration essentially unrelated to the initial stimulus duration and presentation. Secondly, stimulus information can be rapidly propagated to many brain sub-systems (Dehaene et al., 2003, 2005, 2006).

Over the past 15 to 20 years a vast array of empirical findings – in particular from the neuroimaging realm - have supported the GNW theory by employing what Baars has called as the “contrastive approach to consciousness” (Baars, 2002); comparing conscious functions or states with closely matched unconscious processes or presentations. Exhaustive reviews of these findings have been put forward elsewhere (Dehaene & Changeux, 2011; Dehaene et al., 2018), but it is worth noting that neuroimaging studies employing vastly different techniques and indexing distinct levels of analyses – e.g., Blood Oxygenation Level Dependent (BOLD) activity, human and non-human primate electrophysiology, single-unit recordings – have supported the GNW theory. For instance, Grill-Spector et al., 2000, used functional Magnetic Resonance Imaging (fMRI) to measure activity evoked by pictures presented below or above the detectability threshold. Activation of the primary visual area V1 was largely unaffected by masking, but the degree of activation in more anterior regions of lateral occipital and fusiform cortex strongly correlated with perceptual reports. Dehaene et al., 2001, extended these results by indexing areas of neural activity uniquely evoked by words that were consciously perceived (vs. not consciously perceived). Areas uniquely recruited during conscious perception included the inferior prefrontal, mesial frontal, and parietal sites (Dehaene et al., 2001). Similarly, early event related-potential (ERP) studies, measuring electrical as opposed to hemodynamic activity, revealed that early visual activation can be fully preserved during masking (Schiller & Chorover, 1966), a finding that has been replicated on numerous occasions in humans (Koivisto et al., 2006, 2009; Melloni et al., 2007; Del Cul et al., 2007; Fahrenfort et al., 2007) and equally observed in animal electrophysiology (Bridgeman, 1975, 1988; Kovacs et al., 1995; Lamme et al., 2002; Rolls et al., 1999). On the other hand, the presence of late (>~200ms) and sustained activity within EEG/MEG, particularly a broadly distributed component called the P3b, has been shown to be discernable solely for perceived (vs. non-perceived) stimuli and to strongly correlate with subjective reports (e.g., Del Cul et al., 2007; Lamy et al., 2009; Fernandez-Duque et al., 2003). In a similar line, single-unit recordings by Logothetis and colleagues have demonstrated that the proportion of neurons that increase in firing activity jointly with the report of their preferred stimulus increases as one ascends the visual cortical hierarchy; from approximately 20% in V1/V2, to 40% in V4, MT, and MST, to as high as 90% in IT and STS (Leopold & Logothetis, 1996; Sheinberg & Logothetis, 1997; Wilke et al., 2006; see Quiroga et al., 2008 in humans). Thus, from a single-unit perspective, as suggested by the GNW theory, empirical evidence suggests that subjective perception is seemingly associated with i) a distributed cell assemblies and ii) single-unit activity of neurons found most commonly in higher (fronto-parietal) associative cortices than primary or secondary sensory cortices.

In sum, therefore, the Global Workspace theories – both in their cognitive (Baars et al., 1988, 2002) and neuronal (Dehaene et al., 2006, 2011) flavors – emphasize the role of consciousness in distributing or integrating information across modules and have received substantial empirical support. Dehaene's version of the theory (Dehaene et al., 2011; van Vugt et al., 2018) further underlines the role of top-down modulations (see Dehaene et al., 2006, for taxonomical distinction between conscious, pre-conscious, and subliminal - emphasizing the joint role of strong bottom-up inputs and top-down feedback) and empirical evidence has suggested that this top-down modulation originates from fronto-parietal cortices (Dehaene et al., 2006, 2011, 2018; Joglekar et al., 2018).

Integrated Information Theory

Tononi's (2004, 2012) Integrated Information Theory (IIT) is similar to the GNW theory (Dehaene et al., 2006; Dehaene & Changeux, 2011) in that it ultimately emphasizes neural integration and differentiation, or complexity (Edelman & Tononi, 2000), as central in engendering consciousness. Distinct from the GNW theory (Dehaene et al., 2006; Dehaene & Changeux, 2011), however, Tononi and colleagues start from what they consider fundamental properties of the phenomenology of consciousness; "axioms of consciousness". That is, the IIT claims to distinguish itself from the rest of consciousness theories by first introspectively determining what are the central phenomenological features of any conscious experience, and then subsequently developing a mathematical formalism encompassing these properties; postulates of consciousness. According to Tononi (2004, 2012), the axioms are "self-evident truths" and must be the central tenet of any theory of consciousness that does not want to leave Qualia (or "what it feels like") out of the equation.

There are 5 central axioms in the IIT (Tononi & Koch, 2015); existence, composition, information, integration, and exclusion. The first axiom (existence) simply echoes Descartes "*Cogito Ergo Sum*" (Descartes, 1641) and states that consciousness exists intrinsically (e.g., for me). The second axiom (composition) states that consciousness is structured in that each experience can consist of multiple features; e.g., a red (1) square (2). The third axiom (information) notes that each conscious experience differs from one another, and as such, it contains information. That is, the fact that one is currently having a particular experience by necessity negates any other potential experience that one could be having at the particular moment. Thus, from an information theory perspective, there is a reduction of uncertainty (i.e., the set of possible experiences collapses onto the sole veritably occuring experience) and hence information associated with the conscious experience. The fourth axiom (integration) states that experiences are irreducible to non-interdependent components. The conscious experience of a red square does not equate to the sum of two different experiences, that of “red” and that of a “square”. The fifth and last axiom (exclusion) states that each experience has definite borders and that spatio-temporal superposition of multiple partial experiences is not possible (Oizumi et al., 2014) In other words, by definition subjective experience is “complete”.

To parallel the above-described phenomenological axioms, the IIT advances a set of postulates physical systems must satisfy in order to generate a subjective experience. In particular it states that a system (biological or not) that exists from its own perspective (axiom 1) and can be sub-divided into discrete components (axiom 2) can in principle be conscious (see Cerullo et al., 2015, for a discussion regarding the panpsychism associated with the IIT). More importantly, the degree to which this system is conscious scales with the amount of intrinsic (axiom 1) integrated (axiom 4) information it possesses (axioms 3 and 5; Oizumi et al., 2014). In turn, consciousness-level is graded.

Tononi and colleagues (Oizumi et al., 2014; Tononi & Koch, 2015; Tononi et al., 2016) claim that for an entity to exist in a physical sense it must have cause-effect power. Other physical entities (e.g., A and B) ought to be able to perturb it (e.g., C), and it (e.g., C) ought to be able to impact other physical entities (e.g., A and B). Now, for an entity to be conscious it must exist intrinsically (i.e., from its perspective), and thus it must have cause-effect power for itself (e.g., system ABC must impact ABC). Next, as experience is structured ("composition" axiom; ABC can be divided into AB, AC, BC, A, B, or C) and multiple different experiences can occur (e.g., "information" axiom; system ABC can be in state "000", "111", "100", etc.), each component of a conscious system must be associated with a cause-effect repertoire (e.g., potential causes for A = 1 or consequence of A = 1 within an "ABC" system). The minimal distance between a constrained (i.e., with knowledge of the state of A, as in A = 1 or A = 0) and unconstrained (i.e., without knowledge of the state of A) cause-effect structure dictates the degree of information a particular node (e.g., A) affords the system as a whole. That is, given a system built appropriately (i.e., with an intrinsic cause-effect repertoire) one may calculate the amount of information associated with knowledge of the state of each component, as well as of the system as a whole. Lastly, as experiences are integrated, the degree to which a system may be conscious (phi, Φ; Tonini et al., 2016) is dictated by the minimal difference between the amounts of intrinsic information present in the system as a whole (e.g., ABC) vs. a partition of the system (e.g., AB or BC; see Oizumi et al., 2014 for more detail).

In essence, therefore, the IIT makes an identity claim between the degree to which a system as a whole is informative to itself (regarding its past and future) above and beyond any of its subsystems, and the degree to which this system is conscious. Unfortunately, this implies that in order to calculate Φ – the IIT's "consciousness-meter" (Tononi et al., 2016) – one must iteratively compute the knowledge gained (in the past and future) by knowing the current state of a node within the system (e.g., A = 1, vs. not knowing if A = 1 or A = 0), for every possible state and node of the system, and for every purview supported by the system (e.g., the whole system and all combination of its subparts; “ABC”, “AB”, “AC”, “BC”, “A”, “B”, “C”). Practically, the computational burden in calculating Φ grows superexponentially (“J-Curve”; Tegmark, 2016, Ibanez-Molina et al., 2018) with the number of nodes present in a system, and currently it is impossible to compute the Φ value associated with systems of more than approximately 20 nodes (Tegmark, 2016; but see Toker & Sommer, 2016, 2017, for interesting approaches circumventing current computing limitations). In turn, to leverage Tononi and colleagues (2016) theory in neurobiological systems, experimentalists have derived a number of tractable measures inspired in the IIT – mostly based on the notions of integration and differentiation (i.e., information; see Canales-Johnson et al., 2017, for a recent example of an elegant study indexing perceptual awareness by employing both measures of integration and differentiation).

The measures most in line with the IIT (and promoted by IIT theorists; Tononi et al., 2016) are the perturbation complexity index (PCI; Casali et al., 2013; Sarasso et al., 2015) and a component of the PCI, Lempel-Ziv complexity (LZ; Lempel-Ziv, 1976). In short, PCI is computed by perturbing the brain via transcranial magnetic stimulation (TMS) and then compressing the spatiotemporal patterns generated by the perturbation via LZ. This latter measure is a lossless compression algorithm that estimates the approximate number of distinct patterns present in a series of binary data. (Incidentally, this compression algorithm is widely used in modern computing and is the same technology behind ZIP files or TIFF images). Arguably, the more complex (i.e., integrated) a neural network, the larger should be the spatiotemporal complexity evoked by TMS, and thus the less compressible should be the evoked neural time-series (Ibanez-Molina et al., 2018). Indeed, PCI has been shown to successfully differentiate between distinct levels of consciousness (Casali et al., 2013; Sarasso et al., 2015). Similarly, LZ has also been directly applied to resting state (Schatner et al., 2015, 2017) and stimuli evoked (Andrillon et al., 2016; Noel et al., 2018) neural activity and has been demonstrated to differentiate between levels of consciousness (Schatner et al., 2015, 2017), as well as between distinct stages of sleep (Andrillon et al., 2016) and percepts (Noel et al., 2018).

Local Recurrence

The Local Recurrence (LC) theory of perceptual awareness emphasizes the role played by local and recurrent processing between early and higher-order sensory (visual) areas (Lamme, 2006) in engendering perceptual awareness. This theory has strong similarities with already-discussed models, such as Baars' (2002) and Dehaene's (2011) Global Workspace, as well as with Edelman's notion of reentry (Edelman & Gally, 2013). An important distinction between the LC model and the Global Workspace theories, however, is that the former posits recurrence within sensory areas as enough to elicit perceptual awareness, while the latter emphasizes the interplay between sensory and higher-order fronto-parietal or cognitive (e.g., language, executive function, attention) areas in engendering conscious content. Because perceptual awareness may occur from recurrent activity exclusively within sensory areas according to the LC theory, within this framework conscious perception is posited to be completely dissociable from other cognitive mechanisms required for attention, memory, and perceptual report. In turn, this leads to the prediction that certain phenomenological states may not be accessible and thus cannot be reported (see Block, 1995, 2005, for a discussion on the role of report in consciousness). Indeed, Block (2007) and Lamme (2006) argue that in paradigms in which subjects cannot report the presence of a stimulus because of inattention (e.g. change blindness, inattentional blindness, attentional blink; Rensik, et al., 1997, Mack & Rock, 1998, Raymond et al., 1992) subjects might still be phenomenally conscious of the stimulus because it induces local recurrence in perceptual brain regions. This line of argument has seen a revival in recent years with researchers making the distinction between “background conditions” necessary for consciousness, or for reporting consciousness, and processes that are directly involved in phenomenological consciousness *per se* (Wilke et al., 2009; Vandenbroucke et al., 2014; Pitts et al., 2014). Much of this work has emphasized the utility of “no-report paradigms” (Tsuchiya et al., 2015) in indexing perceptual awareness.

Higher Order Theories

Higher order or meta-cognitive theories of consciousness (Rosenthal, 2005; Lau & Rosenthal, 2011) postulate that first-order representations of sensory stimuli in isolation are not sufficient to evoke conscious perception. Contrarily, perceptual awareness is associated with higher-order representations, and in particular with states that represent oneself as being in the relevant first-order state (second-order representation; Lau & Rosenthal, 2011). For example, one becomes conscious of a red square only when a second-order mechanism represents oneself as currently perceiving a red square. The basic motivation for this stance is the observation that the same first-order (sensory) representation can lead to a multitude of distinct experiences. Thus, perceptual awareness cannot be primarily determined by bottom-up sensory representation, but ought to be directly related to higher-order representation. From a neuroscientific standpoint, similarly to the global workspace theories (see above), higher-order theories predict that perceptual awareness is determined by activity within fronto-parietal networks (Lau & Passingham, 2006; Rounis et al., 2010; Lau & Rosenthal, 2011). Nonetheless, these theories are distinguished by the fact that according to the GNW theory, the awareness-related activity in the prefrontal and parietal areas is associated with essential behavioral functions, such as flexible control of behavior, cognitive control, and task-performance (Dehaene et al., 2006; Dehaene & Changeux, 2011). The higher-order view, by contrast, is neutral regarding whether consciousness has a functional role at all. Further, researchers supporting higher-order views of consciousness are critical of the fact that the vast majority of studies examining perceptual awareness conflate subjective experience with performance (Lau & Rosenthal, 2011). That is, almost inevitably, when participants report perceiving a stimuli, their performance at the task at hand is increased. In a notable exception, Lau & Passingham, 2006, used visual metacontrast masking to create conditions in which the subjects' ability to discriminate between visual stimuli remained constant while participants claimed to be aware of the stimuli more frequently in a particular condition. This report of awareness was associated with activity in dorsolateral prefrontal cortex. Further, TMS applied to this region modified subjective reports of awareness without impairing task performance (Rounis et al., 2010), hence arguing for the possibility of dissociating between first and second-order representations; awareness being related to the latter (although see Bor et al., 2017, Seth et al., 2018, and Ruby et al., 2017, for a recent debate regarding this finding).

Attention Schema Theory of Awareness

The attention schema theory of awareness starts from the observation that awareness emerges from the brain, and the brain is an information-processing device. This information-processing device has the capacity to focus its resources onto a particular signal via attention. Hence, according to control theory (Camacho et al., 2004), as for any other control system, the brain ought to benefit from an internal model of what is to be controlled; an internal model of attention. According to Graziano's theory, awareness is this internal model of attention (Graziano & Kastner, 2011; Graziano, 2013). That is, the attention schema theory of awareness is a higher-order theory (i.e., awareness is a second-order representation), which specifically postulates that when attention is re-represented, but not when anything else is, an entity experiences awareness. Within this theory attention and awareness are yoked, but dissociable (Webb et al., 2016). Interestingly, the attention schema theory of awareness differs from other higher-order theories of consciousness in that it does not conceive of fronto-parietal areas as important in higher-order representations leading to awareness. Instead, the attention schema theory postulates that the temporoparietal junction (TPJ) may serve the role of abstracting second-order representation from the first-order experiences. This latter claim is heavily based on the observation that lesions to the TPJ lead to neglect – a deficit of awareness for the contralesional visual field (Vallar, 1998; Parton et al., 2004) – and the fact that awareness doesn't only have to be attributed to oneself, but also onto others. Namely, the theory supposes that humans assume others are conscious because we each can individually create a model of other individuals' attentional system (Graziano, 2013). In turn, theory of mind (Saxe & Kanwisher, 2003; Frith & Frith, 2005) becomes a central player in this theory, and numerous studies have pinpointed the TPJ as a key node in theory of mind (Saxe & Kanwisher, 2003). Early evidence probing the attention schema theory of awareness suggests that as hypothesized humans project their own spatial biases onto others during a theory of mind task (Bio et al., 2017), that the TPJ is a key node in a network processing visual awareness independently from visual attention (Webb et al., 2016), and that there is a partial overlap in brain areas that participate in the social attribution of sensory awareness onto others and oneself (Kelly et al., 2014).

Predictive Coding

Arguably, the predictive coding framework originates from von Helmholtz's (1867) observation that perception is an inference problem, is perhaps best categorized as an approach to understanding brain function as opposed to consciousness (although see Clark, 2018; Friston, 2018), and has seen renewed interest given its strong association with the "Bayesian Brain Hypothesis" (Clark, 2013; Hohwy, 2013; see Rao and Ballard, 1999, for an early predictive coding computational model of visual processing). In short, the predictive coding framework stipulates that the brain is continuously attempting to minimize the discrepancy (i.e., prediction error) between feedforward inputs and its emerging models of the causes of these inputs via neural computations approximating Bayesian inference. That is, feedforward inputs carry likelihoods, feedback projections carry priors (i.e., the current model at the particular stage of processing), and these combined via Bayesian computations to generate posteriors representing the discrepancy between likelihood and prior. This discrepancy between what is expected and the sensory evidence that is present is propagated up the neuroaxis (i.e., posteriors at one level form the priors at the next level). Importantly, prediction errors are associated with "precisions" and mechanisms such as attention can modify these relative reliabilities and thus the weighting associated to sensory input vis-à-vis prior expectancies (see Seth, 2013 for review).

The predictive coding framework, therefore, overturns the more traditional conception of perception as largely a bottom-up process of evidence accumulation and instead stipulates that perceptual content is specified by top-down predictive signals that emerge from hierarchically organized models of the causes of the sensory signals. That is, the content of consciousness is as much imposed onto the world by prior sensory experiences, as it is driven by sensory input.

Minimal Phenomenal Selfhood

The minimal phenomenal selfhood approach to consciousness is scaffolded on the philosophical argument that in order for there to be an experience, there has to be a subject to have the experience (Legrand, 2006; Legrand et al., 2007; Faivre et al., 2015). Thus, before we can perceive the world at large, the nervous system must build a minimal representation of the self; an undertaking the minimal phenomenal approach argues has been largely forgotten by other theories of consciousness (Blanke et al., 2015; Faivre et al., 2015, see Friston, 2018, for a free-energy argument suggesting that consciousness requires self-consciousness). Blanke and Metzinger (2009) posit that this minimal proto-self has three components; body ownership at the level of the whole body (i.e., self-identifying with a body), self-location (i.e., experience of where 'I' am in space), and a first-person perspective (i.e., from where 'I' perceive the world).

Interestingly, while at first it may appear that the sense of being encapsulated within a body one possesses is immutable, clever experimental manipulations have demonstrated that bodily self-consciousness is incredibly malleable. In the Rubber-Hand Illusion (RHI; Botvinick & Cohen, 1998) administration of temporally congruent tactile stimulation on the real hand and visual stimulation on a rubber hand results in the eerie sensation that the rubber hand is one's own (i.e., ownership over a fake limb). Since the original description by Botvinick & Cohen (1998) a panoply of studies have delineated constraints to this phenomenon. For instance, studies have shown that for ownership of an artificial hand to be induced, the artificial hand must be placed in the same orientation as the real hand (Tsakiris & Haggard, 2005), must visually resemble a human hand (Tsakiris & Haggard, 2005), must be within a certain spatial range of the real hand (Lloyd, 2007; Samad et al., 2015), and visuotactile stimulation on the rubber hand must be applied in the same direction as that applied to the veridical hand (Makin et al., 2008).

Similarly, the RHI has been shown to not only result from synchronous visuo-tactile stroking, but also from multisensory integration of other body-related signals, such as visuo-proprioceptive (Kalckert & Ehrsson, 2012) or visuo-cardiac (Suzuki et al., 2013) signals.

Importantly, early neurophysiological recordings by Graziano and colleagues (1997, 1999, 2000) showed that the non-human primate brain has a fronto-parietal network composed of visuo-tactile and audio-tactile neurons that possess depth-restricted receptive fields, and are anchored on the body. That is, these neurons encode for the peri-personal space; the multisensory space immediately adjacent to and surrounding the body (Rizzolatti et al., 1997; di Pellegrino et al., 1997; Serino et al., 2015). Further, prolonged visuo-tactile stroking of a monkey's arm—similarly as that used to induce the RHI (Botvinick & Cohen, 1998) — affected the tuning properties of these PPS neurons (Graziano et al., 2000). After selecting for neurons whose response preference depended on the location of the real (proprioceptive), but not of the fake (visual) arm, researchers applied synchronous visuo-tactile stroking repeatedly to the monkey's hidden real and visible fake arm. Re-evaluating the visual tuning of these neurons immediately after visuo-tactile stroking revealed that these neurons were now tuned to the visual location of the fake arm (Graziano et al., 2000), as if they now coded the proprioceptive location of the hand as being at the position of the fake visual hand. These results clearly argue that the RHI is a multisensory illusion and that ownership of limbs depends on the dynamic integration of multisensory cues within the peri-personal space (see Blanke, 2012).

However, it has been argued that limb and full-body ownership are categorically distinct (Blanke, 2012; Noel et al., 2018). Namely, humans do not consider a particular limb to enclose their self, nor is there a particular egocentric perspective (i.e., first-person perspective) associated with one's arms or legs. In the RHI one's egocentric perspective remains unchanged. To probe bodily self-consciousness experimentally, Lenggenhager and colleagues (2007), as well as Ehrsson (2007), modified the RHI in order to induce a full-body version equivalent of the illusion. Under conditions of synchronous (but not asynchronous) visuo-tactile stroking where a participant saw themselves in virtual reality from 2 meters away and felt touch on their back (Lenggenhager et al., 2007) or chest (Ehrsson, 2007), participants reported feeling as if drifting toward a virtual avatar (Lenggenhager et al., 2007; Ehrsson, 2007). Further, this full-body illusion (FBI; Lenggenhager et al., 2007; Ehrsson, 2007) does not only alter self-location and full-body ownership. In fact, when participants lay in supine position and are presented gravitationally ambiguous visual stimuli, the FBI can equally impact first-person perspective (Ionta et al., 2011). Thus, it has recently been argued that multisensory integration of body-related signals within the peri-personal space does not only play a role in body part ownership, but also scaffolds bodily self-consciousness (Blanke, 2012; Blanke et al., 2015).

Idiosyncrasies and Similarities Across Theories of Consciousness; the Role of Integration

In the previous section we have emphasized a number of theories of consciousness. These, by no means represent an exhaustive list, but arguably do highlight the diversity of conceptual frameworks in studying perceptual awareness. Indeed, the modern empirical science of consciousness started as an organized activity only about two or three decades ago (Lau, 2017; the "Association for the Scientific Study of Consciousness" meets yearly since 1997). Therefore, as a young field of study it is to be expected that we are just commencing to understand how to pose interesting and fruitful questions. Which avenue of study will afford the most explanatory value? The theoretical stances reviewed above represent votes as to how best study consciousness, and thus it may be of interest to examine (and organize) their idiosyncrasies, as well as underline their similarities.

Idiosyncrasies; an "outside-in" to "inside-out" spectrum that is narrowing

The theories discussed above differ in myriad aspects, both in their details and perhaps more revealingly in their philosophical approach or perspective. In terms of the more global idiosyncrasies, the GNW (Dehaene et al., 2006; Dehaene & Changeux, 2011) and LC (Lamme, 2006) differ with respect to which regions of the brain they consider essential in engendering consciousness. Nonetheless, these two theories clearly conceive that it is the neural dynamics occurring within networks that lead to perceptual awareness. The IIT (Tononi et al., 2016) on the other hand, is also a network-level theory, yet this theory is more concerned with the nature of the architecture itself – namely, whether it could in principle support intrinsic information integration – than with the dynamics occuring within it. In recent work (Koch et al., 2016) the IIT posits a "posterior hot zone" as a likely generator of high integrated information within the brain, and thus, in their eyes, consciousness. Now, neither of these theories – GNW, LC, or IIT – make use of the notion of second order representation. Thus, while different in their own right, the above-mentioned theories are also categorically distinct from higher-order theories (Rosenthal, 2005; Lau & Rosenthal, 2011; Graziano, 2013); the latter being more concerned with a network or brain region representing or summarizing input-evoked activity, than with the input-evoked activity itself. Now, all of the above-described theories claim that their subject of study is perceptual awareness. Implicitly, however, one must understand that their subject of study is perceptual awareness of the external environment – not of the self. This last distinction differentiates between GNW, LC, IIT, and higher-order theories on one hand, and the minimal phenomenal selfhood approach to consciousness (Blanke & Metzinger, 2009) on the other hand.

Interestingly, these peculiarities suggest that the mentioned theories (and possibly others too) can be placed on a continuum; from the "outside-in" to the "inside-out". On one hand we have theories that fundamentally aim at explaining how (visual) information is first filtered through sensory periphery and then re-assembled up the neural hierarchy (e.g., from orientations to angles to objects) ultimately leading to (visual) experience. On the other hand we have theories that point in the opposite direction; perceptual awareness is imposed on the environment either given a bodily representation (and the ability to perform actions and modify the environment; Gibson, 1978; O'Regan & Noe, 2001; Bekkering & Neggers, 2002) or perceptual/cognitive second order representations (Rosenthal, 2004). NWG, LC, and IIT would all be examples of theories closer to the "outside-in" extreme of the continuum, while predictive coding, the attentional schema theory, and the minimal selfhood approach would be closer to the "inside-out" end of the spectrum.

In the rest of this section I first further stress the distinction between "outside-in" and "inside-out" approaches to consciousness and describe empirical evidence associated with these perspectives. Then, I argue that the spectrum from the "outside-in" to the "inside-out" is narrowing with findings and theories emphasizing the strong interplay between both "bottom-up" and "top-down" signals, as well as between "outside-in" and "inside-out" approaches. In fact, Friston has recently argued that "the answer entertained here [regarding consciousness and self-consciousness] rests upon the two-way coupling between a system and the world" (Friston, 2018). Lastly, I suggest that accentuating the complementary roles of the different ends of the spectrum leads to the postulate that "integration" is a key computation in perceptual awareness. However, a definition of “integration” and ascription of a functional role to it are still nebulous.

Outside In

The vast majority of perceptual awareness studies have utilized the contrastive approach (Baars, 1988) wherein different experimental conditions are matched as closely as possible, while evoking different subjective experiences. The use of bistable (e.g., Alais & Blake, 2005), masked (e.g., Sperling, 1965), and faint (e.g., Chessman & Merikle, 1984) stimuli has proven particularly fruitful within this context and insights from these studies (e.g., Tong et al., 1998; Pascual-Leone & Walsh, 2001; Koivisto & Revonsuo, 2003, 2010; Del Cul et al., 2006, 2007; Gaillard et al., 2009) gave rise to a number of scientific theories of consciousness (e.g., GWT, GNW, LC). Further, this work has generated lively debates regarding whether neural activity at different levels of the neuraxis index and/or are necessary for (visual) awareness (see Tong, 2003, and Blake & Logothetis, 2002 for reviews). Early studies in humans revealed clear EEG modulations from occipital sensors – i.e., perhaps early visual areas - during rivalry (Lansing, 1964; Cobb et al., 1967) and later fMRI studies showed analogous effects while pinpointing this activity to V1. Indeed, fMRI modulation during rivalry in monocular V1 were as large as those evoked by physical changes of the stimuli (Tong & Engel, 2001), and of equal magnitude to rivalry modulations in higher visual areas (e.g., V4; Polonsky et al., 2004). Thus, it could be argued that at minimum activity in V1 co-varies with subjective reports. In contrast, neurophysiological recordings have shown a clear organization where firing rates are closely in line with subjective reports in higher-order regions (e.g., infero-temporal cortex) but not earlier (Logothetis & Schall, 1989; Leopold & Logothetis, 1996; Sheinberg & Logothetis, 1997; Silvanato et al., 2005). Thus, the neurophysiological approach has argued that subjective reports are most in line with activity beyond early visual cortex. Of course, as lesion studies have demonstrated (Holmes, 1918; Inouye, 2000), possessing an intact V1 may be necessary to relay information, but according to neurophysiological observations V1 is not central for visual awareness (for review see Rees et al., 2002; Crick & Koch, 1995).

This debate over which areas of the brain are necessary and sufficient for visual awareness is far from over, with many researchers actively searching for the "neural correlates of consciousness" (NCC; Koch, 2004; Aru et al., 2012). In fact, as alluded to above this debate (and search) represents the distinction between the GNW and LC theories of consciousness. Most importantly for the current argument, this debate and the GNW and LC theories are clear illustrations of the "outside-in" perspective on consciousness. Namely, researchers administer rigorously controlled stimuli and examine what changes occur in the brain due to stimuli presentation and leading to consciousness. It is taken that sensory stimuli in the environment perturb the brain insofar as to induce a subjective experience, and the topic of study is the (admittedly non-linear and recurrent) transformation of this energy; from the external milieu up the cognitive hierarchy.

Inside Out

Instead of starting from the environment, a number of the theories reviewed in the previous section start from the body or the brain. Arguably, this is most clearly exemplified by the minimal phenomenal selfhood approach (Blanke & Metzinger, 2009), which does not deal directly with exteroceptive awareness but with awareness of the self. As indicated above, this approach argues that awareness starts with a primitive form of self-awareness and that a conscious experience may not be understood without the self. Similarly, the predictive coding framework (Rao and Ballard, 1999; Seth, 2013) and even higher-order theories (Rosenthal, 2005; Lau & Rosenthal, 2011; Graziano, 2013) are more concerned with what already exists in the brain and/or in phenomenal content, as opposed to occurrences in the environment. In fact, these theories exemplify the "inside-out" approach and most clearly reflect von Helmholtz's "perception as inference" insight by arguing that perceptual awareness is imposed on the environment as much as it is driven by it. For example, within the predictive coding framework the content of awareness in the absence of sensory input (likelihood) is simply the prior – what already exists in the brain. In higher order theories, the content of awareness does not necessarily need to do with first-order sensory processing, but with a second-order re-representation. There is (or can be) a stronger disconnect with what is presented in the environment and what is perceived.

While the study of bodily self-consciousness (e.g., Halligan et al., 1995; Berlucchi & Aglioti, 1997; de Vignemont, 2011; Blanke, 2012; Blanke et al., 2015; Bernasconi et al., 2018; Noel et al., 2018) and the indexing of error-related (Gehring et al., 1993, 2012; Herrmann et al., 2004) and mismatch (Näätänen, 1995; Garrido et al., 2009) negativities, the latter concepts being closely related to the predictive coding framework, have a long tradition, less work has examined the interplay between these processes and perceptual awareness (see Nieuwenhuis et al., 2001; Charles et al., 2014; Dehaene, 2018, regarding error potentials and consciousness). However, a number of recent studies are noteworthy in highlighting the "inside-out" impact on perceptual awareness (although it must be emphasized that traditionally the minimal phenomenal selfhood approach to consciousness does not include exteroceptive awareness within its purview; it is concerned with the study of the self and not the environment). Faivre and colleagues (2015) questioned whether the Taylor Illusion (Gregory, 1959) – an illusion suggesting that an afterimage projected onto one's hand changes in size depending on the hand's location and thus proprioceptive cues – was modulated by hand ownership. The researchers induced the RHI in a number of participants and observed that indeed the afterimage projected onto the participant's hand drifted depending on illusory ownership. In a similar study, Van der Root and colleagues (2017) employed continuous flash suppression (CFS; Tsuchiya & Koch, 2005) to suppress the image of a hand while concurrently manipulating the sense of ownership over the hand through visuotactile stimulation. Their findings suggested that ownership, but not mere visuotactile stimulation, increases the dominance of the hand percept. Lastly, Tallon-Baudry and colleagues (Park et al., 2014; Richter et al., 2017; Park & Tallon-Baudry, 2014) have demonstrated over a number of studies that spontaneous fluctuations in neural responses to heartbeats (i.e., "heartbeat evoked potentials") may predict visual detection. All of these studies, therefore, highlight the great impact of internal states on exteroceptive processing.

Convergence of Outside-In and Inside-Out approaches

The "outside-in" and "inside-out" approaches are closely tied with, but not identical to, bottom-up and top-down processing. Indeed, the minimal phenomenal selfhood approach is unapologetically bottom-up in that it argues that by understanding relatively simple phenomena (i.e., body-related multisensory integration in the peri-personal space) we will ultimately comprehend self-consciousness. This approach, however, is clearly "inside-out" in that it argues that perceptual awareness is imposed onto the world. The fact that we have a body we feel agency and ownership over is not incidental, but truly dictates how we perceive the environment (see Gibson, 1978, for a related argument). The "outside-in" to "inside-out" spectrum delineated above is more a matter of perspective – where does the burden for explanation for perceptual awareness lie? What components of human/brain-environment interactions drive perception? – than a matter of feedforward vs. feedback processing.

Nonetheless, in recent years we have seen a rapprochement between these two perspectives, and it is true that this narrowing of the theoretical spectrum is largely driven by the “outside-in” theories (e.g., GWN, LC) emphasizing the role of feedback signals in generating perceptual awareness. Indeed, likely no theoretician today would argue that consciousness arises purely from a feedforward process, and thus not only features of the stimuli must be meticulously detailed in experimental paradigms, but also internal features of the nervous system (see Musall et al., 2018 and Stringer et al., 2018, for recent studies demonstrating the profound impact of the “internal backdrop” on the processing of incoming sensory stimuli). Recent work has noted, for instance, that the phase (Mathewson et al., 2009; Busch et al., 2009; Van Rullen & Koch, 2003) and peak frequency (Samaha & Postle, 2015) in alpha cycles can profoundly confine visual perception. That is, identical visual presentations may engender drastically different subjective experiences given prior and/or concurrent internal neural states (e.g., the phase of an alpha cycle at which visual stimuli is presented).

In summary, therefore, whereas philosophically there is still a wide spectrum of consciousness theories – from those emphasizing the impact of exogenous features on endogenous neural fluctuations to those emphasizing endogenous representations almost regardless of exogenous occurrences – arguably from a practical standpoint they all agree that the interplay between bottom-up and top-down signals, as well as between world-driven and self-driven computations dictates perception.

Similarities; Integration as convergence of the outside-in and inside-out approaches

The distinct theories of consciousness cover a large conceptual space, yet interestingly they also by and large all posit integration (or “binding”) as a crux of their theory (Mudrik et al., 2014). Indeed, the interdependency between consciousness and integration can be drawn all the way back to Descartes ("since our soul is not double, but one and indivisible, [...] the part of the body to which it is most immediately joined should also be single and not divided into a pair of similar parts"; Descartes, 1660) and James (‘‘We cannot even […] have two feelings in mind at once"; James, 1890) and more recently features in influential writings by Treisman ("Conscious access reflects binding. Conscious access in perception is always to bind objects and events [...] consciousness combines information from many brain areas, and it binds that information to form integrated objects and events [...] Within this framework, binding is central to conscious experience"; Treisman, 2003), Dehaene and Naccache ("The global interconnection of those five systems can explain the subjective unitary nature of consciousness and the feeling that conscious information can be manipulated mentally in a largely unconstrained fashion", Dehaene & Naccache, 2001), as well as Tononi and Edelman ("Categorizations of causally unconnected parts of the world can be correlated and bound flexibly and dynamically together inside consciousness but not outside it", Tononi & Edelman, 1998), among others.

Now, the functional role ascribed to integration and consciousness, as well as the definition of integration varies widely across theories. In terms of the functional relationship between these two, some have suggested that consciousness enables integration (Baars, 2002; Damasio, 1999; Dehaene & Naccache, 2001), others have claimed consciousness is enabled by integration (Treisman, 2003; Engel et al., 1999), and yet others claim an identity relation between (information) integration and wakefulness (Tononi et al., 2016). The claim that integration is needed for consciousness is most commonly derived from the phenomenological observation that awareness is undivided and experienced as a singular stream (Treisman, 2003; Bayne, 2010). On the other hand, the claim that consciousness is needed for integration is most commonly derived from the postulate that consciousness is needed for planning (Crick & Koch, 2003), learning (see Cleeremans & Jimenez, 2002), and flexible behavior (Searle, 1992), among other executive functions. Thus, almost as a corollary, consciousness is needed to arbitrate and route information between these different cognitive modules (Baars, 2002), i.e., solving a binding problem (see Revonsuo, 1999, for a review of the different "binding problems"). Empirical evidence, in fact, suggests that integration across space and time (e.g., Faivre & Koch, 2014), of high-level semantic information (Kang et al., 2011; Mudrik et al., 2014, but see Lin & Murray, 2014; Sklar et al., 2012), and of novel associations (e.g., Raio et al., 2012) is hindered under unconscious vis-à-vis conscious conditions (see Mudrik et al., 2014, for a review). Nonetheless, the exact interdependencies between these processes, their mechanistic link, and how this relationship may or may not change across the neural and cognitive hierarchy, as well as across levels of description (i.e., single neurons, ensemble of neurons, behavior) is vastly underexplored. Indeed, while at the behavioral level integration appears impaired when stimuli are presented unconsciously (see above), the strict interdependency between consciousness and integration is certainly not one of necessity, as sensory signals are integrated – insofar as to alter firing rates – at early neural stages (e.g., superior colliculus) and even when animals are unconscious (e.g., Stein & Meredith, 1993; Wallace et al., 2006; Wallace & Stein, 1997).

With regard to the definition of integration, theories also differ. As discussed above, Baars' (2002) GWT states that consciousness integrates across distinct cognitive modules, and routes information between them. But no clear definition of integration exists beyond the notion that it associates representations. This definition becomes somewhat further crystalized in Dehaene and colleagues' (2006) GNW version of the theory, which suggests that long-distance cortico-cortical synchronization at beta and gamma frequencies supports consciousness. Hence, integration within this framework involves neural coherence enabling the binding of bottom-up sensory representations and top-down attentional signals (see Crick & Koch, 1990, Llinas & Ribary, 1993; Engel et al., 1999, for empirical support and theories postulating neural synchronization as key in binding and consciousness). At difference from the GWT/GNW, Tononi's IIT (Oizumi et al., 2014; Tononi et al., 2016) does provides a very clear definition for integration. Integrated information is information that is present in the system as a whole above and beyond what is present in the subcomponents of the system. Unfortunately it remains unclear what biological entity constitutes a "node" or a "subsystem" within this framework (but see Hoel et al., 2013, for theoretical work suggesting that information integration defined "a la IIT" is greater at a macro- than micro-scale). Lastly, the minimal phenomenal selfhood approach states that a pre-reflexive self must exist as subject to experience, and this proto-self is seemingly assembled through the process of multisensory integration. Thus, this latter approach to consciousness has a strong definition for integration, a definition borrowed from the multisensory field (see detail below). Higher-order theories of consciousness and the predictive coding framework do not emphasize integration as strongly as the rest of theories discussed above.

Taken together, a large portion of contemporary theories of consciousness – in fact those at the extreme of the "outside-in"/"inside-out" spectrum - emphasize the notion of integration as scaffolding perceptual awareness. This represents common ground in the philosophical approaches taken in studying consciousness, i.e., these theories share a common notion, and further, this concept implies that the "outside-in" and "inside-out" extremes are unlikely to account for consciousness in isolation; we ought to understand the synthesis of these approaches. However, the exact nature of the integration occurring (i.e., its definition) and the role of integration in consciousness differs across theories and remains elusive. In the next section I will argue that a path forward is to leverage the process of multisensory integration in studying consciousness. Examining consciousness from the multisensory perspective re-aligns the study of perceptual awareness with our daily experience of a multisensory world (Deroy et al., 2014; 2016). Moreover, it permits using the strong definitions for integration that exist within the multisensory field (Murray & Wallace, 2012).

Multisensory Integration and Consciousness

In the previous sections I have outlined contemporary theories of consciousness, discussed their idiosyncrasies and similarities, and argued that while these adopt vastly distinct approaches they by and large posit the process of integration as key for consciousness. Interestingly, despite this proposed link featuring in a number of theories (e.g., GWT, GNW, LC, IIT, minimal phenomenal selfhood), perceptual awareness has nonetheless traditionally been studied in terms of single sensory modalities and not from the multisensory perspective (Deroy et al., 2016; Faivre et al., 2016). The study of consciousness is most developed within the visual neurosciences (Koch, 2004), is present and growing within the auditory modality (Allen et al., 2000; Bekinschtein et al., 2009; Giani et al., 2015; Gutschalk et al., 2008; Haynes et al., 2005; Ro et al., 2003; Tzovara et al., 2013; King et al., 2013; Dykstra et al., 2017), and is almost absent in somatosensation (de Lafuente et al., 2005, 2006; Gallace and Spence, 2008, 2014) as well as olfaction and taste (Stevenson & Attuquayefio, 2013; see Faivre et al., 2016, for a review). The visual bias in consciousness studies is likely due to an array of reasons, such as the existence of numerous experimental methods to control the visibility of presented stimuli (Kim & Blake 2005), the relatively advanced understanding of the visual system in comparison to other sensory systems (De Yoe & van Essen, 1988; van Essen & Maunsell, 1983), and recent history. Regarding this last reason, pioneers in the study of perceptual awareness and individuals still driving much of the scientific thought around perceptual awareness explicitly stated: “We made the plausible assumption that all forms of consciousness (e.g. seeing, thinking, and pain) employ, at bottom, rather similar mechanisms and that if one form were understood, it would be much easier to tackle the others. We then made the personal choice of the mammalian visual system as the most promising one for an experimental attack. This choice means that fascinating aspects of the subject, such as volition, intentionality, and self-consciousness, to say nothing of the problem of qualia, have had to be left on one side” (Crick & Koch 1990).

This reductionist approach focusing on the visual system is understandable within a young field of study, however this restrictive focus may equally difficult the goal of understanding the relation between consciousness and integration. Indeed, understanding neural integration is the main question of interest within the multisensory field, and not necessarily within the visual one. More vexingly, our perceptual experience is inherently multisensory (Deroy et al., 2016; Faivre et al., 2016) and thus it is unclear whether theories derived from the visual neurosciences are large enough in scope as to capture fundamental mechanistic features supporting consciousness (e.g., integration). In other words, it is unclear whether Crick & Koch’s (1990) assumption that visual and auditory awareness, for instance, follow the same organizational principles holds or not. More importantly, it is unclear whether we should divide consciousness into distinct modalities. In fact, in a burgeoning area of philosophy of mind, many question whether theoretical and experimental insights derived from visual awareness may apply to the multisensory case (Deroy et al., 2014; Briscoe, 2016, 2017), whether unisensory and multisensory experiences are subject to the same ‘cognitive penetrability’ or phenomenological introspection (Deroy et al., 2015; Briscoe, 2016, 2017), and inclusively whether there is such a thing as multisensory awareness as opposed to a rapid succession of unisensory experiences (Bayne, 2010; Deroy et al., 2014, Briscoe, 2016, 2017). It could similarly be asked whether a purely unisensory perceptual experience is possible? Given that in our daily life we are continuously and concurrently bombarded with sensory information from different modalities, a visual experience may not be encoded as solely the presence of a visual stimuli, but also as the absence of auditory and tactile signals (Shalom & Zaidel, 2018; Noel, in press)

I suggest that insights derived from the study of visual awareness may not generalize to the study of multisensory awareness. Contrarily, perhaps the study of the latter may inform theoretical stances derived from the visual neurosciences. Multisensory integration *de facto* requires the process of integration. Additionally, contrary to the case of, say, visual feature integration (e.g., color and shape), the integrative process in the multisensory context is not corrupted or complicated by fact that the items to be integrated are filtered at sensory periphery and relayed up to the central nervous system via the same channels. Lastly, multisensory integration has a long history in demonstrating behavioral and perceptual benefits (i.e., a function) and strong definitions of "integration" exist within this arena. Thus, it may be possible to leverage the study of multisensory integration in studying consciousness.

In the next sections I first briefly review the process of multisensory integration and subsequently discuss the state of the field of multisensory perceptual awareness.

Multisensory Integration

Definition and Classic Principles

The presence of redundant sensory information from multiple modalities greatly facilitates behavioral performance (Murray & Wallace, 2012). For instance, target detection and discrimination (Frassinetti et al., 2002; Lovelace et al., 2003; Noel &

Wallace, 2016), target localization (Nelson et al., 1998; Wilkinson et al., 1996), speeded reaction times (Morrell, 1968a, b; Diederich & Colonius, 2004; Frens et al., 1995; Nozawa et al., 1994), memory and learning (Shams & Seitz, 2008; Alais & Cass, 2010; Botta et al., 2011) and speech intelligibility (Sumby & Pollack, 1954) are all facilitated in multisensory as opposed to unisensory contexts. Further, this multisensory enhancement is greater than that one may expect given the fact that several channels of information are available. Within the framework of reaction times, for instance, violation of the race-model (Raab, 1962; Miller, 1982, 1986) has been proposed as a benchmark for multisensory integration. Briefly, this model states that multisensory (e.g., audio-visual) reaction times will be faster than unisensory reaction times (e.g., auditory or visual) simply due to statistical facilitation; the fact that a response may be driven by either auditory or visual signals arriving at a putative decision center. Hence, the race model builds a proxy probability distribution of reaction times to-be-expected given statistical facilitation, and interestingly, multisensory reaction times have been routinely found to surpass this benchmark (e.g., Molholm et al., 2002; Van der Stoep et al., 2016; Noel et al., 2018).

From a neural standpoint, early recordings in the feline Superior Colliculus (SC), a subcortical structure and critical node in the network mediating orienting behavior (Mohler & Wurtz 1976; Robinson, 1972; Schiller & Koerner 1971; Schiller & Stryker 1972; Sparks, 1978; Wurtz & Goldberg 1972; Stein & Meredith, 1993) suggested the existence of a population of neurons that not only responded indiscriminately to information from different senses (e.g., vision, audition, touch), but also integrated this information (Stein & Meredith, 1993; Stein & Stanford, 2008). That is, the output of these neurons due to the presentation of a multisensory cue was not the simple sum of unisensory spikes, but at times exceeded this linear prediction (supra-additivity) and at times fell short from it (sub-additivity; Stein & Meredith, 1993; Kadunce et al., 1997; Stein

& Stanford, 2008). Importantly, therefore, some sort of transformation is arguably occuring at the level of the multisensory neuron. These recordings and the characterization of multisensory spiking activity consequent to an array of different spatio-temporal multisensory layouts ultimately led to the formulation of the so-called "principles of multisensory integration" (Stein & Meredith, 1993; Stein & Stanford, 2008). Briefly, the spatial and temporal principles of multisensory integration respectively state that the closer in space or time two unisensory stimuli are from one another, the more readily they will be integrated and a greater degree of multisensory gain will occur. A third principle, that of inverse effectiveness, states that multisensory gain is greatest when unisensory stimuli evoke weak neural responses. That is, an additional source of information is unlikely to play a vital role in guiding behavior or in driving neural activity when a single sensory cue is already sufficiently informative.

Although first established at the level of the single neuron, these principles have also been shown to apply to indices of activity in larger neuronal ensembles, such as scalp (Cappe et al., 2012) and intracranial EEG (Quinn et al., 2014), fMRI (Miller & D'Esposito, 2005), and PET scanning (Macaluso et al., 2004), as well as to indices of animal and human behavior. Interesting examples of behavior relate to multisensory illusions, where the co-occurrence of different sensory modalities lead to a percept not present in unisensory streams (e.g., stream-bound illusion or sound-induced flash illusion; Sekuler et al., 1997, 1999; Shams et al., 2000) and thus arguably are clear examples of integration or fusion (i.e., A+V ≠ AV). The McGurk effect (McGurk & MacDonald, 1976), for instance, is an audio-visual illusion where the presentation of a visual /ga/ and an auditory /ba/ leads to the percept of an audio-visual /da/. As predicted by the principles of multisensory integration, when auditory and visual signals are relatively displaced in time (Munhall et al., 1996) or space (Radeau & Colin, 1999), the McGurk illusion dissipates.

From a Principled to a Computational View

In addition to the spatio-temporal characteristics of stimuli, higher-order features such as semantic congruency can profoundly impact multisensory integration (see Doehrmann & Naumer, 2008 for a review) and thus the principles stated above do not fully account for multisensory integration. Further, multisensory integration has been observed in cortical areas (e.g., Avillac et al., 2007), yet neurons in these areas (e.g., Sugihara et al., 2006; Bizley et al., 2007; Meijer et al., 2017) as well as human behavior less rigorously follow the principles outlined above (Stanford & Stein, 2007; Spence, 2013). Lastly, in development and throughout the lifespan the brain is not sequentially exposed to single multisensory pairings allowing it to determine appropriate spatio-temporal filters for sensory signals that belong to the same or different objects and events. Instead, routinely a number of objects are present at once and events occur dynamically. In turn, the sensory signals emanating from a naturalistic environment ought to be causally segregated and integrated in a fashion permitting the appropriate development of multisensory systems. That is, to successfully combine signals from different sensory modalities, the brain needs to determine the causal structure of the sources (e.g., objects) emitting sensory signals; a process less explicitly addressed within the scope of the “principles of multisensory integration”.

Ernst and Banks (2002) suggested that when multiple and independent sources of sensory information are available, the optimal behavior – inasmuch as to increase accuracy and precision – is to add sensory evidence linearly and weighted by the inverse of their variance (i.e., their reliability). This maximum-likelihood estimation (MLE) model has been demonstrated to apply across the audio-visual (Alais & Burr, 2004), visuo-tactile (Ernst & Banks, 2002), visuo-proprioceptive (van Beers et al., 1998, 1999), and visuo-vestibular (Morgan et al., 2008) pairings. More importantly, over the last decade, the neural instantiation of this computational framework is being established (see Fetsch et al., 2013 for a review). Indeed, although it may appear particularly problematic to implement statistical inference in the noisy biological devices that are neurons, in a hallmark study Ma and colleagues (2006) suggested that it is precisely because of the inherent variance in neural firing that MLE may be performed within the brain. This so-called Probabilistic Population Coding (PPC) framework formalizes that while the MLE mathematically requires multiplication (i.e., estimate from one signal multiplied by its weight given its reliability added to the weighted estimate from the other modality), this operation may be accomplished via linear summation of noisy neural codes. Thus, the PPC shifts the burden of multisensory integration from single neurons to populations of neurons.

Given this theoretical framework, a number of researchers have sought to determine whether as predicted by the PPC, a linear sum of activity derived from unisensory conditions could account for spiking activity engendered during multisensory presentations (Morgan et al., 2008; Fetsch et al., 2013). Findings from these recordings revealed that a linear summation of unisensory responses could account for multisensory responses (Morgan et al., 2008; Fetsch et al., 2013), nonetheless, this summation required weights that were not always equal to ‘1’. Furthermore, these weights were altered by the reliability (i.e., signal-to-noise ratio) of stimuli (Morgan et al., 2008). Thus, while the PPC predicted that simple linear summation would account for statistical inference due to the stochastic firing of neurons, neural recordings demonstrated neurons performed a weighted operation that was somehow impacted by signal reliability. In turn, an explanation for shifting neural weights was required. Ohshiro and colleagues (2011) proposed that divisive normalization, a prevalent neural operation normalizing the contribution of each individual neuron to a downstream target by the summed activity of a population of neurons (see Heeger, 1992; Carandini & Fester, 2000; Busse et al., 2009; Louie et al., 2011), could account for the fluctuations in neural weights as a consequence of cue reliability. Elegantly, this theoretical postulation can equally account for the classical observations in subcortical multisensory physiology, such as the spatial or inverse effectiveness principles of multisensory integration (Ohshiro et al., 2011). In fact, as unisensory stimuli evoke stronger and stronger responses, the overall activity of the divisive pool also increases, and hence multisensory gain decreases - as described by the principle of inverse effectiveness.

While the MLE framework is able to account for a host of psychophysical findings and its neural implementation is every day further understood, it is far from a complete model. Most notably, the MLE is a “forced-fusion” model in that it does not solve the correspondence problem (i.e., determining the causal structure of sensory signals), and does not explain why some signals are bound and others are not. In a subsequent iteration of the MLE, researchers have added a “probability of common cause” variable in causal inference models (Kording et al., 2007) or priors in more general Bayesian models (e.g., Battaglia et al., 2003; see Ursino et al., 2017 for a biological-inspired neural network performing Bayesian computations) in order to allow models to predict optimal integration under certain circumstances and segregation of signals under others, effectively solving the correspondence problem (see Rohe & Noppeney, 2015, 2016 for more detail and recent empirical demonstration of Bayesian computations in the human brain). More recently, Parise and colleagues (2012, 2016) have suggested that correlation detection may serve as a general mechanism to determine which signals must be bound and which must be segregated. By using an architecture similar to that of the Hassenstein-Reichardt detector (Hassenstein, 1956) this model uses a series of low-pass filters and simple mathematical operations (summation, multiplication, and convolution) to resolve the correspondence problem, and then pools across spatially aligned multisensory correlation detectors in order to perform MLE (where appropriate). Interestingly, this last step in the model involves divisive normalization, reminiscent of physiological work postulating this same mechanism as culprit in neural re-weighting as a function of stimuli reliability (Parise et al., 2016).

In sum, over the last decade or two the study of multisensory integration has transformed a set of principles first observed in subcortical structures into a powerful computational framework applicable throughout the neocortical mantle. In doing so, researchers have developed a set of concrete definitions of integration at single unit, neural ensemble, and behavioral levels; i.e., the presence of supra- or sub-additive responses in single unit firing rates, population activity that performs a reliability-based weighted summation of incoming sensory signals, behavioral speeded responses that beat the race-model, and/or the report of perceptual experiences that may not be derived from unisensory signals as in the McGurk illusion.

Multisensory Perceptual Awareness

The strongest prediction regarding multisensory integration and perceptual awareness is from Bernard Baars' (2002) GWT which claims that "unconscious input processing is limited to sensory regions […] consciousness is needed to integrate multiple sensory inputs'' Therefore, it is no surprise that the vast majority of studies examining multisensory perceptual awareness have queried whether unconscious multisensory integration is possible.

Cross-modal interactions have been demonstrated between a subliminal visual stimulus – most commonly presented under binocular rivalry (Alais & Blake, 2005) or suppressed via Continuous Flash Suppression (CFS; Tsuchiya & Koch, 2005) – and consciously perceived auditory (Conrad et al. 2010; Guzman-Martinez et al. 2012; Alsius and Munhall 2013; Lupyan & Ward, 2013; Lunghi et al. 2014; Aller et al. 2015), tactile (Lunghi et al. 2010; Lunghi and Morrone 2013; Lunghi and Alais 2013, 2015; Salomon et al. 2015), olfactory (Zhou et al. 2010), vestibular (Salomon et al. 2015), and proprioceptive (Salomon et al. 2013) signals. More recently, it has equally been shown that neural events locked to heartbeats correlate with the detection of a faint visual grating, revealing the impact of unattended cardiac cues on visual consciousness (Park et al., 2014, see also Park et al., 2016, for a demonstration of the impact of visuo-cardiac correlation on bodily self-consciousness). In summary, these studies have shown that the presence of a congruent (but not incongruent) cross-modal signal facilitates access into consciousness of a suppressed visual stimulus, suggesting the possibility for unconscious multisensory integration. Further, these studies have specified that in order for the cross-modal interaction to occur, the different signals must be matched not solely for coarse congruency (e.g., visuo-proprioceptive; orientation of a suppressed hand and one’s real hand, Salomon et al., 2015, or visuo-vestibular; direction of unseen visual motion and self-rotation, Salomon et al., 2013) but also for more fine-grain features such as spatio-temporal frequencies (Lunghi et al., 2010). Thus, seemingly, the cross-modal enhancement of visual consciousness occurs when the different sensory signals can be interpreted as originating from the same object (e.g., same location and fine-grain characteristics), and may originate at early neural processing stages. In turn, as alluded to above, being able to ascribe sensory signals to a common object or cause is a major determinant of multisensory integration (e.g., Kording et al., 2007), and thus it is believed that cross-modal enhanced visual access is due to multisensory integration (although see below).

A second line of research has examined interactions between different sensory modalities in states of diminished consciousness. One of the earliest studies in this domain focused on the potential for multisensory associations during pharmacologically induced sleep (Beh & Barratt 1965). Specifically, these researchers showed that repeated presentations of a tone with an electrical pulse during sleep would result in a crossmodal association being formed and subsequently physiologically expressed during wakefulness. Ikeda & Morotomi (1996) replicated the above-mentioned finding while specifying that the association between the tone and electrical pulse occurred only during slow wave sleep. To disentangle the influence of different sleep stages on multisensory interactions, a more recent study investigated auditory–olfactory trace conditioning during non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Arzi et al. 2012). Sleeping humans were able to associate a specific tone with a specific odor during both NREM and REM sleep. Intriguingly, although associative learning was evident in both sleep stages, retention of the formed association during wakefulness was observed only when stimuli were presented during NREM sleep. This may suggest that although new associations between sensory modalities can be created in natural NREM and REM sleep, access to this new information in a different state of consciousness is limited and sleep stage dependent. Finally, regarding multisensory interactions under diminished levels of consciousness, Ishizawa and colleagues (2016) recently recorded from non-human primates primary somatosensory cortex (S1) and ventral pre-motor (vPM) while the animals were anesthetized via propofol administration and presented with auditory, tactile, and audio-tactile stimuli. The administration of propofol altered oscillatory features of local field potentials (LFP) both in S1 and vPM with idiosyncratic time-courses and distinctly indexing different stages of the loss of consciousness. More importantly for the current purpose, the authors also reported that propofol-induced loss of consciousness rendered bimodal neurons (i.e., neurons that responded both to auditory and tactile stimulation) responsive to a single sensory modality, most commonly; touch (see Chapter V of the current dissertation for a re-analysis of this dataset).

These lines of research, probing visual access during cross-modal stimulation and measuring cross-modal or amodal associations during altered states of consciousness are interesting in their own right, but come with a number of limitations. First, while they measure cross-modal associations it is unclear whether multisensory *integration* is truly being indexed (see Papai & Soto-Faraco, 2017). As argued in the previous section, behaviorally this occurrence is most clearly put forward when participants either beat the race-model, are subject to a perception not conveyed by unisensory stimuli (e.g., McGurk effect), or demonstrate cue combination in line with maximum likelihood or causal inference predictions. To the best of my knowledge none of these effects have been reported. In fact, Palmer & Ramsey (2012) report that congruent auditory speech presentation to an unseen visual face mouthing facilitates visual access. However, when the very same stimuli are shown incongruently (A consciously and V unconsciously) and under conditions typically leading to the McGurk illusion (McGurk & MacDonald, 1976), participants do not integrate auditory and visual streams into a novel perceptual experience. Thus, while cross-modal congruency effects are possible, seemingly this is far from indicating unconscious multisensory integration. In a similar vein, a recent study by Barutchu and colleagues (2018) examined multisensory reaction times in a patient with posterior cortical atrophy who was unable to consciously perceive visual stimuli. This patient, when responding to perceived auditory stimuli and unseen visual stimuli demonstrated multisensory enhancement (i.e., multisensory reaction time being faster than the fastest unisensory response) but did not beat multisensory statistical facilitation. Hence, unconscious multisensory *integration* (as opposed to facilitation or association) has not been convincingly demonstrated.

Second, even if the definition of multisensory integration was relaxed and some of the above-mentioned findings were taken to demonstrate integration, results indicating enhanced visual access during cross-modal presentations can easily be accommodated under the GWT (Baars, 2002). Namely, according to this theory, information from consciously perceived stimuli are widely broadcasted throughout the brain, inclusively to early visual nodes. Therefore, when a sensory signal from a non-visual modality is presented consciously (as in all of the above-mentioned studies), this signal can be integrated with the unseen visual stimuli (which is nevertheless still processed in early visual areas). Only experiments where both cues to be integrated are presented unconsciously can effectively probe unconscious multisensory integration in light of the GWT. Following this rationale, Faivre and colleagues (2014) had participants perform a congruency-priming task wherein both cues and targets were presented in auditory and visual modalities. Participants were asked to determine whether the auditory target and visual target represented the same object (e.g., a heard 'two' and a seen '2') or not. The cues could also be the same (e.g., a heard 'm' and seen 'm) or not, and importantly, were presented subliminally. Results indicated that when the relationship between the subliminal cues (e.g., 'same') was congruent with the relationship between the targets (e.g., 'same', as opposed to 'different'), participants were quicker in performing this latter categorization. For this effect to occur, the authors argue that a comparison between unperceived visual and auditory cues must have occurred, and thus concluded that multisensory integration in complete unawareness is possible (Faivre et al., 2014). Nonetheless, one must note that the effect only occurred if participants were trained on the task consciously. Further, it may be argued that this task could be accomplished via semantic comparison as opposed to multisensory integration (see Chapter II; Noel et al., 2015).

Taken together, it remains an open question and a matter of debate whether multisensory integration can occur outside of awareness. In the dissertation I pose this question at the behavioral (Chapter IV), neural ensemble (Chapter III), and single-unit levels (chapter V). Results suggest that multisensory integration can occur outside of awareness at the single-unit level. Contrarily, EEG global field power differed between audiovisual “paired” and “summed” (i.e., A+V) conditions when stimuli were perceived, but not when stimuli were not reported. Similarly, while behavioral performance on a multisensory cue congruency paradigm was graded with level of awareness (i.e., no awareness, partial awareness, full awareness), this performance did not appear to follow the “principles of multisensory integration”. Thus, there was no unequivocal evidence for unconscious multisensory integration at the behavioral and neural ensemble levels. More importantly, beyond questioning whether multisensory integration can occur unconsciously, I believe greater clarity regarding consciousness can be gained by interrogating whether neural and behavioral insights from visual awareness may be borrowed in the study of multisensory awareness. In other words, is Crick and Koch’s (1990) assumption that all forms of sensory awareness employ similar mechanisms correct? In Chapter III we match stimulus features across unisensory and multisensory conditions while indexing the neural correlates of detection/report. Results suggest that reproducibility and complexity measures associated with consciousness do not generalize from the unisensory to the multisensory context, and thus insights derived from the visual neurosciences regarding perceptual awareness may not be readily translated to the multisensory domain. Given these results, in Chapters IV and V I question whether the process of multisensory integration could be utilized to inform existing theories of consciousness (see below for more detail). Subsequently, in the second part of the dissertation I will test multisensory predictions pertaining to the minimal phenomenal selfhood approach to consciousness. In addition to testing these predictions, the second part of the dissertation probes an “inside-out” theory of consciousness. By illustrating how the process of multisensory integration can inform the various ends of the “outside-in” / “inside-out” spectrum I hope to convince the reader that a science of multisensory perceptual awareness is not only more in line with our phenomenological experience, but also may afford significant conceptual and empirical leverage in the study of consciousness.

Roadmap of Dissertation and Relation Between Chapters

This dissertation is divided into two parts. The first part ("consciousness from the outside-in") plays a dual role. It both questions whether unconscious multisensory integration is possible (role 1), and most importantly, it asks whether insights from visual awareness can be transferred to the study of perceptual awareness (role 2). More specifically, after highlighting that the unconscious integration of multisensory stimuli has not been convincingly demonstrated (Chapter I & II), in chapter III we demonstrate that the transition from non-perceived to perceived (or from unreported to reported) is indexed by different neural markers in unisensory and multisensory contexts. In fact, while the metrics used (i.e., sustained activity, inter-trial reproducibility, and neural complexity; McIntosh et al., 2008; Dehaene & Changeux, 2011; Schurger et al., 2010, 2015; Casali et al., 2013) did transfer from visual to auditory modalities, the majority of these did not transfer to the audiovisual domain. Hence, Chapter III suggests that insights and theories derived from the visual neurosciences may not be straightforwardly applied to the study of multisensory perceptual awareness. Given this observation, seemingly a "science of multisensory perceptual awareness" must be developed at least partially in parallel to the study of visual awareness. At minimum studying consciousness from a multisensory perspective will allow probing the generalizability of findings. Further, it is possible that researchers are obviating important aspects of the study of consciousness by focusing almost exclusively in the visual modality.

Conceptually, in Chapters IV and V, we asked the reciprocal question to that asked in Chapter III; insights from the study of visual awareness to do entirely apply to the multisensory case, but can multisensory paradigms be utilized to further probe theories of consciousness that were derived from visual neuroscience? In more detail, in Chapter IV I leveraged the fact that multisensory presentations can result in partially aware trials (i.e., AV stimuli perceived as A or V) to question whether consciousness is "all-or-none" or graded; an issue that two of the major contemporary theories of consciousness – GNW and IIT – differ on (GNW claims that consciousness is "all-or-none" while IIT ascertains it is graded). We built neural networks that are *in principle* capable of supporting audio-visual, audio, visual, or no consciousness *according to the GNW*. That is, these network possess feedback projections from multisensory areas to a unique (A or V), both (A and V), or no unisensory area, and each sensory node is governed by a sigmoidal input-output function, thus resulting in "neural ignition". Interestingly, although the networks were built to support "all-or-none" consciousness from a neural standpoint, decoding of reaction times from these networks suggested a graded relationship between the speed of response and perceptual awareness (from full to partial to no awareness). Behavioral results in a multisensory cue congruency paradigm similarly showed a graded relationship between multisensory performance and perceptual awareness. Taken together, therefore, the findings suggest that an "all-or-none" neural architecture may nevertheless result in graded performance, and hence suppose a reconciliation between GNW and IIT. Most importantly for the current purposes, this chapter illustrates how multisensory processes and stimuli can be used to inform existing theories of consciousness, in this case by allowing for partially aware trials that can then be employed to probe the relation between perceptual awareness and behavioral performance.

In a similar line, in Chapter V we aimed at arbitrating between GNW and IIT, but this time from a single cell perspective. We use an agreed upon definition of integration at the single unit level to label neurons either as "convergent" (i.e., neurons that respond to stimulation from two different sensory modalities but does not show a multisensory non-linearity; i.e., AT = A + T) or "integrative" (i.e., cells most readily driven by multisensory than unisensory stimulation; AT ≠ A + T) and advance detailed neurophysiological predictions regarding the behavior of these neurons in light of the GNW (Dehaene & Changeux, 2011) and IIT (Tononi et al., 2016). Findings overall support the GNW theory, suggesting that by studying multisensory integration we may arbitrate between prominent theories of consciousness at the single unit level. Taken together, this first part of the dissertation suggests that an understanding of multisensory awareness (and its neural markers) may not directly follow from the study of unisensory consciousness. More importantly, it also illustrates that by leveraging partially aware conditions afforded by multisensory presentations and examining neural dynamics associated with multisensory processing, one may arbitrate between different "outside-in" theories of consciousness.

The second part of the dissertation ("consciousness from the inside-out") aims at testing predictions from the minimal phenomenal selfhood approach to consciousness (Blanke & Metzinger, 2009; Blanke, 2012; Blanke et al., 2015). This approach to consciousness lies on the opposite end of the "outside-in"/"inside-out" continuum as compared to the GNW (Dehaene & Changeux, 2011) or the IIT (Tononi et al., 2016). Thus, by empirically testing (and ratifying) multisensory predictions regarding bodily self-consciousness, we not only emphasize that the synthesis across the senses is central in some theories of consciousness, but also illustrate how the study of multisensory integration can inform theories across the entire "outside-in" / "inside-out" spectrum. More specifically, while the RHI (Botvinick & Cohen, 1998) appears to be spatially restricted to the PPS of the real hand (Lloyd, 2007), and neurophysiological recordings have demonstrated PPS neurons' receptive fields to remap as to include the fake hand during the illusion (Graziano et al., 2000), the role of PPS in bodily self-consciousness (i.e., whole body and not limb-specific) has not been demonstrated. More vexingly, whether PPS neurons demonstrate multisensory *integration* (vs. interaction or convergence) has also not been established. Thus, using ECOG recordings, in Chapter VI we first suggest that the majority of sensors demonstrating a PPS effect (i.e., multisensory responses that are modulated by observer-stimuli distance) also integrate sensory information (i.e., A+T ≠ AT). Given that multisensory integration is indeed central in PPS encoding (Chapter VI), next in Chapter VII we test and confirm Blanke's (2012) prediction that multisensory PPS shifts during the FBI (Lenggenhager et al., 2007) as to encode for the self-space and not the physical location of the body. In Chapter VIII we replicate the findings from Chapter VII while using CFS (Tsuchiya & Koch, 2005) to render subliminal either the stimuli utilized to measure PPS or that utilized to induce the FBI. This contribution is of theoretical significance as the minimal selfhood approach to consciousness is rooted in the notion that there ought to be a proto-self to experience the external environment. This minimal self is pre-reflective (Legrand, 2006) and scaffolded on the process of multisensory integration (Blanke, 2012; Blanke et al., 2015). However, the fact that unconscious multisensory interactions can shape overt bodily self-consciousness had never been demonstrated. In the closing experimental chapter (Chapter IX) we use the electrophysiological measure of PPS established in Chapter VI, the fact that PPS encoding seemingly scaffolds self-awareness (Chapters VII and VIII), and the fact that PPS is at the intersection of perceptual and motor systems (Serino et al., 2015) to probe whether an electrophysiological index of PPS may aid in diagnosing patients with disorders of consciousness (DOC; Bernat, 2006). These patients are routinely misdiagnosed (van

Erp et al., 2015) seemingly in large part due to cognitive-motor dissociations (Schiff, 2015); they can understand commands, but not overtly respond to them. By indexing PPS in DOC patients we can potentially probe a neural system that feeds into the motor system and that has been shown to remap due to the intent to move (Brozzoli et al., 2009; 2010). In turn, PPS indexing may in the future signal intentionality and a primitive level of self-awareness, two crucial components of consciousness. In Chapter X I summarize key results from the experimental chapters, interpret these findings in light of the relevant literature, and discuss potential future directions as well as limitations of the current work.

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PART I: CONSCIOUSNESS FROM THE OUTSIDE-IN

CHAPTER II

COGNITIVE NEUROSCIENCE: INTEGRATION OF SIGHT AND SOUND OUTSIDE OF AWARENESS?

The contents of this chapter are adapted from

Noel, J.P., Wallace, M., Blake, R. (2015). Cognitive Neuroscience: Integration of Sight and Sound Outside of Awareness? Current Biology, 25 (4), R-157-159;

doi:10.1016/j.cub.2015.01.007

Main Text

A recent study found that auditory and visual information can be integrated even when you are completely unaware of hearing or seeing the paired stimuli — but only if you have received prior, conscious exposure to the paired stimuli.

Many of the objects and events we encounter during our everyday lives are made up of distinct blends of auditory and visual information: dogs barking, motors whining, people talking. Even though the physical signals conveying those qualities are fundamentally different — for example, photic energy versus acoustic energy — our brain seamlessly integrates, or ‘binds’, this information into a coherent perceptual Gestalt. The unitary nature of these multisensory perceptual experiences raises an important question in the context of prevailing theories of consciousness (Revonsuo and Newman, 1999): specifically, can such binding take place prior to the emergence of consciousness, or is it an emergent property of consciousness? Earlier work has indicated that audible sounds can impact invisible pictures suppressed from awareness during binocular rivalry (Chen et al., 2011), but can auditory and visual signals interact when both are presented outside of awareness? A recent study by Faivre *et al.*, 2014, provides an answer to this question by unequivocally demonstrating the interaction of subthreshold auditory and visual cues. Left unanswered, however, is whether this interaction represents genuine multisensory integration or, instead, arises from interactions at amodal, semantic levels of analysis (Figure 1).

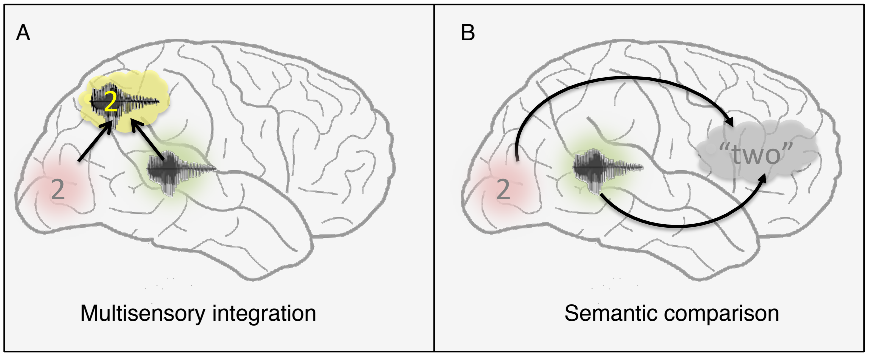

Figure 2.1. Multisensory Integration vs. Semantic Comparison. Schematic representations of alternative ways in which auditory and visual information may interact in the priming design of Faivre *et al.*, 2014. (A) Multisensory integration involves combination of sensory signals from visual cortex (denoted by red) and auditory cortex (denoted by green), resulting in an integrated representation in regions of multisensory cortex (for example, superior temporal and/or parietal regions, denoted by yellow). (B) With semantic comparison, two independent sensory representations, one auditory (green) and the other visual (red), signify the same object and, thus, activate a common semantic concept (the abstract concept of the number, represented by 'two', in this case) within higher level, cognitive areas.

In the new study (Faivre et al., 2014), participants were briefly presented a priming stimulus made up of a pair of digits — one presented as a visual stimulus and the other as an auditory stimulus — that were sometimes identical (for example, a spoken ‘2’ and a printed ‘2’) and other times were not (for example, a spoken ‘8’ and a printed ‘2’). This prime was then followed by an audio-visual pair of target letters that were either identical or not. Participants had to judge whether this second pair was the same (for example, a spoken and printed ‘*b*’) or different (for example, a spoken ‘*m*’ and a printed ‘*b*’). Crucially, the first audio-visual digit pair — the priming pair — was presented at subthreshold intensities and durations. This clever design meant that the pair of primes and the pair of targets could either be congruent (both pairs the ‘same’ or both pairs ‘different’) or incongruent (one pair the ‘same’ and the other pair ‘different’). With this design, by contrasting reaction times to target-relationship identification as a function of whether or not that pair was congruent with the prime-relationship, the authors were able to determine whether the subthreshold primes were integrated (as evidenced by reduced reaction times). Indeed, a congruency effect would be dependent on the successful determination of the semantic relationship between the subliminal auditory and visual digits. The authors also assessed priming under conditions where the auditory and visual digits were suprathreshold.

Remarkably, following repeated exposures to primes presented at suprathreshold levels, subliminal pairs were able to impact reaction times for judging the auditory-visual target relationship, an outcome implying that these subliminal auditory and visual signals were integrated outside of awareness. But what is being integrated in such a situation? Is it the low-level visual and acoustic features of the priming stimuli (thus arguing for true multisensory integration)? Or is it the higher-order semantic features of the stimuli, thus arguing for a process based on comparison of congruence of semantic information arising from two sources, rather than on genuine integration?

The results from the Faivre *et al.*, 2014, study do not allow us unequivocally to answer this question. They do, however, provide important clues suggesting that the process may be taking place at the semantic level. These clues are founded in one of the hallmark features of multisensory integration — the concept of inverse effectiveness — whereby the multisensory gain is most pronounced when the paired unisensory signals are weak (Stein and Stanford, 2008; Murray and Wallace, 2012). If the priming signals were being integrated in a multisensory manner, one would expect that the weaker the primes, the greater the gain when they were integrated, and thus, the larger the effects sizes. Conversely, if the results were entirely driven by sensory-independent semantic congruency priming, we would expect that the stronger the priming signal, the bigger the effect size.

Although inverse effectiveness was not directly tested, there are several informative aspects of the experimental results that bear on the interpretation. The first emerges from a comparison of the results of experiments 1 and 2 with those of experiment 3. In the first two experiments the auditory (experiment 1) and visual (experiment 2) primes were presented at levels sufficiently strong to render them unequivocally suprathreshold, while in experiment 3 they were both presented subliminally. Despite these differences in stimulus effectiveness, the priming effects were comparable in magnitude for each of these three experiments. The second clue emerges from the comparison of results from the first three experiments, where participants were exposed to suprathreshold primes before subliminal testing, to the results from experiment 4, where subliminal testing was *not* preceded by exposure to suprathreshold prime pairs. Subliminal priming worked in experiments 1–3 but did not work in experiment 4. Framed in the context of inverse effectiveness, it is not at all obvious why prior exposure would be necessary before weak stimuli could be integrated in order to facilitate performance. Thus, this pattern of results also seems incompatible with the concept of inverse effectiveness, but compatible with semantic priming.

We believe that, in addition to effectiveness manipulations, another key set of principles governing multisensory integration may be used in future work to further differentiate between unconscious multisensory integration and unconscious semantic comparison. It is well established that the spatial and temporal structure of paired sensory cues — here, the spoken and written digits — are a major determinant of the probability that these cues will be integrated. Stimuli in close spatial and temporal correspondence have a high likelihood of being integrated (Wallace and Stevenson, 2014). In contrast, semantic priming should be independent of the spatial location at which stimuli are delivered, as well as more dependent upon the relative timing between primes and targets (rather than on the timing between the primes themselves; Vorberg et al., 2003).

In our opinion, the jury is still out on the question of the nature of the information being combined when a subliminal auditory digit is presented together with a subliminal visual digit within a priming paradigm. We believe that this question can be resolved by exploiting several of the classic features of multisensory integration. Regardless of the resolution of that question, however, the study by Faivre *et al*., 2014, stands as a provocative contribution to the question of binding and consciousness by definitively showing that the property of congruence between auditory and visual information can be established outside of awareness.

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CHAPTER III

PROBING ELECTROPHYSIOLOGICAL INDICES OF PERCEPTUAL AWARENESS ACROSS UNISENSORY AND MULTISENSORY MODALITIES

The contents of this chapter are adapted from

Noel, J.P., Simon, D., Thelen, A., Maier, A., Blake, R., Wallace, M. (2018). Probing Electrophysiological Indices of Perceptual Awareness Across Unisensory and Multisensory Modalities. Journal of Cognitive Neuroscience, 30, 4, doi: 10.1162/jocn_a_01247

Abstract

The neural underpinnings of perceptual awareness have been extensively studied using unisensory (e.g., visual alone) stimuli. However, perception is generally multisensory, and it is unclear whether the neural architecture uncovered in these studies directly translates to the multisensory domain. Here we use electroencephalography (EEG) to examine brain responses associated with the processing of visual, auditory, and audiovisual stimuli presented near threshold levels of detectability, with the aim of deciphering similarities and differences in the neural signals indexing the transition into perceptual awareness across vision, audition and combined visual-auditory (multisensory) processing. More specifically, we examine: 1) the presence of late evoked potentials (~ > 300 ms), 2) the across trial reproducibility, and 3) the evoked complexity associated with perceived vs. non-perceived stimuli. Results reveal that while perceived stimuli are associated with the presence of late evoked potentials across each of the examined sensory modalities, between trial variability and EEG complexity differed for unisensory versus multisensory conditions. Whereas across trial variability and complexity differed for perceived versus non-perceived stimuli in the visual and auditory conditions, this was not the case for the multisensory condition. Taken together, these results suggest that there are fundamental differences in the neural correlates of perceptual awareness for unisensory versus multisensory stimuli. Specifically, the work argues that the presence of late evoked potentials, as opposed to neural reproducibility or complexity, most closely tracks perceptual awareness regardless of the nature of the sensory stimulus. In addition, the current findings suggest a greater similarity between the neural correlates of perceptual awareness of unisensory (visual and auditory) stimuli when compared with multisensory stimuli.

Introduction

During waking hours, signals are continually impinging upon our different sensory organs (e.g., eyes, ears, skin), conveying information about the objects present and the events occurring within our environment. This flood of information challenges the limited processing capabilities of our central nervous system (James, 1890). As a consequence, much work within cognitive psychology and neuroscience has sought to understand how the human brain tackles this challenge by effectively filtering, segregating, and integrating the various pieces of sensory information to generate a coherent perceptual Gestalt (Broadbent, 1958; Treisman & Gelade, 1980; Murray & Wallace, 2012).

The bulk of the evidence to date with regard to the intersection between the bottleneck of information processing and perceptual awareness has been derived from studies focused on the visual system (Zeki et al., 2003; Koch, 2004; Dehaene et al., 2017). In fact, all major neurobiological theories regarding perceptual awareness, all emphasizing the importance of engaging widely distributed brain networks (Naghavi & Nyberg, 2005; Tallon-Baudry, 2012; van Gaal & Lamme, 2012), have been derived from observations within the visual neurosciences (Sanchez et al., 2017; Faivre et al., 2017). In parallel, the neural markers associated with perceptual awareness have been derived from observations probing the visual system. Early functional Magnetic Resonance Imaging (fMRI; Dehaene et al., 2001), electroencephalographical (EEG; Sergent et al., 2005; Del Cul et al., 2007) and electrocorticographical (ECoG; Gaillard et al., 2009) studies suggested that perceptual awareness was associated with the broadcasting of neural signals beyond primary (visual) cortex (Lamme, 2006), and more specifically engaging fronto-parietal regions (Dehaene et al., 2006). Arguably the most consistent signature associated with this generalized neural recruitment is the P3b event-related potential. Namely, while early EEG components are similar regardless of whether or not stimuli enter perceptual awareness, stimuli that are perceived (vs. non-perceived) additionally yield components at later latencies. Subsequent studies converged on the observation that perceived stimuli broadcasted or triggered activity beyond that disseminated by non-perceived stimuli, but emphasized that, the neural ignition associated with awareness resulted in neural patterns that were both more reproducible (Schurger et al., 2010) and stable (Schurger et al., 2015) than patterns seen for non-perceived stimuli. In the latest itineration of the argument emphasizing the recruitment of global neural networks, researchers have highlighted the pivotal role of neural networks that are both integrated and differentiated (Tononi et al., 2016; Koch et al., 2016; Cavanna et al., 2017). Within this latter framework, the complexity of both resting state and evoked neural responses has emerged as a marker for perceptual awareness (Casali et al., 2013; Sarasso et al., 2015; Andrillon et al., 2016; Schartner et al., 2015, 2017).

It has been assumed that these theories of and neural markers for perceptual awareness gleaned from the visual system apply across sensory domains, an assumption that indeed comes with some supporting evidence. For example, there is late sustained neural activity in perceived as opposed to non-perceived auditory stimulation conditions (Sadaghiani et al., 2009). However, there are also important differences across sensory modalities, such as the association of auditory awareness with neural activity in fronto-temporal, as opposed to fronto-parietal, networks (Joos et al., 2014). In an important recent contribution, Sanchez and colleagues (2017) demonstrated that by applying machine learning techniques it is possible to decode perceptual states (i.e., perceived vs. non-perceived) across the different sensory modalities (i.e., vision, audition, somatosensory). While it is interesting that decoding of perceptual states across modalities is feasible, this observation does not tell us whether (and how) the brain performs this task. Lastly, Sanchez and colleagues (2017) have probed perceptual states across unisensory modalities, but to the best of our knowledge no study has characterized differences between perceived and non-perceived stimuli across both unisensory and multisensory modalities. This knowledge gap is important, as in recent years, keen interest has emerged concerning the role played by multisensory integration in the construction of perceptual awareness (Deroy et al., 2014; Spence & Deroy, 2013 Faivre et al., 2017; O'Callaghan, 2017). Indeed, as discussed above, theoretical models posit an inherent relationship between the integration of sensory information and perceptual awareness. For example, mathematical and neurocognitive formulations, such as integrated information theory (IIT; Tononi, 2012), global neuronal workspace theory (Dehaene & Changeaux, 2011), and recurrent/reentrant networks (Lamme, 2006), postulate – explicitly or implicitly – that the integration of sensory information is a prerequisite for perceptual awareness. For example, IIT posits that a particular spatio-temporal configuration of neural activity culminates in subjective experience when the amount of integrated information is high. In many of these views, subjective experience (i.e., perceptual awareness) relates to the degree to which information generated by a system as a whole exceeds that independently generated by its parts.

Motivated by this theoretical perspective emphasizing information integration in perceptual awareness, and noting that our perceptual Gestalt is built upon a multisensory foundation, we argue that multisensory neuroscience is uniquely positioned to inform our understanding of perceptual awareness (Faivre et al., 2014; Mudrik et al., 2014; Blanke et al., 2015; Noel et al., 2015; Salomon et al., 2017; in addition, see Deroy et al., 2014, for a provocative argument implying that unisensory-derived theories of perceptual awareness cannot be applied to multisensory experiences). Consequently, in the current work we aim to characterize electrophysiological indices of perceptual awareness across both unisensory (visual alone, auditory alone) and multisensory (combined visual-auditory) modalities. More specifically, we aim to establish whether previously reported neural markers of visual awareness generalize across sensory modalities (from vision to audition) onto the promotion of multisensory experiences. In the current study we examine EEG responses to auditory, visual, and combined audiovisual stimuli presented close to the bounds of perceptual awareness. Analyses are centered around previously reported indices of visual awareness; the presence of late components in evoked potentials during perceived but not non-perceived trials (e.g., Dehaene & Changeaux, 2011; Dehaene et al., 2017), as well as changes in neural reproducibility (Schurger et al., 2010) and complexity (Tononi et al., 2016; Koch et al., 2016).

Methods

Participants

Twenty-one (mean age = 22.5 ± 1.9, median = 21.2, range: 19-25, 9 females) right-handed graduate and undergraduate students from Vanderbilt University took part in this experiment. All participants reported normal hearing and had normal or corrected-to-normal eyesight. All participants gave written informed consent to take part in this study, the protocols for which were approved by Vanderbilt University Medical Center's Institutional Review Board. EEG data from 2 participants were not analyzed as we were unsuccessful in driving their target detection performance within a pre-defined range (see below; See Figure 1. dotted lines), and thus data from 19 participants formed the actual analyses presented here.

Materials and Apparatus

Visual and auditory target stimuli were controlled via a micro-controller (SparkFun Electronics, Redboard, Boulder CO) under the control of purpose written MATLAB (MathWorks, Natick MA) and Arduino (Arduino^{TM}) scripts. The micro-controller drove the onset of a green LED (3 mm diameter, 596-572nm wavelength, 150 mcd) and a Piezo Buzzer (12 mm diameter, 9.7 mm tall, 60 dB(SPL), 4kHz, 3V rectangular wave). Target stimuli were 10 ms in duration (square-wave, onset and offset <1 ms, as measured via oscilloscope). The LED was mounted on the Piezo Buzzer thus forming a single audiovisual object that was placed at the center of a 24-inch computer monitor (Asus VG248QE, LED-backlit, 1920x1080 resolution, 60Hz refresh rate). In addition to the targets, to adjust participant's detection rates, we online adjusted the luminance and amplitude of background visual and auditory white noise with the psychophysics toolbox (Brainard, 1997; Pelli, 1997). The luminance (achromatic and uniform) of the screen upon which the audio and visual targets were mounted was adjusted between 0 and 350cd/m^2 in steps of 4 RGB units (RGB range = 0 to 255; initial = [140, 140, 140] RGB) while auditory noise comprised variable intensity white noise broadcast from two speakers placed symmetrically to the right and left side of the monitor (Atlas Sound EV8D 3.2 Stereo). The white noise track initialized at 49 dB and adjusted in 0.4 dB increments (44.1 kHz sampling rate). Visual and auditory noise were adjusted by a single increment every 7 to 13 trials (uniform distribution) to maintain unisensory detection performance between 30 and 45%. This low unisensory detection rate was chosen to assure satisfactory bifurcation between 'perceived' and 'non-perceived' trials in both unisensory and multisensory trials (Murray & Wallace, 2012).

Procedure and Experimental Design

Participants were fitted with a 128-electrode EGI Netstation EEG and seated 60 cm away from the stimulus and noise generators. Participants completed 12 to 14 blocks containing 200 repetitions of target detection, in which no-stimulus (catch trials), auditory-only, visual-only, and audiovisual trials were distributed equally and interleaved pseudo-randomly. We employed a subjective measure of awareness (similar to a yes/no detection judgment; Merkile et al., 2001; see Figure 1) in conjunction with an extensive set of EEG analyses (electrical neuroimaging framework; Brunet et al., 2011, see below). Thus, albeit perceptual awareness may arguably occur without the capacity for explicit report (see Eriksen, 1960) here we operationalize perceptual awareness as the detection and report of sensory stimuli (see below for signal detection analyses suggesting that criterion for detection was unchanged across experimental condition and hence detection reports likely reflected perceptual awareness). Participants were asked to respond, via manual response (button press), as quickly as possible when they detected a stimulus. Inter-stimulus interval comprised a fixed duration of 800 ms, plus a uniformly distributed random duration between 0 and 2000 ms. The total duration of the experiment was approximately 3h30 min, with rest periods in between blocks of approximately 5 minutes.

EEG Data Acquisition and Rationale

We contrasted participants EEG responses for perceived (i.e., detected) versus non-perceived (i.e., non-detected) unisensory (i.e. either visual or auditory) and multisensory (i.e., conjoint visual and auditory) stimuli to determine whether indices of visual awareness generalize across sensory domains. High density continuous EEG was recorded from 128 electrodes with a sampling rate of 1000Hz (Net Amps 200 amplifier, Hydrocel GSN 128 EEG cap, EGI systems, Inc.) and referenced to the vertex. Electrode impedances were maintained below 50kΩ throughout the recording procedure and were reassessed at the end of every other block. Data was acquired with Netstation 5.1.2 running on a Macintosh computer and online high-pass filtered at 0.1 Hz.

Analysis

Behavioral

Data were compiled for detection as a function of the sensory modality stimulated, where ‘detection’ refers to a manual response immediately following presentation of a stimulus or a pair of stimuli. Two participants generated false alarm rates (reports of stimulus detection on catch trials when no stimulus was presented) that exceeded 2.5 standard deviations of the population average (false alarm rates ~20% compared to 8.2%, See Figure 1), leading to exclusion of their data from further analysis. Data were analyzed for reaction times and in light of signal detection theory (SDT; Tanner & Swets, 1954; Macmillan & Creelman, 2005). To quantify sensitivity and response bias to the detection of near-threshold sensory stimuli across different sensory modalities reports of detection during the presence of an auditory, visual, or audiovisual stimuli were considered as hits. Analogously, reports of the presence of sensory stimulation during a catch trial were taken to index false alarms. Noise and signal distributions were assumed to have an equal variance, and sensitivity (i.e., d’) and response criteria (i.e., c) were calculated according to equations in Macmillan & Creelman, 2005. Note that the assumption of equal variance does not affect quantification of the response criteria, and simply scales sensitivity (Harvey, 2003). Regarding reaction times, data were trimmed for trials in which participants responded to stimuli within 100ms of stimulus (total 0.9 % data trimmed) and were then aggregated.

EEG Preprocessing

As illustrated in Figure 1A, after 200 trials of each sensory condition (4 blocks) relatively few adjustments of auditory and visual noise were needed to maintain participants within the pre-defined range of 30-45% unisensory detection performance (see also *Control Analyses* in *Supplementary Materials* online*)*. That is, 65.42% for all audio noise adjustments were undertaken during the first 200 trials (thus 34.58% were undertaken during the last 500 experimental trials) and 60.75% of visual noise adjustments happened during that same period (leaving 39.25% of visual noise changes occurring during the 500 trial experimental phase. Thus, EEG analysis (below) was restricted to the last 400-500 trials per sensory condition to reduce variability in the stimulus statistics. Data from these trials was exported to EEGLAB (Delorme & Makeig, 2004), and epochs were sorted according to sensory condition (i.e., A, V, AV, or none) and detection (perceived versus non-perceived). Epochs from -100 to 500 ms after target onset were high-pass (zero phase, 8th order Butterworth filter) at 0.1hz and low-pass at 40hz, notch filtered at 60hz, EEG epochs containing skeletomuscular movement, eye blinks, or other noise transients and artifacts were removed by visual inspection. After epoch rejection, every condition (4 [sensory modalities: none, audio, visual, and audiovisual] X 2 [perceptual report: perceived and non-perceived]) comprised an average of 179.16 ± 39 trials (average epoch rejection = 23.5%), with the exception of the catch-perceived condition, which had 23.2 ± 3.9 trials, and catch non-perceived condition, which had 307.45 ± 31.5 trials. Excluding catch trials, there was no effect of sensory modality, perceptual report, or interaction between these with regard total amount of trials, all $p > .19$). Channels with poor signal quality (e.g., broken or excessively noisy electrodes) were then removed (6.2 electrodes on average, 4.8%). Data were re-referenced to the average, and baseline corrected to the pre-stimulus period. Excluded channels were reconstructed using spherical spline interpolation (Perrin, Pernier, Bertrand, Giard, & Echallier, 1987). To account for the inherent multiple comparisons problem in EEG, we set alpha at < 0.01 for at least 10 consecutive time points (Guthrie & Buchwald, 1991), and hence most statistical reporting in the results states significant time-periods as ‘all $p < 0.01$’.

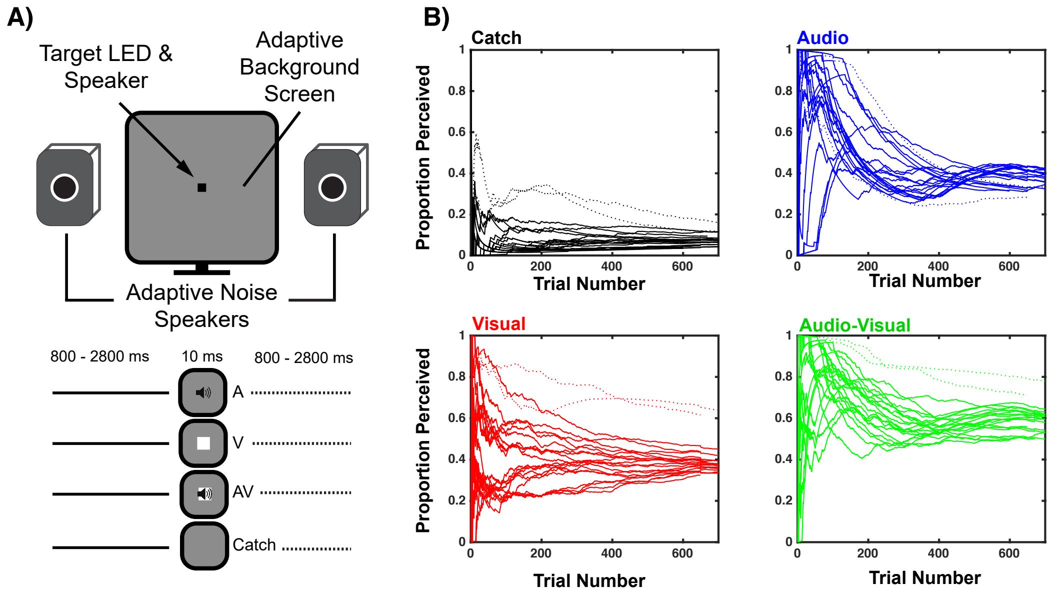

Figure 3.1. Experimental Design and Methods. A) Experimental Design. Participants fixated a small audiovisual device controlled via a micro-controller and reported via button press the detection of targets (audio, visual, or audiovisual). Targets were presented within visual and auditory noise whose levels were adaptively adjusted over trials. Catch trials (no targets) were also presented. B) Auditory and visual noise levels were adjusted online for each participant to generate auditory and visual detection rates between 30 and 45%. Each line represents a single participant and plots their detection rate as a function of trial number. Participants converged on stable performance after approximately 200 trials per stimulus condition. Thus, these first 200 trials were not analyzed. Two participants exhibited high false detection rates (catch trial; dotted lines) and thus their EEG data were not analyzed. These same participants are depicted with dotted lines for audio (blue), visual (red), and audiovisual (green) conditions. Note that

false alarms (catch trials) remain stable across the duration of the experiment, indicating that results are not likely to be affected by training or fatigue effects.

Global Field Power

The global electric field strength was quantified using global field power (GFP; Lehman & Skrandies, 1980). This measure is equivalent to the standard deviation of the trial-averaged voltage values across the entire electrode montage at a given time point, and represents a reference- and topographic-independent measure of evoked potential magnitude. This measure is used here to index the presence (or absence) of late evoked potentials during perceived vs. non-perceived visual, auditory and audiovisual trials. On a first pass, we calculated average GFPs for each subject, as well as for the sample as a whole (i.e., grand average) and for every condition. Then, the topographic consistency test (TCT; Koening & Melie-Garica, 2010) was applied across the entire epoch (-100 to 500 ms post-stimulus) for each condition in order to determine whether there was statistical evidence for a consistent evoked potential. Subsequently, the TCT was applied at each time-point for those conditions demonstrating a significant evoked potential in order to ascertain time-period during which evoked potentials were reliably evoked. For these analyses alpha was a priori set to 0.05 FDR corrected (Genovese et al., 2002); the default alpha assumed by the test (Koening & Melie-Garica, 2010). After demonstrating the presence of evoked potentials relative to baseline (see above), we conducted a 3 (sensory modality: audio, visual, audiovisual) X 2 (perceptual state: perceived versus non-perceived) repeated measures ANOVA at each time-point (-100 pre-stimuli onset to 500 ms post-stimuli onset). Separate t-tests across states of perception (perceived vs. non-perceived) for the different modalities (audio, visual, and audiovisual) were equally conducted. Lastly, to ascertain true multisensory interactions, we contrasted the GFP evoked by the audiovisual condition, to the sum of the unisensory responses (e.g., Cappe et al., 2012). As a control, we equally index the GFP evoked by detected (i.e., false alarms) and non-detected (i.e., correct rejections) catch trials to ascertain whether either the noise features utilized to mask targets or the simple fact of reporting detection were sufficient to engender a GFP differentiation between conditions. The GFP analysis was solely conducted on participants with at least 20 false alarm trials (13/20 participants). For this analysis, a random subset of correct rejection trials were pulled for each individual in order to match the number of false alarm and correct rejection trials at an individual subject level. Complementing the GFP analyses, the topography exhibited by the different conditions were likewise examined. However, these are presented in the *supplementary materials* (see Figure S2) and not in the main text, as no strong theoretical prediction exist regarding a neural correlate of consciousness across unisensory and multisensory domains in topography (although see Britz et al., 2014).

Inter-Trial Variability Analyses

To probe the reproducibility of evoked potentials during different perceptual states and as elicited by stimuli of different modalities in a relatively simple manner, PCA was performed within each participant. More specifically, PCA identified the number of orthogonal dimensions, expressed as a proportion of the total possible (e.g., number of trials analyzed), needed to express a certain amount of the trial-to-trial variability (90% in the present case) for each channel. In a deterministic system with highly stereotyped responses, only a few dimensions are needed to capture most of the variability. To the extent that trial-to-trial recordings differ from one another, total variability increases, and hence PCA dimensionality increases. In the present case, each participant's data were divided into channel- and experimental-condition specific matrices of single trial data with trials as rows and time points as columns. The dimensionality of each matrix was determined as a minimum number of principal components capturing 90% of the variance across trials. This number was further expressed as a percent of the total number of dimensions and was taken as a measure of trial-to-trial variability for a given channel. For the audio, visual, and audiovisual conditions (for both perceived and non-perceived trials), the 120 trials whose mean most faithfully represented the average GFP's (determined via minimization of absolute value residuals), and thus the average response, were analyzed to maintain the number of potential dimensions equal across conditions. For the catch trials, all false alarm catch trials were taken, and an equal number of correct-rejection catch trials were randomly selected on a participant-by-participant basis. This PCA analysis was performed on a 101 ms wide sliding window (first originating at -100 and terminating at 0 ms post-stimuli onset, 1 ms step size), to determine the temporal time-course of the trial-to-trial variability (note that this timecourse analysis is thus smoothed). Results (Figure 5) are reported as the percentage of extra dimensions need for each sensory modality to explain trial-to-trial variance in the perceived versus non-perceived condition. As for the GFP analyses, catch trials were separately analyzed as a control procedure. A random subset of correct rejection catch trials was sampled for each participant in order to match the number of correct rejections and false alarm trials. This last analysis was solely undertaken for participant with at least 20 false alarm trials (13/20 participants).

Lempel-Ziv complexity

Lastly, Lempel-Ziv (LZ) complexity was quantified for each condition, as a measure of complexity indirectly related to functional differentiation/integration (Casali et al., 2013; Koch et al., 2016; Tononi et al., 2016; Sanchez-Vives et al., 2017). LZ is the most popular out of the Kolmogorov class (routinely used to generate TIFF images and ZIP files), and measures the approximate amount of non-redundant information contained within a string by estimating the minimal size of the 'vocabulary' necessary to describe the entirety of the information contained within the string in a lossless manner. LZ can be used to quantify distinct patterns in symbolic sequences, especially binary signals. Before applying the LZ algorithm, as implemented in *calc_lz_complexity.m (Quang Thai, 2012)*, we first down-sampled our signal from 1000 to 500 Hz, and converted it to a binary sequence. For every participant and every trial separately we first full-wave rectified the signal and then assigned a value of '1' to a time point if the response was 2 standard deviations above the mean baseline value for that particular trial (-100 to 0 ms post-stimuli onset). If the response was not 2 standard deviations above the mean baseline, a value of '0' was assigned (see Figure 7, left panel). Next, binary strings were constructed for each trial by column-wise concatenating the values at each of the 128 electrodes (Casali et al., 2013) for the entire period post-stimuli. Finally, the LZ complexity algorithm determined the size of the dictionary needed to account for the pattern of binary strings observed. The same procedure was repeated after shuffling the binary data after column-wise concatenation. This procedure was undertaken to calculate surrogate data with a-priori maximal complexity given the entropy in the original dataset. Finally, LZ was normalized by expressing it as the fraction of non-shuffled complexity divided by the shuffled version of the measure (see Andrillon et al., 2016 for a similar approach).

Results

Behavioral – Reaction Time

As expected from classical multisensory paradigms, a one-way repeated measures ANOVA with 4 sensory conditions (none, audio, visual, audiovisual) demonstrated a significant effect on reaction times (F(3, 60) = 103.193, $p < 0.0001$). As illustrated in Figure 2A, this effect may have been driven by false alarms during catch trials, which were very slow (mean catch trials = 0.975 ± 0.10 seconds [mean ± 1 S.E.M]) since neither stimulus was presented. In fact, the mean reaction time for catch trials (.975 seconds) was no different from the statistically expected value drawn from a fixed duration of 800 ms, plus a random duration between 0 and 2 seconds described by a uniform distribution (one-sample t-test to .9, $p = 0.09$). That is, on average participants false alarmed half way through the inter-stimulus interval. Thus, a one-way repeated measures ANOVA with 3 conditions (audio, visual, audiovisual) was performed and demonstrated a significant effect of sensory modality (F(1, 20) = 720.19, $p < 0.001$, h2 = 0.97). The main effect was driven by the multisensory condition being fastest (M = 0.555 ± 0.09 seconds), followed by the auditory (M = 0.588 ± 0.10 seconds), and then the visual (M = 0.633 ± 0.11 seconds) condition (all comparisons are paired-samples t-test with $p < 0.046$ Bonferroni-corrected). Detection of audiovisual stimuli was faster than detection of the fastest unisensory stimulus defined on a subject t-by-subject basis (audiovisual versus fastest unisensory, $p = 0.012$; see Figure 2A and *Methods* for details).

Behavioral – Sensitivity

On average, participants responded “yes” on 8.2% (mean) ± 1.1% (standard error of the mean) of the catch trials (i.e., false alarms), 45.1% ± 3.9% of the audio trials (d’ = 1.21, c = 0.92), 41.7 ± 4.6 % of the visual trials (d’ = 1.27, c = 0.89), and 64.8 ±

4.7% ($d' = 1.83$, $c = 0.88$) of the audiovisual trials (Figure 2B). Thus, we were successful in driving participant’s performance to a detection rate that allowed the bifurcation of data with regard to perceptual report; perceived versus non-perceived. Note, as illustrated in Figure 1, false alarm rates remained constant throughout the experiment, suggesting little fatigue or learning effects. A one-way ANOVA and subsequent paired-samples t-tests on sensitivity (i.e., d') values extracted from signal detection analyses (SDT; Tanner & Swets, 1954; Macmillan & Creelman, 2005) suggested that participants were most sensitive to the multisensory presentations ($F(2, 40) = 19.84$, $p < 0.001$; paired-samples t-tests on audiovisual d' versus most detected unisensory d', $p = 0.007$). Lastly, response criterion (i.e., c) was unchanged across the different sensory conditions ($F(2, 40) = 0.05$, $p = 0.94$; See Figure 2B). Thus, the behavioral data from this task illustrates multisensory facilitation in the form of the frequency, sensitivity, and speed of stimulus detection, while showing no change in response criterion. This last observation is particularly important as it suggests that participants’ overt reports of stimulus detection reflect perceptual awareness as opposed to a change in what they consider ‘reportable’.

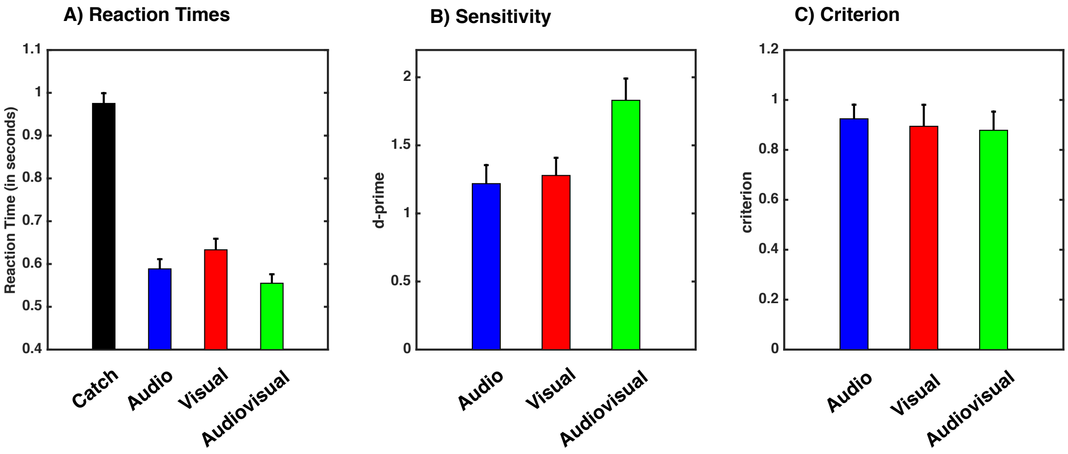

Figure 3.2. Psychophysical Results. A) Mean reaction times per sensory modality condition in response to perceived stimuli. Please note y-axis does not commence at 0 ms, but 400 ms. B) Sensitivity (i.e., d') and C) criterion for audio (blue), visual (red) and audiovisual (green) conditions. Error bars indicate +1 S.E.M. across participants.

Global Field Power

Topographic consistency test (TCT; Koeing & Melie-García, 2010) over the entire post-stimuli interval demonstrated a reliable evoked potential when subjects were presented with auditory, visual, or audiovisual stimuli, both when participants reported perceiving or not perceiving the stimuli (all $p < 0.01$, FDR corrected). In contrast, no consistent evoked potential was apparent during catch trials, regardless of whether participants reported a stimulus or not (all $p > 0.08$, FDR corrected).

For auditory stimuli, examination of the temporal time-course of evoked potentials revealed deviations from baseline between 64 and 112 ms post-stimulus and then from 134 ms post stimulus throughout the rest of the epoch for trials in which the stimulus was perceived, and for the interval between 72 ms and 448 ms post-stimulus and then again from 461 ms post stimulus throughout the rest of the epoch when the stimuli were not perceived. For visual stimuli, deviations from baseline were seen between 76 and 90 ms post-stimulus and then from 138 ms post stimulus throughout the rest of the epoch when the stimuli were perceived, and between 90 ms and 354 ms post-stimulus and then from 387 ms post stimulus throughout the rest of the epoch when the stimuli were not perceived. Finally, for the audiovisual condition evoked potentials were consistently seen beginning at 45 ms post-stimulus and throughout the rest of the epoch when the stimuli were perceived, and beginning at 92 ms post-stimulus and throughout the rest of the epoch when the stimuli were not perceived.

Contrasts of the Global Fields (GFPs) between conditions demonstrated a significant difference between perceived versus non-perceived stimuli for each of the three sensory conditions (see Figure 3). The statistically significant difference between perceptual states (i.e., main effect of perceptual state in a 2 [perceptual state] x 3 [sensory modality (excluding catch trials)] repeated-measures ANOVA, N = 19, all $p < 0.01$) was transient for the interval spanning 53-72 ms post-stimulus onset and sustained after 102 ms, with an almost complete absence of late (i.e., +300 ms) response components for non-perceived stimuli (see Gaillard et al., 2009; Del Cul et al., 2007; Dehaene et al., 2001; Sergent et al., 2005; Sperdin et al., 2014; Sanchez et al., 2017, for similar results, as well as Dehaene & Changeux, 2011 for a review). Stated simply, both perceived and non-perceived stimuli generated similar early sensory responses (< ~120 ms post-stimuli onset). In contrast, the presence of relatively late (> ~ 120 ms post-stimuli onset) response components was associated with perceived stimuli. Also statistically significant was the main effect of stimulus modality in the intervals between 110-131 ms post-stimulus (N = 19, all $p < 0.01$; this likely reflects auditory evoked potentials) and between 194-240 ms post-stimulus (N = 19, all $p < 0.01$; this likely reflects visual evoked potentials; Luck, 2005). Not surprisingly given the lack of significant evoked potentials in these conditions (see above), paired-sampled t-tests revealed no difference in the GFP evoked by ‘perceived’ and ‘non-perceived’ catch trials (all $t(12) < 1$, all $p > 0.57$), although this analysis relied on a considerably reduced number of trials (see *Methods*). Further, results revealed a significant interaction between perceptual state and sensory condition 115 post-stimuli onset and onward. Separate t-tests across perceptual states (perceived vs. non-perceived) for the different sensory conditions (audio, visual, and audiovisual) revealed that for auditory stimuli, the GFP diverged for perceived vs. non-perceived stimuli at 121 ms post-stimulus onset. For visual stimuli this divergence occurred at 219 ms, while for multisensory stimuli the divergence began 234 ms after stimulus onset.

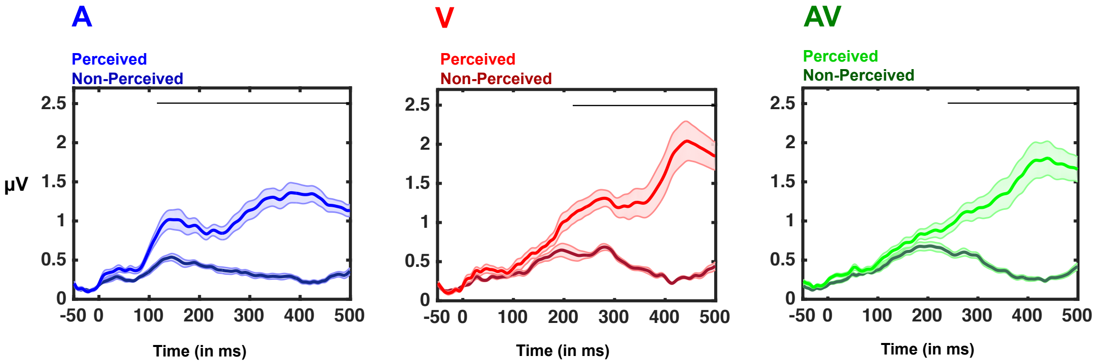

Figure 3.2 Audio, Visual, and Audiovisual Global Field Power. Mean global field power (GFP) across the entire montage of electrodes for each experimental condition; auditory (blue), visual (red), and audiovisual (green). Lighter shades are used for perceived stimuli, while darker colors are used for non-perceived. Shaded areas represent S.E.M. over all participants and black bars indicate intervals over which GFP was significantly different ($p < 0.01$) across perceptual states. On the x-axis, 0 indicates stimulus onset.

Next, we determined whether the difference in GFP magnitude for perceived vs. non-perceived multisensory stimuli could be explained by a simple combination of the unisensory responses. To do so, we compared the multisensory responses (perceived and non-perceived) to the sum of the unisensory responses (perceived and non-perceived; see Cappe et al., 2010, 2012 for a similar analysis). To do so, the evoked potentials for the unisensory conditions were first summed and then the GFP was extracted (see Methods). This analysis showed a significant main effect of sensory modality (A + V > AV; see Figure 4) beginning at 183 ms (N = 19, repeated-measures ANOVA, all $p < 0.01$), and a main effect of perceptual state (perceived > non-perceived; See Figure 4 bottom panel) between 97-188 ms post-stimulus onset and from 222 ms onward (N = 19, repeated-measures ANOVA, all $p < 0.01$). Most importantly, the results indicated a significant interaction such that multisensory responses to perceived stimuli were weaker than the sum of the two unisensory responses in a manner that differed significantly from the comparison of multisensory responses to non-perceived stimuli (N = 19, 2 [perceptual state] x 2 [sum unisensory vs. multisensory] repeated-measures ANOVA interaction all $p < 0.01$, 251 ms onward; see Figure 4; dark area, and line indicating significance). Follow up analyses using paired t-tests showed no difference between the pair and the sum when stimuli were not perceived (all $p > 0.043$), but a difference between these conditions beginning194 ms post-stimulus onset ($p < 0.01$), when the stimuli were perceived.

Collectively, these GFP results highlight that audiovisual stimuli that are perceived result in late evoked potentials that are not present when stimuli are not perceived, mirroring what has been well established within the visual neurosciences (e.g., see Dehaene & Changeaux for a review), and what seems to be emerging within the auditory neuroscience (e.g., see Sadaghiani et al., 2009),. Interestingly, the presence of this late component exhibits sub-additivity when contrasting the sum of unisensory and the multisensory condition (e.g., see Cappe et al., 2012 for a similar results), an observation that is not true when stimuli are not perceived – due to the lack of late evoked potentials.

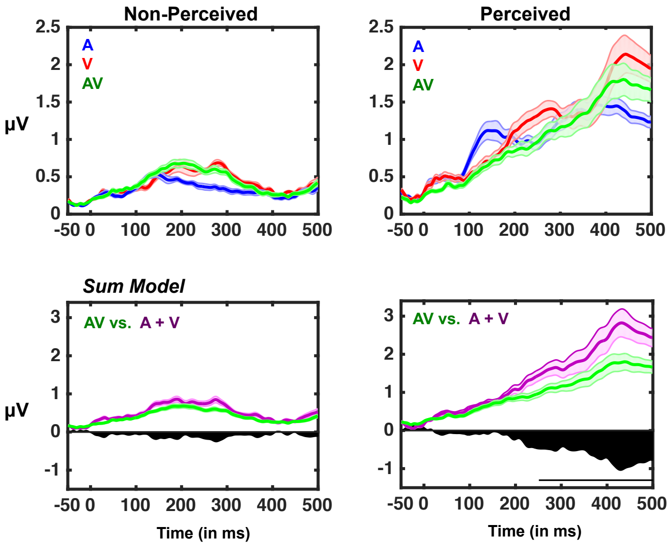

Figure 3. 4. Global Field Power as a Function of Sensory Modality, Perceived State and Comparisons between the Sum of Unisensory Conditions to Multisensory Condition. Top row: Same as Figure 2, with average GFP traces over all participants for the three sensory conditions superimposed for non-perceived (left) and perceived (right) trials. Bottom row: a linear model of GFP depicting the actual multisensory response (green) relative to an additive model (sum; A + V) (purple). Black area below the 0 microvolts line represents the difference between predicted and actual multisensory responses. Note the strong deviations from summation for the perceived multisensory conditions, and the lack of such differences for the non-perceived conditions. The black horizontal bar indicates significant difference ($p < 0.01$) between the GFP of the summed unisensory evoked potential and the GFP of the multisensory condition when perceived. Shaded area represents +/- 1 S.E.M. across participants.

Inter-Trial Variability

To extend analyses beyond response strength, we further employed measures that capture the variability (i.e., reproducibility) and complexity (next section) of EEG responses. Specifically, there are several measures that have been leveraged successfully for the characterization and differentiation of states of consciousness (e.g., coma versus awake versus anesthetized versus dreaming; Casali et al., 2013; Schurger et al., 2015; Ecker et al., 2014). In the current work, we implement a relatively straightforward version of this strategy. To evaluate response variability across sensory conditions and perceptual states, we performed principal component analysis (PCA) on the EEG signal for each trial and participant on an electrode-by-electrode basis, and identified the minimum number of principle components needed to capture 90% of the trial-to-trial variability (McIntosh et al., 2008). As illustrated in Figure 5, more dimensions were needed to account for inter-trial response variability of perceived (vs. non-perceived) conditions. However, this difference was more prominent for unisensory conditions compared to multisensory conditions (Figure 5). More specifically, a 2 (perceived vs. non-perceived) x 3 (sensory modality; A, V, AV) repeated measures ANOVA demonstrated a significant main effect of sensory modality beginning 107 ms post-stimulus onset and persisting throughout the entire epoch ($p < 0.01$), a main effect of perceptual state beginning at 95 ms post-stimulus onset and persisting throughout the rest of the epoch ($p < 0.01$), and a significant interaction between these variables beginning 99 ms post-stimulus onset and persisting throughout the rest of the epoch ($p < 0.01$). The interaction is explained by a difference in the time at which the PCA bifurcated between perceptual states (if at all) for the different sensory conditions. For the unisensory condition, beginning at 91 ms following the auditory stimulus, and at 239 ms following the visual stimulus, there was a significant increase in response variability trials in which the stimulus was perceived ($p < 0.01$; $N = 19$, paired-samples t-test, for both contrasts; Figure 5). In contrast, this increased variability for perceived trials was not apparent for the audiovisual stimuli ($p > 0.09$, $N = 19$, paired samples t-test). Inter-trial variability as quantified by the PCA analysis was similar across perceptual states for the catch trials (all $t(12) < 1$, $p > 0.74$).

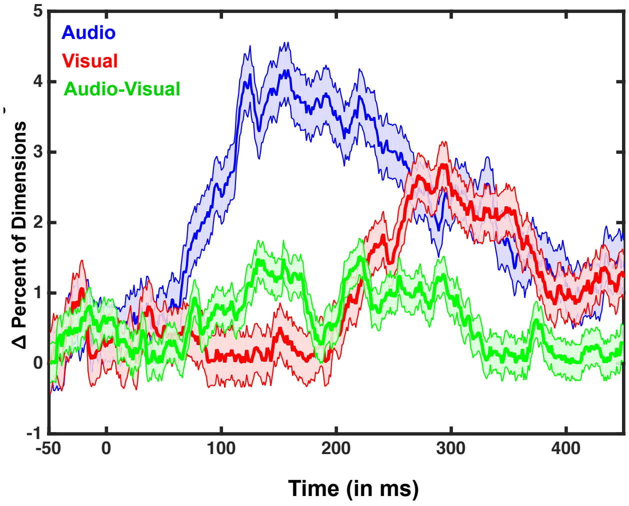

Figure 3.5. Trial-by-Trial EEG Variability as a Function of Sensory Modality and Perceived State. For this analysis, principal component analysis (PCA) was performed on all channels and for every participant and the number of dimensions needed to explain 90% of the trial-by-trial variance was calculated. 120 trials were selected for each condition, giving a theoretical maximum dimensionality of 120. The figure illustrates the number of additional dimensions needed (in percentage) to explain trial-by-trial variability in the perceived as opposed to the non-perceived state as a function of time for the three sensory conditions. Results suggest that audio (blue) and visual (red) trials exhibit a marked increase in dimensions needed to explain trial-to-trial variance during the time-course of an epoch, a feature not seen in the audiovisual (green) condition. Shaded areas around curves represent S.E.M. over all participants.

EEG Complexity

The final theory-driven measure of interest here is a measure of capacity for information reduction - Lempel Ziv (LZ) complexity. This measure is of interest due to recent observations indicating that perceptual awareness may not emanate simply for the recruitment of broadly distributed networks, but rather for the differentiation and integrations of activity among these networks (see Cavanna et al., 2017 for a recent review). These networks are postulated to fulfill axiomatic observations related to awareness (Tononi & Koch, 2015) that embody complex neural signatures of that mental state. Thus, here, LZ complexity – a measure of information reducibility – was measured across the post-stimuli period of audio, visual, and audiovisual stimuli that were either perceived or not, and we queried whether similar patterns complexity would apply across modalities (i.e., from visual to auditory) and number of modalities (i.e., from unisensory to multisensory). As illustrated in Figure 6, a 4 (sensory modality; none, audio, visual, audiovisual) x 2 (perceived vs. non-perceived) repeated measures ANOVA revealed a significant main effect for sensory modality ($F(3, 57) = 44.92$, $p < 0.001$), a significant main effect for perceptual state ($F(1, 18) = 40.82$, $p < 0.001$), and a significant interaction between these variables ($F(3, 57) = 3.21$, $p = 0.029$. The main effect of perceptual state was due to higher complexity for non-perceived stimuli (M = 0.24, S.E.M = 0.01) than for perceived stimuli (M = 0.19, S.E.M = 0.005; paired t-test, $t(18) = 6.32$, $p < 0.001$). Regarding the main effect of sensory modality, post-hoc paired t-tests (Bonferroni corrected) revealed that catch trials exhibited the most informationally complex patterns of activity, on average, (M = 0.27, S.E.M = 0.007, all $p < 0.001$), followed by auditory evoked potentials (M = 0.21, S.E.M. = 0.010, contrasts to catch and audiovisual conditions significant with all $p < 0.03$, but not the contrast to visual trials, $p = 0.659$), followed by visual evoked potentials (M = 0.19, S.E.M = 0.010, contrast to audiovisual trials being non-significant, p = 0.253), and finally by the multisensory evoked potentials (M = 0.18, S.E.M = 0.008). The complexity of these multisensory responses was not significantly different from those of visual responses. The significant interaction was driven by the fact that there was a significant difference in evoked complexity between perceptual states (perceived vs. non-perceived) for catch trials (perceived; M = 0.24, S.E.M = 0.03, non-perceived; M = 0.30, S.E.M = 0.06, t(19) = 3.40, p = 0.003), auditory trials (perceived; M = 0.19, S.E.M = 0.05, non-perceived; M = 0.24, S.E.M = 0.04, t(19) = 6.63, p < 0.001), and visual trials (perceived; M = 0.17, S.E.M = 0.04, non-perceived; M = 0.22, S.E.M = 0.05, t(19) = 4.45, p < 0.001) stimulation. In contrast, this difference was not seen for audiovisual trials (perceived; M = 0.17, S.E.M = 0.03, non-perceived; M = 0.19, S.E.M = 0.04, t(19) = 1.32, p = 0.203). In fact, for the multisensory condition, Bayesian statistics suggested that not solely there is no evidence against the null hypothesis (as inferred via Frequentists analyses described above), but in fact there was considerable evidence for it (BF_{10} = 0.298 < 0.03, typically suggested as cutoff favoring the null hypothesis; Jeffreys, 1961). Taken together, these analyses suggest that while EEG complexity is generally decreased when stimuli are perceived (vs. non-perceived and normalizing for overall entropy) for unisensory stimuli, this is not true for multisensory stimuli. Interestingly, the decrease in complexity is also observed during catch trials when participants report perceiving a stimulus that is not present. Thus, the decrease in EEG evoked complexity is not only associated with physical stimulation, but seemingly also with perceptual state.

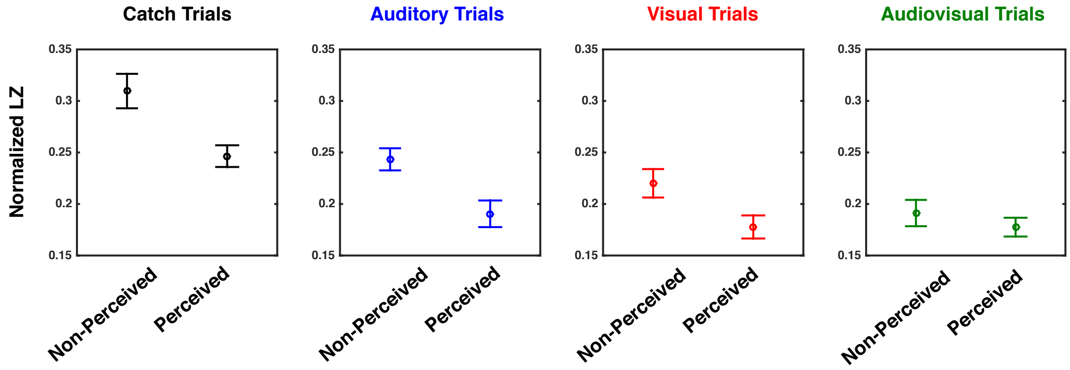

Figure 3.6. Neural Complexity Differs as a Function of Perceived State and Sensory modality. Lempel-Ziv Complexity as a function of experimental condition; catch (leftmost), auditory (second panel), visual (third panel), or audiovisual (rightmost) panels. Results suggest a significant difference between detected and non-detected stimuli for catch (black), auditory (blue), and visual (red) conditions, but not for audiovisual (green) trials. Y-axis is normalized Lempel-Ziv during the entire post-stimuli epoch (LZ for un-shuffled data divided by shuffled data). Error bars indicate +1 S.E.M. across participants.

Discussion

A number of different neural markers of perceptual awareness have been proposed; from “neural ignition” and the presence of late evoked potentials (P3, P300, P3b; Dehaene & Changeaux, 2011; Dehaene et al., 2017), to increased neural reproducibility (Schurger et al., 2010), to a high degree of information integration that can be indexed through measures such as EEG complexity (Casali et al., 2013; Tononi et al., 2016; Koch et al., 2016). Here, we sought to extend the use of these various measures posited to represent credible neural signatures of perceptual awareness for visual stimuli to multisensory perceptual processes – as much of our perceptual gestalt in constructed on a multisensory foundation. Collectively, our results support and extend prior work implicating neural signatures of perceptual awareness revealed in measures of EEG response strength, reproducibility, and complexity. We show, as has earlier work, that reproducibility and complexity indices of perceptual awareness are similar for visual and auditory conditions, but we also show that there exist significant differences in the indices of awareness associated with multisensory stimulation, differences that likely have important implications for furthering our understanding of multisensory perceptual awareness.

Neural Response Strength as a Modality-Free Indicator of Perceptual Awareness

More specifically, conditions in which visual, auditory or both visual and auditory stimuli were presented resulted in reliable variations in EEG response strength (as indexed via global field power – GFP) that covaried with perceptual state (i.e., was the stimulus perceived or not). In each of these conditions, comparison of perceived vs. non-perceived stimuli revealed the presence of late evoked potentials that were only present under perceived circumstances. Thus, the presence of late evoked potentials appears to be a strong index of perceptual awareness under both unisensory and multisensory conditions. The striking absence of late EEG components to non-perceived stimuli resembles “ignition”-like single unit responses to perceived stimuli that have been found in the temporal lobe of epileptic patients (Dehaene, 2014). This response pattern fits the assumption that conscious percepts arise late in the evolution of sensory responses, possibly because they necessitate more global brain activity (Dehaene & Changeux, 2011; Gaillard et al., 2009; Noy et al., 2015). This “ignition-like” effect, which at times has been difficult to capture in previous work (e.g., Silverstein et al., 2015), likely results from several aspects of the current experiment. First, it may be argued that the lack of observable late responses in EEG signals may be due to our adaptive, online method of adjusting stimulus intensity – and not reflective of the manner in which individuals become aware of stimuli. This account, however, does not fully explain the GFP effects, as EEG analyses were restricted to the last 400-500 trials and in which auditory and visual noise levels were relatively fixed in intensity and the minimal changes in stimuli intensity did not provoke a change in GFP (see *Control Analyses;* Figure S1 online). Second, the current experiment is different from most previous EEG studies presenting stimuli at threshold (and demonstrating the occurrence of late EEG components, e.g., see Koch et al., 2004) in that here we interleave stimuli from different modalities (see Sanchez et al., 2017 for a similar observation of abolished late evoked responses for undetected stimuli in a multisensory context). Finally, it is possible that the clear presence of late evoked potentials in perceived trials but not in non-perceived trials arises because participants were working below the 50% detection rate and not at threshold (most prior work presented stimuli at threshold).

EEG Subadditivity in Multisensory Integration is Associated with Perceived Stimuli

A second interesting observation regarding the GFP results relates to the comparison between the sum of unisensory evoked potentials ("sum") and the multisensory response ("pair"). When stimuli were not perceived there was no significant difference between the multisensory GFP and the GFP predicted by the sum of unisensory responses (i.e., no difference between sum and pair). In contrast, when the stimuli were perceived, the GFP of the audiovisual condition was distinctly subadditive when compared with the sum of the unisensory responses. Hence, although neural response strength (i.e., GFP) differentiates between perceptual states under both under unisensory and multisensory conditions, the perceived multisensory response does not reflect a simple addition of the two unisensory responses. Indeed, subadditivity in EEG responses is often seen as a hallmark of multisensory processing (see Cappe et al., 2010, 2012, for example), and here it was evident only under perceived multisensory conditions, suggesting links between multisensory integration and perceptual awareness (see Baars, 2002, for a philosophical consideration arguing that conscious processing is involved in the merging of sensory modalities). While a number of studies suggest that multisensory interactions may occur when information from a single sense is below the threshold for perceptual awareness (Lunghi & Alais, 2013; Lunghi et al., 2014; Aller et al. 2015; Salomon et al., 2015; 2016), or when both are presented at subthreshold levels following a period of associative learning (Faivre et al., 2014), or even when participants are unconscious (Beh & Barratt, 1965; Ikeda & Morotomi, 1996; Arzi et al., 2012), evidence for multisensory integration in the complete absence of perceptual awareness (without prior training) is conspicuously lacking (Noel et al., 2015; Faivre et al., 2017). The current results provide additional support for the absence of multisensory integration outside of perceptual awareness, but, as null results, must be interpreted with caution.

Across trial EEG Reproducibility Differentiates Between Perceived and Non-Perceived Unisensory but not Multisensory Stimuli

The next putative index of perceptual awareness used in the current study was that of neural reproducibility (Schurger et al., 2015). This measure is predicated on the view that spatio-temporal neural patterns giving rise to subjective experience manifest as relatively stable epochs of neural activity (Fingelkurts et al., 2013; Britz et al., 2014). To address the stability of responses, we measured inter-trial variability via a relatively straightforward metric, i.e., PCA. Those results disclosed similar levels of neural reproducibility for visual and auditory conditions (although with different time-courses), and a categorically distinct pattern for multisensory presentations. Specifically, there was no difference in neural reproducibility across trials for perceived vs. non-perceived trials for the multisensory conditions, but there were reliable differences associated with the unisensory conditions. The increased variability for perceived unisensory stimuli runs counter to the view that responses to perceived trials are more reproducible (Schurger et al., 2010; Xue et al., 2010). However, we did not observe late response components to non-perceived stimuli, which reduces the amount of principle components that are needed to explain the variance of this part of the response. Indeed, the increase in principle components that are needed to explain the trial-to-trial variability for the perceived stimuli occurs very close in time to the bifurcation between perceived and non-perceived GFPs (auditory: GFP at 121 ms vs. PCA-dimensionality increase at 91 ms; visual: GFP at 219 ms vs. PCA-dimensionality increase at 239 ms). Thus, the relevant observation here is that both the strength (as indexed via GFP analyses) and the between-trial variability (as indexed via PCA analyses) seen in response to perceived multisensory stimuli are reduced in comparison to the unisensory conditions, with both of these effects appearing around the same time in the neurophysiological responses. On the other hand, in contrast to the observation that late evoked potentials seemingly index perceptual awareness regardless of sensory modality, the increase in reproducibility associated with perceived stimuli (Schurger et al., 2015) is most readily evident for multisensory stimuli. That is, while the observation derived from visual neurosciences indicating increased reproducibility for perceived stimuli (Schurger et al., 2015) may be applied to auditory neurosciences – same pattern of results between auditory and visual modalities, although at different latencies – the PCA seem categorically different when probing perceived and non-perceived multisensory stimuli. These results highlight that, at least in the case of neural reproducibility, conclusions drawn from unisensory studies may not generalize to multisensory studies for work attempting to better understand the neural correlates of perceptual awareness.

The finding that signals of neural variability under multisensory conditions changed little as a function of perceptual state is consistent with computational models based on Bayesian inference (e.g., Kording et al., 2007) and Maximum Likelihood Estimates (MLE). These models have been applied to psychophysical (Ernst & Banks, 2002), neuroimaging (Rohe et al., 2015; 2016) and electrophysiological (Fetsch, Deangelis, Angelaki, 2013; Boyle et al., 2017) observations concerning supra-threshold multisensory performance, and collectively illustrate that the combination of sensory information across different modalities tends to decrease variability (i.e., increases signal reliability). Although the current study was not designed or analyzed to specifically pinpoint neural concomitants of multisensory integration, our findings may inform the models mentioned above by showing that, at least for the task employed in the current study, variance in the evoked neural response is more comparable across perceptual states for multisensory conditions compared to unisensory conditions. Interestingly, stimulus-induced reduction in neural variability has been observed across a wide array of brain areas, and has been posited to be a general property of cortex in response to stimulus onset (Churchland et al., 2010). In subsequent work it will be informative to examine whether, at the level of single neurons, variability (as measured through indices such as Fano Factor; Eden, 2010) decreases equally across perceptual states (while maintaining stimulus intensity near detection threshold) and whether these changes differ for unisensory brain responses compared to multisensory responses.

EEG complexity Differentiates Between Perceived and Non-Perceived Unisensory but not Multisensory Stimuli

Finally, consider that aspect of our results dealing with measured neural complexity associated with evoked responses due to visual, auditory, or audiovisual stimuli and as a function of perceptual state. In previous work, a derivative of this measure has successfully categorized patients along the continuum ranging from awake to asleep to minimally conscious and, finally, to comatose (see Casalli et al., 2013). This work has shown that when neural responses are evoked via transcranial magnetic stimulation (TMS), they are less amenable to information compression when patients are conscious relative to when they are unconscious. To our knowledge, however, the present report is the first to examine EEG data complexity (compressibility) as a function of perceptual state and not as a function of level of consciousness. Our results indicate that evoked responses are less complex when either visual or auditory stimuli are perceived (compared to non-perceived). Interestingly, this difference was not evident under multisensory conditions. Further, this measure was able to differentiate between the catch trials that were correctly “rejected” (i.e., no stimulus reported when no stimulus was presented) and false alarms (i.e., reports of the presence of a stimulus when none was presented – a possible analog of an hallucination). The switch in effect direction between levels of consciousness (i.e., more complex when patients are conscious) and perceptual state (i.e., more complex when stimuli are not perceived) likely is due to the fact that in the former case neural responses are artificially evoked – thus recruiting neural networks in a non-natural manner – while in the current case neural responses are evoked by true stimulus presentations. As an example, in the case of visual stimulus presentations, the present results indicate that neural information in the visual neural network architecture is more stereotyped for perceived vs. non-perceived trials.

Conclusions

Taken together, the overall pattern of results: 1) question whether multisensory integration is possible prior to perceptual awareness (see Spence & Bayne 2014 and O'Callaghan 2017 for distinct perspectives on whether perceptual awareness may be uniquely multisensory or simply a succession of unisensory processes), and 2) question the implicit assumption that all indices of perceptual awareness apply across all sensory modalities and conditions. Indeed, if assumed that the search for the neural correlates of perceptual awareness must result in a set of features that are common across all sensory domains (e.g., visual awareness, auditory awareness, audiovisual awareness), then the current findings would argue that the presence of late evoked potentials, as opposed to neural reproducibility or complexity, most closely tracks perceptual awareness. On the other hand, if one instead assumes that visual awareness, auditory awareness, and audiovisual awareness are categorically distinct (or non-existent in the case of multisensory awareness; Spence & Bayne, 2014), then the current findings suggest a greater similarity between the neural correlates of perceptual awareness across visual and auditory modalities, and not between unisensory and multisensory perceptual processes.

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Supplementary Material

Supplemental Analyses

Control Analyses

GFP analyses (similarly to the rest of EEG analyses) were limited to the final 400-500 trials per sensory condition to minimize the variability in stimuli statistics (i.e., the alteration in auditory and visual noise strength during performance titration). Nonetheless, it is conceivable that the distinct neural responses between perceptual states were engendered by differences in the amount of sensory noise. To test for this potentially confounding variable, we conducted two control analyses; i) the intensity of auditory and visual noise (i.e., distractors) were contrasted as a function of whether participants reported being aware of the target or not, and ii) within each sensory modality (audition and vision) we compared the GFP of the 100 trials acquired during the greatest and least amount of sensory noise (within the last 400-500 trials). That is, in the example of auditory target presentations, for each participant we coalesced the 100 trials presented with the most and least auditory noise, irrespectively of subjective report of perception. These conditions were then contrasted to one another to examine whether a slight difference in the stimuli statistics might account for the difference observed when comparing perceived vs. non-perceived stimuli.

Topographic Analyses

Changes in EEG topography follow from changes in the configuration of the underlying active electric dipoles (Lehmann, 1987; although the contrary is not necessarily true), and thus, we performed topographical analyses to index when experimental conditions activated distinct sets of brain networks. To test the topography of evoked potentials as a function of sensory modality and perceptual state independently of their strength, we used a Global Dissimilarity (DISS) measure (Lehmann and Skrandies, 1980). DISS is equivalent to the root-square-mean difference between the potentials measured at each electrode for different conditions, normalized by the instantaneous GFP (L2-norm, in this case). Statistically, the DISS value at each time point is compared to an empirical distribution derived from permuting the condition label of the data from each participant. This analysis is based on a non-parametric randomization procedure (5000 randomizations per time point) and is implemented in the RAGU software (Koenig et al., 2011). Significance threshold is set here to alpha < 0.05. A time-wise 3 (sensory modality) x 2 (perceptual state) topographic ANOVA (TANOVA) on DISS values was performed to identify statistical differences between neural generator configurations for the distinct sensory modalities as a consequence of perceptual state.

Spectral Analysis

To ascertain that differences in complexity or variability measures were not due to co-varying factors, we sought to rule out the possibility that arousal might vary with stimuli presentation (versus no stimuli presentation, as in the catch trials). Thus, we performed a Fast Fourier Transform (FFT) on the entire epoch (-100 to 500ms) for every participant, trial, and experimental condition, and computed the power (squared amplitude) exhibited within delta (defined as 1-5 Hz) and beta (20-25 Hz) frequency ranges (Prior, 1987). The ratio between these two (delta-to-beta) was computed on each trial and compared across sensory modalities and perceptual states via a 3 X 2 repeated measures ANOVA.

Supplemental Results

Global Field Power – Control Analyses

Regarding the analysis of the distractor stimuli themselves, numerically the auditory noise was on average lower in cases when participants reported perceiving the target (M = 53.40 dB, SEM = 2.67 dB) than when they reported not perceiving the auditory target (M = 55.01 dB, SEM = 4.34 dB), however this difference was not statistically significant (paired-samples t-test t(18) = 0.31, p = 0.75; See Figure S1). Similarly, with respect the visual noise, the RGB values were numerically closer to zero (black screen) in the case when participants reported perceiving the visual target (M = 151.10, SEM = 6.62) than when they did not reported being aware of the stimuli (M = 161.76, SEM = 6.50), however this contrast equally failed to reach significance (paired-samples t-test t(18) = 1.14, p = 0.25, see Figure S1). Evidently, then, stimuli characteristics did not systematically differ between trials in which participants reported being aware of the stimuli vs. trials in which participants did not report perceiving the targets.

Nonetheless, even if the stimuli differed only marginally between trials, it is possible that this difference in sensory stimulation was sufficient to impact neural dynamics. Hence, we bifurcated trials with respect to auditory and visual noise (extreme low vs. extreme high) as opposed to perceptual state, and compared GFP between conditions. Time resolved paired t-tests were conducted both for the audio targets and visual targets. As illustrated in Figure S1, neither the audio-target evoked GFP (N = 19, all p > 0.17) nor the visual-target evoked GFP (N = 19, all p > 0.13) differed as a function of the distractor noise applied (which as illustrated in the stimuli-statistic analyses were well constrained). These results suggest that the reported modulations in GFP are related to different perceptual states and not due to differences in stimuli features.

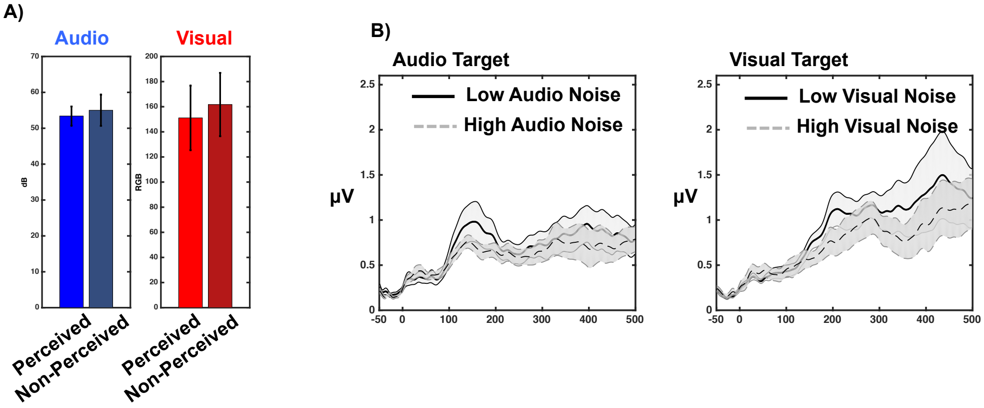

Figure 3.7. Control Analyses. A) Auditory and visual noise levels were varied adaptively over the course of the last 400-500 trials to maintain hit rate between 35 and 45%, but this variation is unlikely to account for EEG results. There was no significant difference in intensity in auditory (blue) or visual (red) noise across perceptual states. **B)** Similarly, to ascertain that the slight putative variation in stimuli characteristics did not significantly impact brain dynamics as measured via EEG, GFP was compared for the most extreme cases (on the positive and negative end) of sensory noise. Neither the auditory (left) nor the visual (right) GFPs differed significant as a function of sensory noise (solid lines = low; dashed lines = high). Shaded areas represent SEM across participants and 0 indicates target onset.

Topographic Results

We next examined differences in the topography of EEG responses to the different experimental conditions via an index of global dissimilarity (DISS, Lehman & Skrandies, 1980). DISS is an orthogonal measure to GFP that is independent of response strength (see *Methods*). Using this measure, we found a relatively early topographic differentiation based on perceptual state ($p < 0.05$, 112 ms post-stimulus and onward) regardless of sensory modality (main effect of perceptual state, non-parametric randomization test; TANOVA, see *Methods*). Particularly noteworthy is that this analysis indicated an even earlier divergence in topographic organization for perceived and non-perceived multisensory stimuli (52 ms post-stimuli onset, $p < 0.01$, TANOVA, $N = 19$) relative to the two unisensory conditions (auditory; $p < 0.01$ at 148 ms, visual; $p < 0.01$ at 141 ms post-stimuli onset; $N = 19$, TANOVA; See Figure S2). This difference was also significant when tested as an interaction; multisensory divergence versus earliest unisensory divergence, all $p < 0.05$, TANOVA, $N = 19$). The latency of these results again illustrate that unisensory responses modulated by perceptual state are inadequate to completely account for the response differences (perceived vs. non-perceived) for the multisensory condition. Topographical analyses equally revealed a main effect of sensory modality initiating 137 ms post-stimuli onset, and a significant interaction ($p < 0.05$) occurring at 165 ms post-stimuli onset.

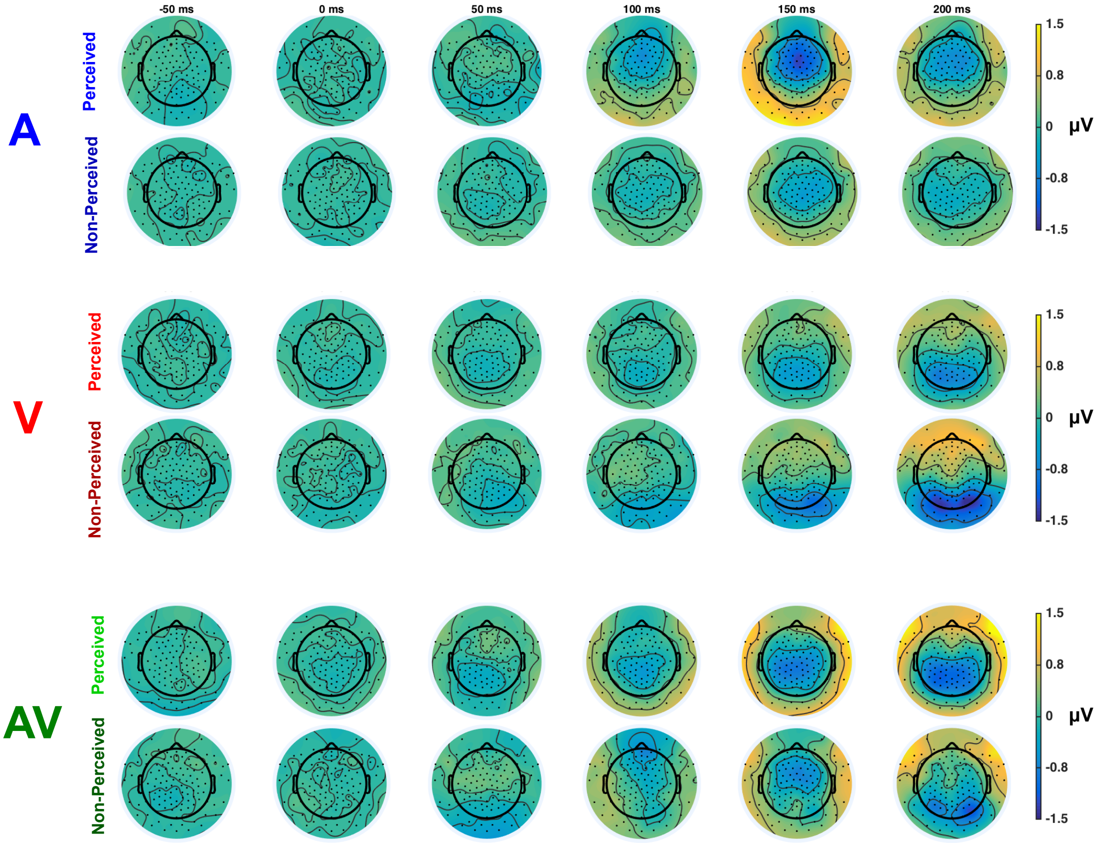

Figure 3.8. Topographical Distribution of Voltages as a Function of Sensory Modality, Perceptual State, and Time. Top two rows represent auditory responses, the following two show visual, and the bottom two rows illustrate audiovisual topographical distributions. At about 150 ms following stimulus onset there is a clear frontal/central topography for auditory stimuli, and at about 200 ms the topography indicates a source at the back of the head for visual stimuli. Multisensory stimuli exhibit patterns that

resemble both auditory and visual topographies. Warm colors (yellow) indicate positive voltages, while cold colors (blue) indicate negative voltages.

Next, to index multisensory interactions, we performed a 2 (perceptual state) x 2 (multisensory versus sum of unisensory) TANOVA. In contrast to the GFP analysis, the interaction between perceptual state and the sum versus pair (i.e., audio + visual vs. audiovisual) comparison was not significant (all $p > 0.082$). We did observer a significant main effect for state of perceptual state (102 ms onward), as well as a significant main effect of sensory modality (multisensory versus sum of unisensory; 71-83 ms and 176-210 ms).

CHAPTER IV

IS PERCEPTUAL AWARENESS GRADED OR CATEGORICAL?

The contents of this chapter are adapted from

Noel, J.P., Faivre, N., Magosso, E., Blanke, O., Alais, D., Wallace, M. (in prep). Is Perceptual Awareness Graded or Categorical?

Main Text

Our introspective experience suggests that perceptual awareness is graded. Conversely, neuroscientific evidence suggests that mechanisms associated with conscious access are "all-or-none", wherein upon crossing a threshold, neural signals are subsequently globally broadcasted throughout the brain and result in conscious reports. Here, we measure perceptual performance in a multisensory cue congruency priming task – structured such that the cues can be perceived, partially perceived, or non-perceived – in conjunction with computational modeling and comprehensive psychophysics (~290 hours of testing) to evaluate whether perceptual awareness is graded or categorical. We built a series of networks which *in-principle* could support multisensory, unisensory, or no consciousness, given their feedback connectivity patterns and the fact that individual nodes (i.e., sensory areas) possess a sigmoidal activation function allowing for “neural ignition” and the global broadcasting of sensory signals. Interestingly, despite being built to support an “all-or-none” account of consciousness, these neural architectures generated reaction times consistent with a graded relation between perceptual awareness and task performance. Behavioral results in the congruency-priming task agree with the modeling findings demonstrating a graded rather than categorical relation between perceptual awareness and multisensory processing.

Theories of consciousness such as Global Neural Workspace (GNW; Dehaene & Changeux, 2001) and Local Recurrence (LC; Lamme, 2006) emphasize global processing, positing that recurrent activity among neural structures leads to consciousness. These theories state that stimuli reach awareness when ascending sensory input is either strong enough in isolation or amplified via top-down attentional signals to result in “neural ignition” – the step-function broadcasting of sensory information throughout the neocortical mantle (van Vugt et al., 2018). Thus, while these neural models view consciousness as an “all-or-none” phenomenon (van Vugt et al., 2018; Joglekar et al., 2018), it is a matter of debate whether the behavior and phenomenological experience is categorical or graded (Cleeremans & Jimenez, 2002; see Tononi et al., 2016 for a graded theory of consciousness). For example, philosophers question whether multisensory awareness is cohesive and singular (i.e., categorical change from no experience in dreamless sleep to multisensory experience), or a collection of unisensory experiences dynamically mixing throughout daily life (Deroy et al., 2014).

To inform this debate, we structured computational models that formalized the role of feedback connections and neural non-linearities (Figure 1, upper row) in biologically-inspired non-spiking neural networks. The retina and cochlea project to reciprocally connected visual (V) and auditory (A) areas, and these subsequently project to a multisensory (AV) area (Figure 1, second row; see *Supplementary Information (SI)* online). Importantly, in line with theoretical postulates (Dehaene & Changeux, 2001; Lamme, 2006; Joglekar et al., 2018), AV-consciousness was operationalized by the presence of feedback from AV back to unisensory regions (Figure 1, rightmost panel), while a network was considered not to support consciousness when no feedback was present (second row, leftmost panel). Additionally, each sensory area processes information via a sigmoidal activation function resulting in neural ignition following strong sensory input. Unsurprisingly, the model's performance (i.e., reaction times generated to cue presentation) was best under an architecture supporting AV consciousness compared with no consciousness (third row, left panel). We then created versions of these networks in which feedback from AV was limited to either A or V areas, creating networks that were *a priori* capable of A-consciousness or V-consciousness, but not AV-consciousness (Figure 1, second row, middle columns). These networks allowed us to probe an intermediate state between fully conscious and fully unconscious, thus allowing to index whether the relation between perceptual awareness and performance is graded or categorical. Interestingly, when given AV stimuli, these models *in principle* supporting partial awareness did not demonstrate a step-function wherein they behaved as AV-conscious networks, but instead lay closer to a linear interpolation between fully conscious and fully unconscious networks (Figure 1, third row). Importantly, as biological entities possess a single neural architecture and not several, we replicate the same modeling results while instantiating a single neural network capable of AV-, A-, V-, no-consciousness (see SI; Figure 1 depicts results from the singular network).

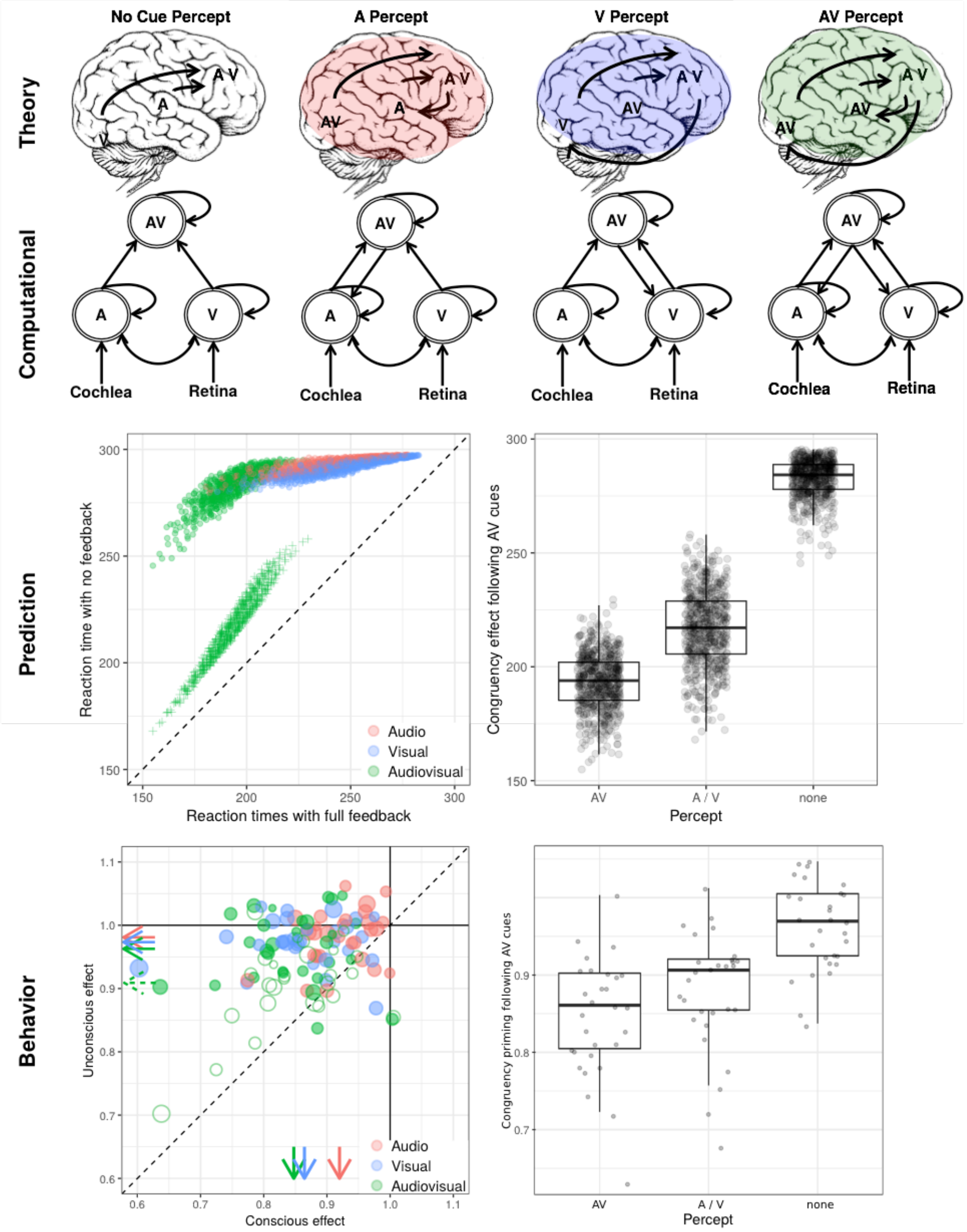

Figure 4.1. Theoretical framework, computational implementation, and results of the relation between perceptual awareness and cue congruency priming. Top row: According to the Global Neural Workspace (GNW) and Local Recurrence (LC) theories

of consciousness, a stimulus becomes conscious when it engages both feedforward and feedback projections, hence establishing a recurrent network of sustained activity and neural information is widely broadcast throughout the brain. Hence, as illustrated in the leftmost column of the top panel, when the neural response to visual (blue) and auditory (red) stimuli remains encapsulated within its primary sensory area or solely engaged feedforward mechanisms, the system is in theory incapable of a conscious percept. On the contrary, when feedback projections are engaged and a recurrent network is formed, the system is capable of auditory-alone (top row, second column; no feedback projection to V), visual-alone (top row, third column; no feedback projection to A), or audiovisual consciousness. In the second, third, and fourth column the entire brain is colored red, blue, and green to illustrate, respectively, the fact that auditory, visual, and audiovisual information is broadcast throughout the brain. **Second row**: Computational implementation of consciousness theories in a non-spiking neural network. **Third row**: Observed pattern of reaction times as a function of auditory, visual, and audiovisual cues, and whether the network is capable of no consciousness and full consciousness (left-hand plot; no feedback or full feedback; results plotted are from the "unique" model – see SI). Left panel equally plots AV presentations that are partially perceived (e.g., AV perceived as V or A, green crosses) vs. fully perceived trials (x-axis). A total of 625 dots/crosses are plotted, each being the average of 100 trials simulated for a given parameter set (625 sets of parameters). Right panel emphasizes the reaction times to AV stimulation (green in left panel) when they were fully perceived as AV, partially perceived as A or V, and not perceived at all. **Fourth row**: Behavioral data showing the effect of auditory, visual, and audiovisual cues to a lateralized tactile detection task with cues presented at detection threshold. Left panel shows the ratio of mean reaction times for valid relative to invalid cues where values less than 1 indicate a congruency priming effect for tactile targets when preceded by an auditory (red), visual (blue), or audiovisual (green) cue. The data are subdivided by whether participants perceived the cue consciously (x-axis) or reported no-cue (y-axis). Additionally, open green circles (and dashed green arrow on the y-axis) represent audiovisual trials where participants were only partially aware; reporting either A or V percept, but not AV. Every dot represents a participant and the colored arrows on the axes of the scatter plot show the mean of the group. Right panel shows boxplot and individual subject data for the congruency effect associated with AV presentation when participants reported the full percept (left-most), a partial percept (middle), and no percept (right-most), demonstrating a graded effect of awareness on multisensory performance.

To test whether the neural network findings apply to human behavioral performance we recruited 29 healthy volunteers (14 females, mean age 20.9±2.3 years) to take part in 10 hour-long sessions in which they performed a congruency priming task. Subjects had to discriminate the laterality of tactile targets administered to their left or right index finger in a speeded task. Tactile targets were preceded by A, V, or AV cues (80% valid, 20% invalid) presented near detection threshold (Figure S1) and located adjacent to their fingertips. Reaction times (RTs) for correctly discriminating the tactile targets were binned based on participants' subjective reports of cue-awareness into one of three categories: conscious cue (e.g., report of AV-consciousness after AV cue), partially conscious cue (e.g., report of A-consciousness after AV-cue), and unconscious cue (report of no cue after the presentation of a cue). The high number of sessions permitted us to collect a sufficient sample of trials with partially perceived stimuli (>300 trials/subject).

A linear mixed-effect analysis on RTs in trials where cues were consciously perceived revealed a main effect of congruency ($F(1,29) = 54.97$, $p < 0.001$), and an interaction between cue modality (A, V, or AV) and congruency ($F(2,32148) = 45.21$, $p < 0.001$), revealing that AV cues induced a larger congruency effect (median of normalized congruency effect = 0.861 ±0.03; a value of 1 indicates no effect) than A cues (0.925 ±0.02, $p < 0.001$). The difference between AV and V cues did not reach significance (0.857 ±0.03, $p = 0.40$). The same RT analysis for trials where the cue was not perceived revealed a main effect of congruency ($F(1, 28.5) = 22.70$, $p < 0.001$), but importantly, no interaction between cue modality and congruency ($F(2,22990) = 1.93$, $p = 0.15$), revealing that unconscious cues in different modalities elicited equivalent congruency effects (AV: 0.969 ±0.02; A: 0.988 ±0.02; V: 0.974 ±0.01). Taken together, these findings indicate that congruency priming is present and modality-dependent when subjects consciously perceive cues, but these effects disappear when cues are not perceived (Figure 1, bottom left panel). In line with the modeling results, when including AV cues that were partially perceived (as either A or V) congruency effects suggest a graded pattern. Thus, effects are smallest when AV cues are not perceived (median of normalized congruency effect = 0.96 ±0.02; t-test to 1, $t(28) = 3.56$, $p = 10^{-3}$), intermediate when they are partially perceived (0.91 ±0.03, $t(28) = 8.52$, $p = 10^{-9}$), and largest when they are fully perceived (0.86 ±0.03; $t(28) = 10.84$, $p=10^{-11}$; one-way ANOVA, $F(1.81, 50.67) = 30.53$, $p < 0.001$).

Taken together, these results suggest that neural models of consciousness built upon an architecture structured to support categorical transitions to awareness (van Vugt et al., 2018; Joglekar et al., 2018) may nonetheless support a graded relation between perceptual awareness and multisensory processing (Kouider et al., 2010; Faivre et al., 2014; Noel et al., 2015).

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Supplementary Material

A total of 6 psychophysical experiments and 2 neural network-modeling approaches were undertaken for this study. Experiment 1 was a pilot and was followed by Experiments 2a–e. As detailed below, Experiment 1 was analogous to the psychophysical experiment described in the main text, where 31 subjects took part in a sole hour of multisensory spatial congruency priming testing. In Experiments 2a–e, six subjects took part in multiple hours of testing in the experimental setup described in the main text. This was to ensure that enough trials with partially perceived congruent cues were obtained (on average, 325±34 across all participants). Experiments 2b–e differed slightly in that subjects were also administered trials in which the temporal or spatial relation between auditory and visual cues was misaligned. Overall, the temporal and spatial relation between cues did not significantly modulate reaction times (global mixed model with all spatiotemporal manipulations: F=1.05, p=0.31) or congruency priming (F=0.97, p=0.32), and hence the main text focuses on the conditions shared across Experiment 2a–e (see Figure S1). Detailed results for all conditions are given below.

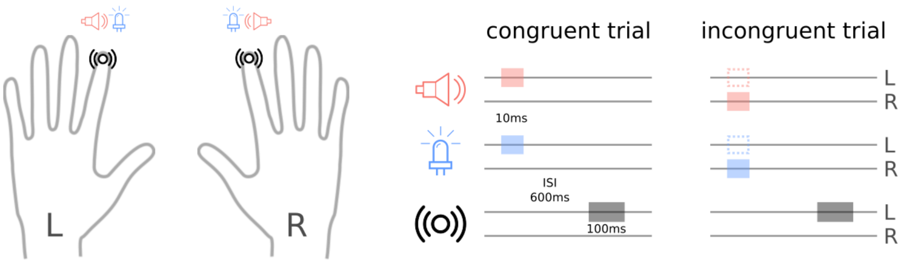
Methods

Experiment 1 – pilot.

Participants. Thirty-one subjects (19 females, mean age = 21.0 ±3.2 years) took part in this experiment. All participants self-reported normal hearing and touch, and had normal or corrected-to-normal visual acuity. Participants gave written, informed consent to partake in the study, which was approved by Vanderbilt University Medical Center’s ethics board.

Materials and Apparatus. In a congruency-priming task, participants were prompted toward either their left or right hand via auditory, visual, or audiovisual cues located at the fingertips before the delivery of a target tactile stimulation to one of the index fingers. Auditory stimuli consisted of a pure tone presented for 10 ms at a frequency of 2.3 kHz and 50 dB SPL intensity, via a Piezo Buzzer (F/UCW 06 Piezo Buzzer, Digisound, Norderstedt, Germany). Participants wore headphones (HD 558, Sennheiser, Wedemark, Germany) over which broadband noise was continuously delivered (range: 57 dB SPL – 91 dB SPL). The ratio between the tone and noise was determined using a staircase procedure, in order to titrate detection performance to perceptual threshold (see below). Visual stimuli consisted of a transient luminance increase produced by a white LED (3 mm diameter, Adafruit, New York, United States; background luminance: 200 mcd; increased by 2 mcd, as determined by a staircase procedure; see below). Audiovisual cues consisted of the synchronous and co-localized presentation of auditory and visual cues at their predetermined threshold level. The target stimuli consisted of a 100 ms supra-threshold vibrotactile stimulation (model 312-101, Precision MicroDrives, London, United Kingdom) presented 600 ms after the cue offset. A vibrator was attached with medical tape to the left and right index finger (medial phalange) of participants. Auditory, visual, and tactile stimulation were controlled via a micro-controller (clock rate: 16 MHz; ATmega1280, Arduino, Italy) in serial communication with a PC (Dell Vostro, 7000 Series, Round Rock, TX, USA; Baud rate: 115200 Hz). LEDs were connected to Pulse-Width-Modulated (PWD) pins, which allowed dividing input voltages into 250 steps. General experimental procedures were controlled via purpose-made MATLAB (MathWorks Inc., Natick, USA) scripts in conjunction with the Psychophysics Toolbox extension (Brainard, 1997; Pelli, 1997, Kleiner et al., 2007). Timing of all experimental components was verified with an oscilloscope (HM507, Hameg, Germany).

Procedure. Participants sat in an unlit and sound-attenuated room (WhisperRoom^{TM}) and rested their chin on a chinrest approximately 60 cm from a CRT monitor (Mitsubishi Diamond Pro 2070SB, Sydney, Australia). Before undertaking the main experiment, auditory threshold in noise and visual difference threshold were measured. In separate blocks for audition and vision, an adaptive 1-up-1down staircase approach was undertaken wherein auditory noise was initially delivered at 65 dB SPL and adjusted in steps of 0.5 dB SPL, while visual targets had an initial differential of 30 mcd with respect to a baseline of 200mcd and were adjusted in steps of 2 mcd. In the case of the auditory staircase, participants performed a two alternative forced choice (2AFC) task wherein they were asked to indicate whether a 10 ms beep had occurred leftward or rightward of fixation. Similarly, in the visual staircase they were asked in a 2AFC task to indicate whether the leftward or rightward LED (10 ms) had flashed. The locations of auditory and visual signals were the same during the staircase procedure and the main experiment. The staircases were continued for a total of 40 trials yielding a final split of approximately 50% of targets correctly discriminated. The final auditory noise and LED intensity differentials were set as parameters to be utilized in the main experiment. Once auditory and visual parameters were set, participants were asked to place their left and right index fingers on response keys situated immediately in front of them, parallel to their left and right shoulders, respectively. The Piezo Buzzer delivering the auditory cues and LEDs emitting the visual cues were placed at shoulder width and three centimeters further in depth from the response keys (see Figure S1). Participants were informed that a peri-threshold auditory, visual, or audiovisual cue would occasionally precede a tactile target stimulation they ought to respond to as quickly as possible by button press. In 80% of cued trials the cue was congruent with the tactile target (e.g., left hand cued correctly indicated target tactile stimulation on the left hand), while on the remaining 20% of cued trials the cue was incongruent (e.g., left hand cued and target tactile stimulation on the right hand). In addition, participants were informed that no-cue trials would also occur (10% of all trials). After responding to tactile stimulation by button press, a fixation point on the CRT monitor turned from red to green, indicating that the tactile response was registered and prompting the participants to answer a second question regarding the sensory nature of the cue; auditory, visual, audiovisual, or no cue. That is, on every trial the participant provided a speeded response to tactile stimulation, and a report regarding their subjective experience of the cue. The experiment was divided into 6 blocks, each block composed of 12 tactile stimulations preceded by no-cue (6 left and 6 right index finger), 16 audio congruent cues, 16 visual congruent cues, 16 audiovisual congruent cues, 4 audio incongruent cues, 4 visual incongruent cues, and 4 audiovisual incongruent cues. In total, each cue was repeated 96 times in the congruent condition, and 24 times in the incongruent condition. All trial types were randomized within-blocks and inter-trial interval lasted between 1.0 and 2.5 s (randomly sampled from a uniform distribution). Participants were allowed to take a short break between blocks, and before initiation of the main experiment, half a block of practice trials was administered. The entire duration of Experiment 1 was about 60 minutes.



	Cues spatio-temporally congruent 0 ms and 0 cm offset)	Cues temporally offset by 100 ms	Cues temporally offset by 300 ms	Cues spatially offset by 15 cm	Cues spatially offset by 45 cm
Experiment 1 & 2a	X				
Experiment 2b	X	X			
Experiment 2c	X		X		
Experiment 2d	X			X	
Experiment 2e	X				X

Figure 4.2. Experimental Paradigm and Design. Top panel illustrates the experimental paradigm that is common across all experiments (red highlight in bottom panel). Participants were given a valid (80% of trials, middle column top panel) or invalid (20% of trials, rightmost panel top panel), auditory (red), visual (blue), or audiovisual (both red and blue, as illustrated) cues as to the location of a subsequent tactile target (black) they had to respond to as fast as possible. Spatial cues were titrated before each experimental session in order to be at detection threshold. Bottom panel; in addition to the standard experimental paradigm, separate experiments varied the temporal (Experiments 2b and c) and spatial (Experiments 2d and e) relation between the auditory and visual cues. For the temporal manipulation, either the visual or auditory component of a multisensory cue was advanced in time by 100 ms (Experiment 2b) or 300 ms (Experiment

2c) in order to always allow the same 600 ms asynchrony between the offset of a cue and the onset of the tactile target (see top panel). For the spatial offset, the auditory component was moved laterally with respect to the visual component by either 15 cm (Experiment 2d) or by 30 cm (Experiment 2e). The visual component was not displaced in order to keep it within the field of view of participants gazing at a central fixation cross. Overall, the data show that temporal and spatial manipulations of the cues did not play a large role in spatial cueing (see Supplementary Results), and hence the main text presents the experimental findings common across Experiments 2a,b, c, d, and e.

Analysis. The cue in a given trial was defined as conscious if it was properly classified by the participant's subjective report (e.g. a 'visual' report following a visual cue, an 'audiovisual' report following an audiovisual cue), and as unconscious if it was missed (i.e., report of no sensory experience following auditory, visual, or audiovisual cues). Trials were excluded if the cue was misclassified (e.g., visual report following an audio cue). Partially conscious trials were defined as those in which AV stimuli were presented, but solely A or V was reported. Trials with incorrect tactile discrimination, or with reaction times faster than the 2.5th percentile or slower than the 97.5th percentile for a given participant and condition of conscious access were excluded (amounting to 1.6% and 5.4% of total trials, respectively). The remaining reaction times were analyzed with linear mixed effects models (lme4 and lmerTest packages: Bates et al., 2014, Kuznetsova et al., 2013), with the fixed effects being cue (visual, auditory, or audiovisual) and congruency (congruent or incongruent), and random intercepts for subjects. Random slopes for each fixed effect were included in the model, following model selection based on Bayesian information criterion (BIC). Significance of fixed effects was estimated using Satterthwaite's approximation for degrees of freedom of F statistics (Satterthwaite, 1946). Conditions of conscious access of cues (i.e., conscious, unconscious, or partially conscious) were analyzed separately. All behavioral analyses were performed with R (2016) with ggplot2 (Wickham, 2009) for graphical representations.

Experiment 2a

Participants. Six subjects (2 females, mean age = 22.5 ±3.1 years) took part in this experiment. One of the participants was an experimenter involved in the project (JPN). All participants self-reported normal hearing and touch, and had normal or corrected-to-normal visual acuity. Participants gave written informed consent to partake in the study, which was approved by Vanderbilt University Medical Center's ethics board.

Materials and Apparatus. Materials and apparatus were exactly as described in Experiment 1.

Procedure. The experimental procedure was the same as that in Experiment 1, with the following exceptions. Participants took part in 10 different 50-minute experimental sessions, and hence instead of completing 6 blocks, they completed 50 blocks (over 5000 trials per participant). A maximum of 2 experimental sessions were conducted per participant on the same day.

Analyses. The same analysis as in Experiment 1 was conducted. Excluded trials with incorrect tactile discrimination, or with reaction times outside the 2.5th and 97.5th percentile for a given participant and condition of conscious cue access amounted to 1.6% and 5.0% of total trials, respectively. Besides group-level statistics with linear mixed models, the significance of normalized congruency effects (i.e., mean reaction time in the congruent condition normalized by mean reaction time in the incongruent condition) for each cue and condition of conscious cue access were assessed at the individual level. To statistically test individual subject data, non-parametric permutation tests were used. Namely, 5000 surrogate congruency effects were generated by permuting congruency labels with no replacement, respecting the same number of trials as in the original data set. A normalized congruency effect was considered as significant at the individual level if it was smaller than the 2.5th percentile or bigger than the 97.5th percentile of the surrogate distribution.

Experiment 2b

Participants. Six subjects (3 females, mean age = 22.1 ±2.9 years) took part in this experiment. All participants self-reported normal hearing and touch, and had normal or corrected-to-normal visual acuity. Participants gave written informed consent to partake in the study, which was approved by Vanderbilt University Medical Center's ethics board.

Materials and Apparatus. Materials and apparatus were identical to those in Experiment 1 and 2a.

Procedure. The experimental procedure was identical to that in Experiment 2a, with the following exceptions. In order to test the temporal principle of multisensory integration, a delay was included between the auditory and visual components of audiovisual cues. That is, the task included audiovisual congruent and incongruent trials in which a temporal delay was included between the cues themselves (both audio-leading and visual-leading). These cue conditions were included in addition to those described above: auditory congruent and incongruent, visual congruent and incongruent, and audiovisual congruent and incongruent, and no-cue. Hence, each block consisted of the same repetitions as in Experiment 1 and 2a, in addition to 16 audio-leading congruent audiovisual cues, 16 visual-leading congruent audiovisual cues, 8 audio-leading incongruent audiovisual cues, and 8 visual-leading audiovisual cues. That is, each block consisted of a total of 120 trials, and participants completed a total of 50 blocks, for a grand total of 6000 trials per subject. In the case of asynchronous audiovisual cues, the auditory and visual components were offset by 100 ms, while always keeping the delay between the offset of the second cue and the target fixed at 600 ms (as in Experiment 1 and 2a).

Analyses. The same analysis as in Experiment 2a was conducted, with the factor delay as fixed and random effect in the linear mixed model. Excluded trials with incorrect tactile discrimination, or with reaction times beyond the 2.5th and 97.5th percentiles for a given participant and condition of conscious access amounted to 3.1% and 5.0% of total trials, respectively.

Experiment 2c

Participants. Six subjects (3 females, mean age = 19.9 ±3.4 years) took part in this experiment. All participants self-reported normal hearing and touch, and had normal or corrected-to-normal visual acuity. Participants gave written informed consent to partake in the study, which was approved by Vanderbilt University Medical Center's ethics board.

Materials and Apparatus. Materials and apparatus were identical to those in Experiment 1, 2a, and 2b.

Procedures. Procedures were identical to Experiment 2b, with the exception that the offset between delayed audiovisual cues was set to 300 ms, as opposed to 100 ms in Experiment 2b.

Analyses. The same analysis as in Experiment 3 was conducted. Excluded trials with incorrect tactile discrimination, or with reaction times shorter beyond the 2.5th percentile and 97.5th percentile for a given participant and condition of conscious access amounted to 1.4% and 5.0% of total trials, respectively.

Experiment 2d

Participants. Six subjects (4 females, mean age = 21.0 ±2.1 years) took part in this experiment. Two of the subjects were individuals involved in data-collection for the project but were naïve regarding the experimental hypotheses. All participants self-reported normal hearing and touch, and had normal or corrected-to-normal visual acuity. Participants gave written informed consent to partake in the study, which was approved by Vanderbilt University Medical Center's ethics board.

Materials and Apparatus. Materials and apparatus were identical to those in Experiment 2a, with the following exception. In order to test the spatial principle of multisensory integration, an additional two Piezo Buzzers (e.g., speakers) and LEDs were employed. The additional visual cues were equally placed 3 cm further in depth from the response keys, but 5 cm inward toward the midline in reference to the shoulders. Similarly, the additional auditory cues were placed at the same depth as all other cues, but 10 cm laterally from the participant's shoulders. The additional visual and auditory cues were not offset symmetrically in order to maintain the visual cue within the visual field of participants gazing at the fixation point, and maintain a clear disparity between cues delivering tactile stimulation to the left and right index fingers. Hence, in addition to including audiovisual congruent and incongruent cues, Experiment 5 included audiovisual congruent and incongruent cues that were spatially misaligned by 15 cm.

Procedure. Experimental procedures were identical to Experiment 2a, with the following exception. In addition to auditory congruent and incongruent, visual congruent and incongruent, audiovisual congruent and incongruent, and no-cue, Experiment 5 included auditory congruent and incongruent cues in which the further lateralized auditory cues were offset, visual congruent and incongruent cues in which the further medial visual cue was offset, and finally audiovisual congruent and incongruent cues in which the spatially incongruent cues were offset. That is, in addition to the repetitions present in Experiment 2a, each block in Experiment 5d included an additional 16 congruent and 4 incongruent (lateralized) auditory cues, 16 congruent and 4 incongruent (medial) visual cues, and 16 congruent and 4 incongruent spatially disparate audiovisual cues.

Analyses. The same analysis as in Experiment 2a was conducted, with the factor offset added as fixed and random effect in the linear mixed model. Excluded trials with incorrect tactile discrimination, or with reaction times beyond the 2.5th percentile and 97.5th percentile for a given participant and condition of conscious access amounted to 0.8% and 5.0% of total trials, respectively.

Experiment 2e

Participants. Five subjects (2 females, mean age = 19.8 ±3.7 years) took part in this experiment. All participants self-reported normal hearing and touch, and had normal or corrected-to-normal visual acuity. Participants gave written informed consent to partake in the study, which was approved by Vanderbilt University Medical Center's ethics board.

Materials and Apparatus. Materials and apparatus were identical to those in Experiment 2d, with exception that the additional auditory cue was placed 40 cm (vs. 10 cm in Experiment 2d) laterally from the participant's shoulders. Thus, in the case of spatially disparate audiovisual cues, the auditory and visual components were misaligned horizontally by 45 cm.

Procedure. Experimental procedure was identical to that in Experiment 2d.

Analyses. The same analysis as in Experiment 2d was conducted. Excluded trials with incorrect tactile discrimination, or with reaction times beyond the 2.5th percentile and 97.5th percentile for a given participant and condition of conscious access amounted to 1.8% and 5.0% of total trials, respectively.

Neural Network Modeling

Network Description. The network simulates a hypothetical subject exposed to an external visual, auditory, or audiovisual stimulus. In the case of audiovisual stimulation, auditory and visual stimuli are temporally and spatially coincident. In its general form, each neuron in the network receives a net input and responds to it via its intrinsic temporal dynamics (i.e., a low-pass first order dynamics) and a sigmoidal activation function. The net input activity is the sum of external network-based inputs as well as auto-excitatory inputs. The neuron's response generates an output activity, which represents the neuron's firing rate. Due to the sigmoidal activation function, each neuron's output is constrained between 0 (neuron's spontaneous activity) and 1 (neuron's maximal activation). Each simulated trial lasts sufficiently long (120 ms) for the network to exhaust its initial transient phase and reach a new steady-state condition.

The networks developed here encompass five neural areas (see Figure 1): a region representing the cochlea, area A representing a cortical auditory area, a region representing the retina, region V representing a cortical visual area, and finally region AV representing a cortical audiovisual multisensory area. For simplicity, each cortical area is simulated by a single neuron. Of course, here, each single neuron does not represent a single biological cell but an ensemble of cells sharing similar properties.. In the networks, the cochlea and the retina are intended just as a replica of the external input (i.e., they simulate the presence of a sensory auditory and visual stimulus respectively, applied for a given time interval) with the addition of a noise drawn randomly on each trial from a normal distribution. From these peripheral regions, the input is then propagated to cortical areas. The cochlea projects to area A with weight, W^{ac} while the retina projects to area V with weight W^{vr}. In turn, unisensory cortical areas project to the multisensory area with feedforward strengths W^{ma} and W^{mv}, respectively, in the case of audition and vision. Further, unisensory areas are reciprocally connected via inhibitory connections of strength I^{av} (from visual area to auditory area) *and* I^{va} (from auditory to visual area). Direct connections between unisensory areas are well established anatomically in biological systems (see Kayser et al., 2009 for review) and the mutual inhibitory pattern is routinely employed in computational models in order to instantiate competition between areas (Cisek, 2007; Seely & Chow, 2011). Further, these inhibitions contribute to prevent the formation of “phantom activation” (e.g., activation of area V under auditory stimulation alone) due to feedback connections. The multisensory area, in turn, depending on the particular model (see second row of Figure 1), may or may not send feedback connections in return to unisensory areas; to A with weight $B^{am}$and to V with weight B^{vm}. Lastly, in order to simulate the role of lateral synapses within each area, regions A, V, and AV receives excitatory self-connections with weight

L^a, L^v, L^m, respectively. See Figure 1 for network diagrams and Table S1 for the values of model parameters. It is important to note that an array of 625 different parameter values (parametrically varied) were used, indicating that the reported results are specific to network architectures and not the particular parameters we use.

Table 1. Parameter values.

Dynamics and sigmoidal activation function within nodes

$\Delta t = 0.1$ ms τ = 3 ms T = 120 ms

$\varphi_a = [8: 0.5: 10]$* $\varphi_v = [8: 0.5: 10]$* $\varphi_m = [5: 0.5: 7]$**

$\xi_a = 0.75$ $\xi_v = 0.75$ $\xi_m = 0.75$

External auditory and visual stimuli
(Mean μ and standard deviation δ of the Gaussian from which the random input was drawn)

$\mu = 10$ $\delta = 2.5$

Inter-area and lateral synapses

W^{ac} = 1 W^{vr} = 1

L^{a} = 1 L^{v} = 1 L^{m} = 1

W^{ma} = [8:0.5:10]*** W^{mv} = [8:0.5:10]***

I^{av} = 4 I^{va} = 4

B^{am} = [4:0.5:6]**** B^{vm} = [4:0.5:6]****

Consciousness decoding ("unique model")

$T_u = 0.2$ $T_m = 0.8$

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* Range utilized during different simulations. Central point of the sigmoidal activation function in area A and V were always yoked.

** Range of utilized values for the central point of the multisensory area's sigmoidal activation function.

*** Weight of feedforward projection from unisensory to multisensory areas was modulated in different simulations yet A and V projections were always the same.

**** Weight of feedback projections from the multisensory to unisensory areas was modulated in different simulations yet projection weights were always the same to both A and V areas.

Network Implementation and readout

"A priori models". All equations were implemented and numerically solved within the MATLAB (MathWorks Inc., Natick, USA) software environment using a simulation time step Δt = 0.1 ms. Simulations started at $t = 0$ from the resting condition (unperturbed network). Then, an external input, representing a visual and/or auditory stimulus, was applied after 20 ms of simulation (i.e., 200 time steps, hence onset of stimuls application is t_{on} = 20 ms) for a duration of 10 ms (100 time steps, as in all the behavioral Experiments, hence offset of stimulus application is t_{off} = 30 ms). Simulations terminated after 1200 iteration steps, corresponding to t_{end} =120 ms. This simulation length was utilized as it was largely sufficient for the network to exhaust its initial transient response and reach a new steady state in response to the stimulation.

The overall input (i.e., $u(t)$) to a generic neuron in the network is processed via functions governing first-order temporal dynamics $(Eq. 1)$ and sigmoidal activation $(Eq. 2)$, generating the neuron's output activity (i.e., $y(t)$):

$$\tau \frac{dq_s(t)}{dt} = -q_s(t) + u_s(t) \qquad (Eq. 1)$$

$$y_s(t) = F\big(q_s(t)\big) = \frac{1}{1 + \exp(-(q_s(t) - \varphi_s)\xi_s)} \qquad (Eq. 2)$$

where subscript *s* may assume value *a*, *v*, or *m* (auditory area A, visual area V or multisensory area AV). In Eq. 1 τ represents the internal time constant of the neuron (we assume the same time constant for all neurons), and ξ_s and φ_s are parameters which establish respectively the slope and the central position of the sigmoidal relationship (see Table S1 for parameter values). According to Eq.2, the output activity of each neuron is constrained between ~ 0 (i.e., neuron's spontaneous activity) and 1 (i.e., neuron's maximal activity).

The net input $u(t)$ that reaches a neuron may be generally written as the sum of three contributions: an external input $e(t)$ due to a stimulus being presented (auditory, visual, or audiovisual), a lateral input $l(t)$ mimicking lateral synapses, and network inputs coming from neurons in other areas via inter-area synapses (e.g., I^{av} and I^{va} in Equations 3 and 4, and W^{mv} and W^{ma} in Equation 5). Hence, given the network architecture and synaptic weighting, we can more precisely describe these relationships in the following equations (in this case for a network with no feedback connections):

$$u_a(t) = e_a(t) \cdot W^{ac} + y_a(t) \cdot L^a - y_v(t) \cdot I^{av} \qquad (Eq. 3)$$

$$u_v(t) = e_v(t) \cdot W^{vr} + y_v(t) \cdot L^v - y_a(t) \cdot I^{va} \qquad (Eq. 4)$$

$$u_m(t) = y_v(t) \cdot W^{mv} + y_a(t) \cdot W^{ma} + y_m(t) \cdot L^m \qquad (Eq. 5)$$

$e_a(t)$ and $e_v(t)$ in Eq. 3 and Eq. 4 represent the signals from the cochlea and the retina having the following expression:

$$e_s(t) = \begin{cases} 0, & 0 < t < t_{on} \\ E_s, & t_{on} \le t \le t_{off} \\ 0, & t_{off} < t < t_{end} \end{cases} \qquad (Eq. 6)$$

In Eq. 6, *s* holds for *a* and *v*. E_s is a constant value representing input strength drawn randomly on each trial from the normal distribution, $N(\mu, \delta)$ (of course in absence of an external auditory or visual stimulus, E_a or E_v are set to 0). Auditory and visual noise constants are drawn independently on each trial. Contrarily, in a network where both auditory and visual unisensory areas receive feedback, equations 3–5 above would take on the following form:

$$u_a(t) = e_a(t) \cdot W^{ac} + y_a(t) \cdot L^a - y_v(t) \cdot I^{av} + y_m(t) \cdot W^{am} \qquad (Eq. 7)$$

$$u_v(t) = e_v(t) \cdot W^{vr} + y_v(t) \cdot L^v - y_a(t) \cdot I^{va} + y_m(t) \cdot W^{vm} \qquad (Eq. 8)$$

$$u_m(t) = y_v(t) \cdot W^{mv} + y_a(t) \cdot W^{ma} + y_m(t) \cdot L^m \qquad (Eq. 9)$$

Four different models – supporting no consciousness, A-consciousness, V-consciousness and AV-consciousness - were implemented by keeping all parameters equal except for the feedback projections existing from area AV to unisensory areas. Each of these models was initialized with a set of 625 different parameters, parametrically manipulating the key variables φ_a and φ_v (slope of sigmoidal activation function in areas A and V, which were always kept the same), φ_m (slope of the sigmoidal activation function in area AV), W^{am} and W^{vm} (strength of feedforward projection from unisensory areas to the multisensory region, which were always kept the same), and B^{ma} and B^{mv} (strength of feedback projection from the multisensory area to unisensory areas, which were always kept the same; see Table 1 for details). For each of these instantiations, 100 trials were simulated with varying input levels according to the normal distribution, $N(\mu, \delta)$. For each trial, the area under the activation curve in the multisensory region was *a priori* considered to be proportional to reaction times. That is, area under the activation curve in the multisensory area was estimated via the trapezoidal method, and this area was multiplied by 10 (ms) and subtracted from a baseline reaction time of 300 ms. In other words, for a given trial, the area under the activation curve of the multisensory region was inversely proportional to the simulated reaction time and had a slope of 10 ms per unit. The 100 trials for a given parameter set were averaged, and subsequently a grand mean reaction time for all 625 parameter set was calculated for each model (i.e., models supporting no-consciousness, A-consciousness, V-consciousness, and AV-consciousness).

"Unique" Model. The separate "a priori" models described above most clearly illustrate cases in which, according to the GNW and LC theories, networks may be conscious of different perceptual elements (none, A, V, or AV). In addition, we implemented a single "unique" model capable of realizing all forms of consciousness. The "unique" model has feedback connections between all areas but requires an additional assumption to define what activation patterns are considered to be conscious and which are not. Here, inspired by neuroimaging studies (see Tong, 2003 for review), we assume that consciousness is extracted based on the peak activation level in both unisensory and multisensory areas. That is, an input is taken to evoke a conscious perceptual experience when it elicits a neural activation peak above a given threshold in both unisensory (T_u) and multisensory (T_m) areas (see Table 1 for details). When the peak activation in area AV surpasses T_M and peak activation in areas A and V surpass T_u, the stimulus is considered to be AV-conscious (all areas are supra-threshold for consciousness). If area AV surpasses T_M but one of the unisensory areas (e.g., area V) does not peak above the T_u threshold, the stimulus is considered to be perceived as audio alone. With the exception of the decoding of perceptual consciousness (i.e., no-consciousness, A-consciousness, V-consciousness, and AV-consciousness), implementation and readout in the "unique" model followed exactly as described for the "a priori" models.

Results

Neural Network Modeling

Results from the neural network simulations must be assessed qualitatively, as statistical significance in these networks is heavily influenced by the number of trials simulated within a parameter set (analogous to within-subjects trials in psychophysics), the number of parameter sets utilized (analogous to number of subjects in psychophysics), and the RT decoding scheme (differences between conditions may be accentuated or diminished by the arbitrary relation between neural activation and the reaction time output).

Regarding the separate “a priori” models, on average the simulated reaction time under a neural architecture with no feedback projections was 272.05 ms to audio input, 277.60 ms to visual input, and 256.25 ms to audio-visual input. Thus, multisensory facilitation, or the difference between the quickest unisensory condition and the multisensory condition, was on the order of 15.7 ms for a network with no feedback projects and hence in principle not capable of perceptual awareness according to the GNW and LC theories. When feedback projections were inserted between the multisensory area and a single unisensory area (either A or V), the average reaction time to AV stimuli was 243.8 ms, while the average reaction time to the quicker unisensory condition (usually A when feedback from AV to A was present, and V when feedback from AV to V was present) was 264.8 ms, and 274.7 ms for the slower unisensory condition (V when feedback was from AV to A, and A when feedback was from AV to V). Thus, multisensory facilitation of reaction time predicted by the model under partial awareness was on the order of 21 ms. Lastly, when the network was equipped with feedback projections from the multisensory area to both unisensory areas, the average reaction times were 261.3 ms for audio input, 268.1 ms for visual input, and 234.75 for audiovisual input. Hence, in the full multisensory consciousness condition, multisensory facilitation was on the order of 26.5 ms. To summarize, architectures with no multisensory feedback, partial feedback, or full feedback produced facilitated reaction times by 15.7, 21.0 and 26.5 ms, respectively.

A similar pattern of results emerges when considering the “unique” model in which perceptual awareness is decoded relative to an activation threshold (plotted in Figure 1, main text). The average reaction time when both components of an audiovisual stimulus were deemed to be consciously perceived was 193.2 ms. The quickest average unisensory reaction time that was fully perceived (A-consciousness when A was presented or V-consciousness when V was presented) was 238.8 ms, while the slower average was 248.0 ms. Thus, multisensory facilitation under full consciousness was on the order of 45.5 ms. When stimuli were not perceived, the average reaction times (i.e., proportional area under the activation curve in the multisensory area) were considerably slower (292.7 ms for audio stimuli, 291.8 ms for visual stimuli, and 282.6 ms for audiovisual stimuli) and multisensory facilitation was reduced to about 9 ms. Lastly, when the consciousness threshold was surpassed in the multisensory area and one of the unisensory areas (resulting in partial awareness when audiovisual stimuli were presented or full consciousness when a unisensory stimuli was given), the average reaction time to multisensory stimuli (yet experienced as unisensory) was 228.6 ms. The average reaction time to the quickest unisensory stimuli (i.e., the perceived one) was 243.4 ms, while it was 292.3 ms for the slower unisensory stimuli. Thus, under conditions of partial awareness, multisensory facilitation was on the order of 14.8 ms. In summary, whether building distinct neural models formalizing the relationship between consciousness and feedback postulated GNW and LC theories, or building a “unique” model in which both reaction times and consciousness are decoded, multisensory facilitation appears to be most prominent under full consciousness (26-45 ms), intermediate under partial consciousness (15-21 ms), and minimal when not perceived (9-15 ms).

Psychophysics

Experiment 1. A linear mixed effect analysis on reaction times in the conscious condition revealed a main effect of congruency (F(1, 16.47) = 20.15, $p < 0.001$), and an interaction between cue type (audio, visual, or audiovisual) and congruency (F(2, 2613.7) = 4.56, p = 0.01), revealing that audiovisual cues induced a bigger congruency effect (median of normalized congruency effect = 0.80 ±0.19; congruent RT divided by incongruent RT) than auditory cues (0.93 ±0.06, p = 0.003). The difference with visual cues did not reach significance (0.86 ±0.07, p = 0.08). The same analysis in the unconscious condition revealed a trend for an interaction between cue type and congruency (F(2, 2155) = 2.65, p = 0.07), suggesting that audiovisual cues induced a bigger congruency effect (median of normalized congruency effect = 0.90 ±0.09) than auditory (0.99 ± 0.06, p = 0.035) and visual cues (0.98 ±0.09, p = 0.038). No analysis with partially perceived AV stimuli (perceived as either A or V) was undertaken here due to the limited number of such trials.

Experiment 2A. A linear mixed effect analysis on reaction times in the conscious condition revealed a main effect of congruency (F(1, 5.0) = 7.97, p = 0.037), and an interaction between cue type (audio, visual, or audiovisual) and congruency (F(2, 9315.1) = 106.0, $p < 0.001$), revealing that audiovisual cues induced a bigger congruency effect (median of normalized congruency effect = 0.78 ±0.06) than auditory cues (0.90 ± 0.04, $p < 0.001$). The difference with visual cues did not reach significance

(0.80 ±0.09, p = 0.14). Single subject statistics revealed that audiovisual, auditory, and visual cues induced significant congruency effects in most or all participants 6/6, 4/6, and 6/6 subjects, respectively. The same analysis in the unconscious condition revealed a main effect of congruency (F(1, 5.0) = 6.96, p = 0.041), but no interaction between cue and congruency (F(2, 7125.8) = 1.39, p = 0.25), revealing that the different cues elicited equivalent congruency effects (audiovisual: 0.94 ±0.04; auditory: 0.99 ±0.04; visual: 0.97 ±0.03). Single subject statistics revealed that only a minority of participants showed significant congruency effects, 2/6, 1/6, and 1/6 subjects, respectively, for the audiovisual, auditory, and visual cues.

Experiment 2B. A linear mixed effect analysis on reaction times in the conscious condition revealed a main effect of congruency (F(1, 19.6) = 37.91, p < 0.001), a main effect of cue (F(1, 7134.8) = 16.19, p < 0.001), and a trend for an interaction between cue and congruency (F(2, 7440.0) = 2.91, p = 0.055). There was no main or interaction effect with the temporal delay factor (all F < 1). These results indicate that the median of normalized congruency effects changed according to the cue, but independently of the delay between the auditory and visual cues. Single subject statistics revealed that audiovisual, auditory, and visual cues induced significant congruency effects in 2/6, 1/6, and 3/6 subjects, respectively, when the delay was equal to zero. When a delay of 100 ms (either audio-leading or visual-leading) was imposed between the auditory and visual cues within multisensory presentations, 3/6 participants showed a congruency effect (e.g., equivalent to when no delay was present). The same analysis in the unconscious condition revealed a main effect of congruency (F(1, 4.9) = 9.32, p = 0.029), a main effect of cue (F(1, 10407.3) = 27.67, p < 0.001), and an interaction between cue and congruency (F(2, 10233.5) = 3.55, p = 0.028). As in the conscious condition, there was no main effect or interaction with the delay factor (p > 0.1). Single subject statistics revealed that audiovisual, auditory, and visual cues induced significant congruency effects in 2/6, 1/6, and 1/6 subjects when the delay was equal to zero.

Experiment 2C. A linear mixed effect analysis on reaction times in the conscious condition revealed a main effect of congruency (F(1, 5.0) = 16.20, p = 0.01), and an interaction between cue and congruency (F(2, 9910.6) = 3.17, p = 0.042). There was no main effect or interaction with the delay factor (all F < 1). These results indicate that the median of the normalized congruency effects changed according to the cue, but independently of the delay between the auditory and visual cues. Single subject statistics revealed that audiovisual, auditory, and visual cues, respectively, induced significant congruency effects in 5/6, 4/6, and 4/6 subjects when the delay was equal to zero. All 6 subjects showed a congruency effect when a delay of 300 ms was imposed between the auditory and visual cues. The same analysis in the unconscious condition revealed a main effect of cue (F(1, 9519.0) = 14.14, p < 0.001), and an interaction between delay and congruency (F(1, 10019.2) = 4.93, p = 0.026). Contrary to what we obtained in the conscious condition, the congruency effect was bigger when the auditory and visual cues were presented simultaneously (0.94 ± 0.05) vs. with a 300ms delay (0.99 ±0.04). Single subject statistics revealed that audiovisual, auditory, and visual cues, respectively, induced significant congruency effects in 2/6, 0/6, and 0/6 subjects when the delay was equal to zero. When a delay of 300 ms was imposed between the auditory and visual cues within multisensory presentations, 2/6 subjects showed a congruency effect.

Experiment 2D. A linear mixed effect analysis on reaction times in the conscious condition revealed a main effect of congruency (F(1, 4.6) = 34.44, p = 0.003), and a trend for an interaction between cue and congruency (F(2, 7641.6) = 2.62, p = 0.073). There was no main effect or interaction with the spatial offset factor (all p > 0.1). These results indicate that the median of the normalized congruency effects changed according to the cue, but independently of the spatial offset between the cues. Single subject statistics revealed that audiovisual, auditory, and visual cues induced significant congruency effects in 4/6, 3/6, and 4/6 subjects when the spatial offset was equal to zero. When the spatial offset between the auditory and visual cues within multisensory presentations was equal to 15 cm, 4/6 subjects showed a congruency effect. The same analysis in the unconscious condition revealed only a main effect of spatial offset (F(1, 12564.7) = 5.49, p = 0.019), indicating that the congruency between cues and targets had no effect at the group level. Single subject statistics revealed that auditory, visual, and audiovisual cues induced significant congruency effects in 0/6, 1/6, and 1/6 subjects when the spatial offset was equal to zero. When the spatial offset between the auditory and visual cues was equal to 15 cm, the same subject showed a congruency effect.

Experiment 2E. A linear mixed effect analysis on reaction times in the conscious condition revealed a main effect of congruency (F(1, 4.2) = 23.53, p = 0.007), and a an interaction between cue and congruency (F(2, 9466.1) = 4.65, p = 0.01). Contrary to what we found in Experiment 5, we also found a trend for an interaction between congruency and spatial offset (F(2, 10935.8) = 3.68, p = 0.055), and an interaction between cue and spatial offset (F(2, 10446.7) = 6.07, p = 0.002). Single subject statistics revealed that audiovisual, auditory, and visual cues, respectively, induced significant congruency effects in 3/5, 3/5, and 3/5 subjects when the spatial offset was equal to zero. Similarly, when the offset between the auditory and visual cues was set to 45 cm, 3/5 subjects showed a congruency effect. The same analysis in the unconscious condition revealed only a main effect of spatial offset (F(1, 9708.2) = 12.21, p < 0.001), a trend for an interaction between cue and congruency (F(2, 9113.8) = 2.31, p = 0.1), and an interaction between cue and spatial offset (F(1, 9768.0) = 4.87, p = 0.008). Single subject statistics revealed that audiovisual, auditory, and visual cues, respectively induced significant congruency effects in 1/5, 1/5, and 1/5 subjects when the offset was equal to zero. When the spatial offset between the auditory and visual cues within multisensory presentations was set to 45 cm, 2/5 subjects showed a congruency effect.

Summary of Experiments 2a–e

Overall Experiments 2a-e are consistent in demonstrating a significant cue-target congruency by cue modality interaction when cues were consciously perceived (present significantly in all experiments except for 2b where it was present as a strong trend at p = 0.055). A similar consistency was not present when cues were not consciously perceived, where solely Experiment 2b demonstrated a cue-target congruency by cue modality interaction. However, results from these experiments also raise an important caveat. While multisensory cues seemingly result in enhanced tactile target detection when the former are perceived (vs. partially perceived vs. not perceived, see main text), it remains unclear whether the nature of this effect is multisensory or cross-modal. That is, given that speeded responses were always to supra-threshold tactile target and not to the different cues, we could not determine whether multisensory effects were due to statistical facilitation or due to veritable integration. It is possible that the stronger congruency effects during perceived or partially perceived multisensory cue presentations vis-à-vis unconscious cues were due to cross-modal attentional or decisional processes and not multisensory integration. This possibility is bolstered by the observation that spatial and temporal manipulations (Experiments 2b-e) of the cues did not consistently alter the impact of cue modality on cue-target congruency as would be expected if the reported effect was driven by frank multisensory integration. The temporal alignment between multisensory cues interacted with other variables only in Experiment 2c and solely in the unconscious condition, while the spatial manipulation interacted with other variables only in Experiment 2e (full consciousness condition). Hence, we claim that distinctly from neural observations based on the GNW theory, at the behavioral level there is a graded relation between perceptual awareness and multisensory processing, yet the nature of the inter-dependence between multisensory *integration* and perceptual awareness remains unclear (see Baars, 2005, for theoretical predictions and Mudrik et al., 2014, for a review/opinion).

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CHAPTER V

LEVERAGING MULTISENSORY NEURONS AND CIRCUITS IN ASSESSING CONSCIOUSNESS THEORY

The contents of this chapter are adapted from a manuscript in preparation;
Noel, J.P., Ishizawa, Y., Patel, S., Brown, E., Eskandar, E., Wallace, M. (in prep). Leveraging Multisensory Neurons and Circuits in Assessing Consciousness Theory.

Abstract

Detailing the neural mechanisms enabling wakefulness and conscious experience is a central and unanswered question in systems neuroscience despite its paramount clinical implications in a host of disorders of consciousness. Departing from two of the frontrunner theories of consciousness, the information integration theory (IIT) and global neuronal workspace (GNW) theory, we generate a number of concrete neurophysiological predictions. According to the IIT and its "consciousness-meter" (phi, Φ), as an organism is rendered unconscious, it is neurons that integrate information (AND gates), as oppose to those that converge information (XOR gates), which ought to be most readily impacted. Conversely, when an organism is aware, neurons that integrate should exhibit properties of consciousness to a greater degree than neurons

that converge information. We test these predictions by recording single unit activity in primary somatosensory (S1) and ventral pre-motor (vPM) areas in non-human primates that are administered audio-tactile (AT), tactile (T), and audio (A) stimuli and are progressively anesthetized via propofol. Responding to either A or T stimulation is considered to be an index of an XOR gate, while being further driven by the co-occurrence of A and T (i.e., AT) stimulation than to each constituent alone (i.e., multisensory enhancement) is considered to index an AND gate. Contrarily to our predictions derived from the IIT, when animals are rendered unconscious a greater degree to convergent neurons (XOR gates) stop converging than integrative neurons (AND gates) stop integrating. Further, the neural complexity and noise correlations associated with convergent neurons more faithfully track the animals' consciousness state than that associated with integrative neurons. Hence, results so not support the IIT. On the other hand, according to the GNW theory, conscious percepts should result in sustained neural activity and in greater single trial co-activation of S1 and vPM than under unconscious conditions. Both these predictions are supported in the neurophysiological data, hence supporting the GNW theory. Taken together, here we characterize the basic properties of neurons in S1 and vPM during auditory, tactile, and audio-tactile stimulation (e.g., firing rate and fano factor), as well as network-level properties (e.g., noise correlation, complexity, and neural ignition), and leverage distinct classes of multisensory neurons (e.g., convergent vs. integrative) to falsify / support theories of consciousness.

Introduction

Understanding the neural architecture enabling arousal or wakefulness (i.e., level or state of consciousness) and conscious experience (i.e., content of consciousness) remains a central unanswered question in systems neuroscience despite its paramount clinical implications in coma, vegetative-state, minimal-consciousness, and general anesthesia (Laureys et al., 2004; Monti et al., 2010; Giacino et al., 2014). While in recent years a number of electrophysiologically derived measures of consciousness/awareness (used interchangeably) have been proposed (Owen et al., 2006, 2014, 2017; Casali et al., 2013), these by necessity have a greater engineering or practical than scientific flavor, as no neurobiological account of consciousness exists.

Lacking this mechanistic understanding theorists and researchers have departed from empirical observations and/or phenomenological axioms to derive consciousness theories. A majority of these theories share common features – while possessing their idiosyncrasies – as exemplified by arguably two of the most influential frameworks today: Dehaene and colleagues' Global Neuronal Workspace (GNW; Dehaene et al., 2006, 2018; Dehaene & Changeux, 2011) and Tononi and colleagues' Integrated Information Theory (IIT; Tononi, 2012; Tononi & Koch, 2015; Tononi et al., 2016; Oizumi et al., 2014).

The GNW posits that an external stimulus will evoke a conscious experience if the incoming neural information is widely distributed across distinct brain areas and networks – most prominently in the pre-frontal cortex – in a process denominated "Global Broadcasting" (Dehaene & Changeux, 2011). Rendering sensory information globally available results in a coherent neural assembly of sustained activity and is most readily indexed via "Neural Ignition", the non-linear process whereby unconscious states remain encapsulated within their specialized subsystem, yet conscious experiences are widely distributed (See van Vugt et al., 2018, for experimental evidence and Joglekar et al., 2018 for a recent computational treatise).

The IIT is similarly a systems-level theory of consciousness postulating that an intricate neural network subserves subjective experience (Tononi & Edelman, 1998;

Tononi, 2012). Distinctively from the GNW, nonetheless, this latter theory is arguably more focused on the architecture of the network itself, than the neural activity occuring within the network. In more detail, Tononi and colleagues have argued that each conscious experience is highly informative, as it represents a particular instance among a vast repertoire of potential experiences, as well as highly unified, or indecomposable into sub-experiences that are each independently perceived (Tononi & Koch, 2015, see Canales-Johnson et al., 2017 for a recent experimental approach inspired in this framework). In turn, the IIT specifies mathematically (Oizumi et al., 2014) that an organism may bear conscious experience if imbued with an information processing system that is both highly differentiated (i.e., lacking of statistical dependence, as in white noise) and integrated (i.e., strong statistical dependence resulting in a limited state-space, as in a simple tone). In other words, while both the GNW and IIT emphasize the role of complex and intertwined neural networks in engendering consciousness, the GNW leverages neural dynamics, while the IIT specifies that these networks ought to support information integration.

Unfortunately, the neurophysiological data directly probing these theories is limited, in particular the IIT given its computational overhead (Toker & Sommer, 2016, 2017). Indeed, while the IIT explicitly generates a metric of consciousness level, phi (Φ), computing this measure in biological systems is impossible due to its combinatorial search problem (but see Toker & Sommer, 2016, 2017, for interesting approaches circumventing current computing limitations).

Here, thus, in order to either support or falsify frontrunner theories of consciousness we propose simple neurophysiological benchmarks for consciousness as derived from the GNW and IIT, and test them empirically in single unit recordings in non-human primates. For the IIT to be a viable theory of consciousness, as organisms' transition from consciousness to unconsciousness, neurons capable of integration must be those most readily impacted (Prediction #1; see *Results* bellow). That is, following the IIT it may be argued that anesthetics functionally act on integration hubs – thus rendering the animal unconscious. Further, when organisms are conscious, neurons that integrative information ought to demonstrate properties of consciousness to a greater degree than neurons that do not integrative information (Prediction #2, see *Results* bellow). On the other hand, for the GNW to be a viable theory of consciousness, global broadcasting – at the single trial level – must be more readily present in conscious than unconscious states (Prediction #3).

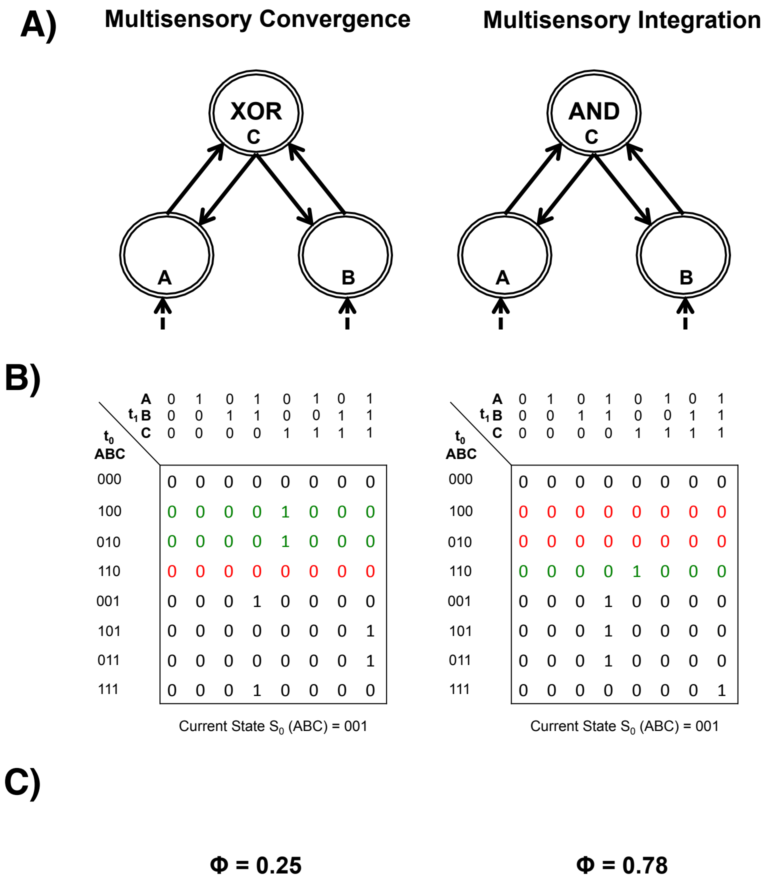
In order to probe these predictions we leverage the process of multisensory integration, where a clear neurophysiological definition of integration exists (Stein & Stanford, 2008; Murray & Wallace, 2012), and simultaneously record single units from the primary somatosensory cortex (S1) and ventral pre-motor cortex (vPM) of non-human primates as they are exposed to audio, tactile, or audio-tactile stimuli. The macaque monkeys were furthermore trained for a behavioral task designed to determine their trial-to-trial alertness during propofol-induced loss of consciousness (see Ishizawa et al., 2016).

First, we formalize the role of multisensory neurons that integrate (operationalized as responding to a greater degree to multisensory stimulation that to unisensory stimulation) vs. converge (operationalized as responding indiscriminately to multiple sensory modalities) within a network and in light of the IIT (see Hartline et al., 1978 for an early characterization of multisensory neurons as Boolean gates). The modeling work suggests that a simple 3-node network (e.g., unisensory audio, unisensory tactile, and multisensory audio-tactile) merging on an integrative neuron (i.e., “AND” gate) bears a greater degree of integrated information than one converging on an indiscriminant (i.e., “XOR” gate) neuron. Next, we categorize both the central (e.g., mean) and dispersion (e.g., variance) tendencies of multisensory responses in S1 and vPM, and bifurcate neurons as integrative or convergent. Subsequently, we characterize the outcome of these neurons (remaining integrative/convergent, or becoming either unisensory or non-responsive) as the animals lose consciousness (testing prediction #1) and the degree to which they exhibit neurophysiological indices of consciousness (Lempel-Ziv Complexity, Lempel & Ziv, 1976, and noise correlations, Ecker et al., 2014) is examined (testing prediction #2). Lastly, we examine single trial neural ignition as a function of consciousness (testing prediction #3). Results generally support the GNW theory but not the IIT.

Results

Formalizing the Role of Multisensory Integration in Consciousness

To formally ascertain the putative role multisensory integrative (vs. convergent) neurons within a network in bearing consciousness (according to the IIT), we built two biologically inspired simple neural networks (Figure 1A). These networks each have 3 nodes, two of which may be considered analogous to unisensory areas (nodes A and B) and a third (node C), which receives projections from the unisensory areas and may be considered analogous to a multisensory area. As is well established in biological systems, the multisensory area equally projected back to unisensory areas (Bizley et al., 2007; Cappe et al., 2009; see Ghazanfar & Schroeder, 2006, for review). The two networks were identical with exception that for one network (Figure 1A, left panel) node C was an “XOR” gate, while for the other it was an “AND” gate (Figure 1A, right panel). The XOR gate results in a logical “true” (or ‘1’/ ‘HIGH’) when the number of true inputs is odd. In this case, given the system architecture, the node C would be active if on the previous time step one and only one of gates A or B was active. Thus, node C can in principle be active following activity in either node A or B, but importantly does not respond preferentially when both are active. On the other hand, the other network, where node C is an "AND" gate, responds exclusively when on the precedent time-step both gates A and B were active. That is, this gate most faithfully mimics the behavior of integrative multisensory neurons that may or may not overtly respond indiscriminately to distinct sensory inputs, but importantly are most driven by spatio-temporally coincident multisensory inputs. Hence, the network formed with an XOR gate (Figure 1A, left) instantiates a network with neurons that are indiscriminant to the nature of sensory input, while in contrast the network formed with an AND gate (Figure 1A, right) instantiates a network with neurons that integrate sensory information, i.e., responds non-linearly to the addition of sensory stimuli from distinct modalities (Stein & Stanford, 2008; Murray & Wallace, 2012). The architecture of these systems dictates the composition of transition probability matrices (TPMs), which guides transitions between states (i.e., neurons that are 'active' at different time-points). In Figure 1B these TPMs have been depicted (left and right respectively for the multisensory convergent and multisensory integrative systems) and highlighted for their distinctive features. Namely, in the case of the convergent network, when ABC nodes are in state 100 (respectively, A, B, and C) or 010 (green rows), activation of the multisensory node will follow. This is not true if the convergent network is in state 110 (red row). The opposite is true for the network that integrates. Given these TPMs, Φ can be calculated when the state of the network is ABC = 001 (multisensory node active; see *Methods* section for details). Results indicate that in fact a network with a node with integrative capacity in principle may bear a greater degree of consciousness (Φ = 0.78) than one that simply responds indiscriminately to stimuli from distinct sensory modalities (Φ = 0.25).



A	0	1	0	1	0	1	0	1
t_1 B	0	0	1	1	0	0	1	1
C	0	0	0	0	1	1	1	1
t_0 ABC								
000	0	0	0	0	0	0	0	0
100	0	0	0	0	1	0	0	0
010	0	0	0	0	1	0	0	0
110	0	0	0	0	0	0	0	0
001	0	0	0	1	0	0	0	0
101	0	0	0	0	0	0	0	1
011	0	0	0	0	0	0	0	1
111	0	0	0	1	0	0	0	0

Current State S_0 (ABC) = 001

A	0	1	0	1	0	1	0	1
t_1 B	0	0	1	1	0	0	1	1
C	0	0	0	0	1	1	1	1
t_0 ABC								
000	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0
010	0	0	0	0	0	0	0	0
110	0	0	0	0	1	0	0	0
001	0	0	0	1	0	0	0	0
101	0	0	0	1	0	0	0	0
011	0	0	0	1	0	0	0	0
111	0	0	0	0	0	0	0	1

Current State S_0 (ABC) = 001

Figure 5.1. Formalizing the role of multisensory integrative neurons in bearing consciousness according to IIT. A) Depiction of a multisensory convergent (left) and integrative (right) network. There is no connection between A and B nodes, as these transition probability values are zero. The dashed connections leading to A and B are to illustrate that these putative unisensory areas receive input from downstream neural areas, yet they play no role in the ITT-driven model. **B)** The transition probability matrices (TPM) for a deterministic (e.g., probability is either 0 or 1) convergent (left) and integrative (right) network are illustrated. State t is represented in the abscissa and t+1 on the ordinate. Green and red rows are highlighted to emphasize key difference

between the convergent and integrative networks, yet these differences are not exhaustive (however do dictate the rest of differences). **C)** The Φ value associated with the convergent (left) and integrative (right) TMPs as determined in *PyPhi* (Mayner et al., 2017).

Multisensory Neurons in S1 and vPM

Given the IIT-driven modeling results suggesting that a network amalgamating on an integrative (vs. convergent) neuron ought to bear a greater degree to consciousness, here we first describe the single-unit multisensory properties of neurons recorded in S1 and vPM, and subsequently bifurcate these (within S1, see detail below) as either convergent or integrative. These latter pools of neurons are then examined for the postulate that integrative neurons ought to be further impacted (e.g., stop integrating) when animals are rendered unconscious (prediction #1) and most readily exhibit properties of consciousness when the animal is conscious (prediction #2).

The data is a subset of a previously published dataset (Ishizawa et al., 2016) and comprised 293 neurons in S1 (228 from Monkey E and 65 from Monkey H) and 140 neurons in vPM (87 from Monkey E and 53 from Monkey H) recorded across 26 sessions (16 in Monkey E and 10 in Monkey H), as the animals were presented with either audiotactile (AT), tactile (T), auditory (A), or no (N) stimuli. The monkeys performed a behavioral task wherein they were asked to press a button and hold the response for 3 seconds after sensory stimulation. Concurrently, animals were progressively anesthetized with propofol, at a rate a priori determined to induce a loss of consciousness within approximately 10 minutes (see Ishizawa et al., 2016, and Methods). Thus, given the pattern of behavioral responses we can bifurcate trials into either aware or unaware states (see Methods), and probe the predictions derived from IIT (predictions #1 & #2) and GNW theory (predictions #3).

In order to examine the fate of convergent and integrative neurons as animals become unconscious, we first bin neurons into these categories, and hence we initially describe the fundamental properties (i.e., firing rate and fano factor) associated with neurons in S1 and vPM as a consequence of AT, T, A, and N stimulation, as well as state of awareness. Regarding the firing rate, analyses on non baseline-corrected activity indicated a clear generalized decrease in firing rate when monkeys were rendered unconscious ($p<0.01$ at all time points; Aware; M = 4.43 spikes/s, S.E.M = 0.008 spikes/s; Unaware; M = 2.44 spikes/s, S.E.M = 0.007), a significant difference in spiking activity across the areas recorded between 50ms and 160ms post-stimuli onset ($p<0.01$, S1, M = 5.68 spikes/s, S.E.M = 0.008 spikes/s; vPM, M = 4.88 spikes/s, S.E.M = 0.006 spikes/s), and a significant main effect of stimulation type (i.e., AT, T, A, N) between 50ms and 480ms post-stimuli onset (AT, M = 4.14 spikes/s, S.E.M = 0.01 spikes/s; T, M = 4.31 spikes/s, S.E.M = 0.01 spikes/s; A, M = 3.75 spikes/s, S.E.M = 0.006 spikes/s; N, M = 3.28 spikes/s, S.E.M = 0.001 spikes/s). Importantly, a stimulation-type by area recorded (i.e., S1 vs. vPM) interaction was also evident ($p<0.01$, between 60ms and 210ms post-stimuli onset), driven by the fact that vPM responded to A stimulation (M = 3.21 spikes/s, S.E.M = 0.10 spikes/s), while S1 did not (M = 2.18 spikes/s, S.E.M = 0.10 spikes/s). Thus, in sum, as expected, these analyses demonstrated that propofol silenced spiking activity generally, that neurons in S1 and vPM responded differently to distinct sensory stimuli between 50 and 480ms post-stimuli onset, and that vPM but not S1 responded to auditory stimulation. The baseline-corrected analyses (depicted in Figure 2, rows 1 and 3) largely demonstrated analogous results, while indicating that the bifurcation in evoked responses (as opposed to baseline responses, as indicated above) between states of consciousness occurred (regardless of sensory modality) 80 ms post-stimuli onset ($p<0.01$, averaged across 80-1000ms post-stimuli onset; Aware, M = 0.48 spikes/s, S.E.M = 0.04; Unaware, M = 0.09 spikes/s, S.E.M = 0.01 spikes/s) and also highlighting a consciousness state by sensory modality ($p<0.01$ between 40-110ms, and 200-380ms) as well as 3-way (modality, state, and area) interaction ($p<0.01$, 410-610ms post-stimuli onset). The time-periods demonstrating a significant difference in evoked activity as a function of state of consciousness are shaded in gray in Figure 2 separated by area recorded and sensory stimulation, while the time-periods demonstrating a significant response vis-à-vis baseline are indicated by horizontal lines in each panel (see Figure 2).

Regarding fano factors (FFs), results demonstrated heightened variability under unaware (M = 1.45, S.E.M = 7.3e-4) than aware (M = 1.16, S.E.M = 5.6e-4) conditions (see Ecker et al., 2014 for a similar result), while both of these were significantly greater than 1 (unaware, $p < 4.76e-92$; aware, $p = 4.76e-92$), and hence likely exhibiting inter-trial variability above and beyond what is presumed to be attributable intrinsically to neurons (i.e., FF = 1). Similarly, FFs were larger in S1 (M = 1.32, S.E.M = 6.91e-4) than vPM (M = 1.22, S.E.M = 5.70e-4), throughout the post-stimuli period ($p<0.01$, for exemption of the period between 80ms and 120ms post-stimuli onset. The period between 50ms and 270ms post-stimuli onset demonstrated a significant difference in FFs as a function of stimulus modality ($p<0.01$), with the AT (M = 1.29, S.E.M = 0.02) and T (M = 1.28, S.E.M = 0.03) conditions being the less variable (AT vs. T, $p = 0.58$) than the A (M = 1.31, S.E.M = 0.02) and N (M = 1.33, S.E.M = 0.02) conditions (T vs. A, $t = 2.03$, $p = 0.041$; A vs. N, $p = 0.43$). Importantly, FFs also demonstrated a consciousness state by recording area interaction ($p<0.01$, between 200ms and 320ms post-stimuli onset) and a recording area by stimulus modality interaction ($p<0.01$, between 50ms and 180ms post-stimuli onset). The latter interaction was driven by a main effect of stimuli modality that was sustained in S1 ($p<0.01$, between 50ms and 250ms, as well as 350ms and 540ms post-stimuli onset) and only transient in vPM ($p<0.01$, between 110 and 140ms post-stimuli onset), while the former is attributable to a rapprochement in FF between consciousness states in S1 and not in vPM. Indeed, this last effect is further appreciable when correcting FFs for baseline (Figure 2) as a further quenching in variability in S1 (vs. vPM) specifically to AT and T sensory stimulation (contrasts between aware and unaware conditions; S1; AT, $p<0.01$ between 160ms-

200ms, T, p<0.01 between 180ms-220ms, never for A and N; vPM, never). As for firing rates, the time-periods demonstrating a significant difference in FF as a function of state of consciousness are shaded in gray in Figure 2 separated by area of recording and sensory stimulation type. Time-periods demonstrating a significant quenching in FF vis-à-vis baseline are indicated by horizontal lines in each panel (see Figure 2).

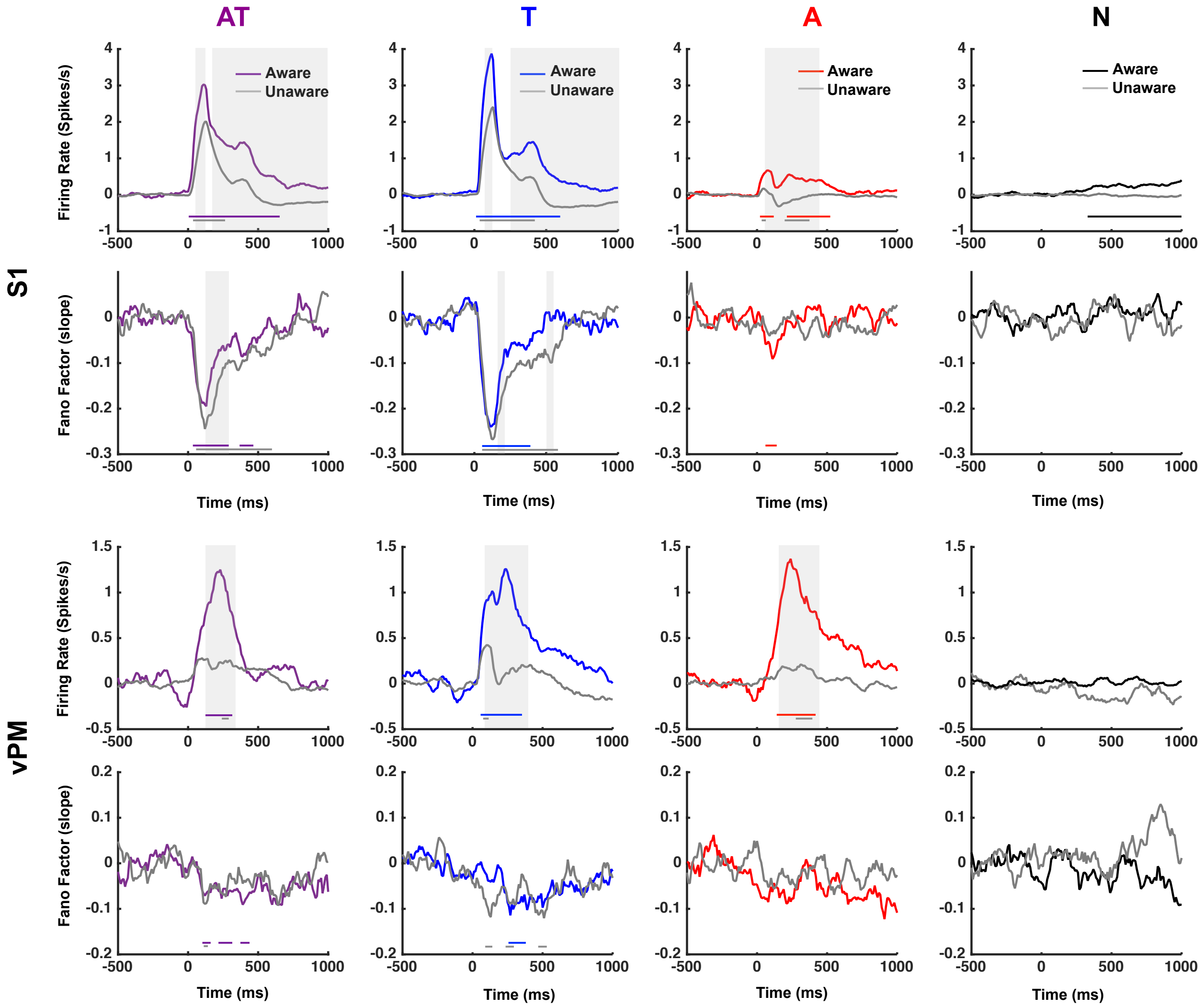


Figure 5.2. Time-resolved firing rates and Fano Factors in S1 and vPM as a function of state of consciousness. Presentation of audiotactile (AT; purple) and tactile (T; blue) stimuli evoked a reliable response in S1, while additionally the presentation of auditory (A; red) stimuli evoked a reliable response in vPM but not S1. Catch trials (N; black) did not evoked an increase in neural responses vis-à-vis baseline firing rate (0 on y-axis). Fano Factors were generally larger under states of unawareness than awareness (not depicted) and interestingly stimuli onset (0 on x-axis) quenched

variability in S1 (particularly onset of AT and T stimuli) but less so (and not differently between states of consciousness) in vPM. The time-periods demonstrating a significant difference in evoked activity/FF as a function of state of consciousness (aware = colored, unaware = gray) are shaded in gray, while periods demonstrating a significant response vis-à-vis baseline are indicated by horizontal lines in each panel.

Taken together, firing rates demonstrate 1) a reliable response to stimuli onset until approximately 500ms post-stimuli, and 2) a reduction in spikes per second when monkeys were rendered unconscious, both with regard to spontaneous (i.e., baseline) and evoked activity. Further, as expected vPM but not S1 generally responded to auditory stimulation. Regarding inter-trial variability, as it has been previously reported (Ecker et al., 2014) FFs were larger in an unconscious state (1.45 here, 2.2 in Ecker et al., 2014) than a conscious one (1.16 here, 1.2 in Ecker et al., 2014). This pattern fits nicely with the notion that conscious neural representations are more reproducible than unconscious ones (Schurger et al., 2010). Interestingly, nonetheless, the quenching of this variability as a function of stimulus onset (Churchland et al., 2010) followed an opposite pattern; inter-trial variability was further reduced during stimuli presentation in unconscious than conscious states. Furthermore, the tightening of the temporal code across trials (i.e., timing of spikes becoming more precise) was not as clearly appreciable in vPM as it was in S1. These observations are important and novel, as previous work exposing the widespread reduction in FFs during stimuli onset across the cortical mantle (e.g., V1, V4, MT, LIP, dPM, etc.; vPM not tested) and consciousness states (aware and unaware) did so across different dataset (Churchland et al., 2010). Here, as S1 and vPM were recorded simultaneously, and conscious and unconscious states during the same session, we can directly contrast these conditions and observe the further reduction in FF during unconscious conditions in S1 selectively. Moreover, this observation negates the possibility that firing rates and FFs are directly yoked (see Ecker et al., 2014, for a similar argument) – i.e., AT evoked activity is greatest when the animals were conscious, but AT FF evoked quenching was greatest unconsciously - and emphasizes the need to examine both central and dispersion tendencies in neural populations.

Following the observation that neural responses due to stimuli presentation were most notoriously present during the half-second – 50ms to 480ms, more precisely (see above) – immediately following stimuli onset, to characterize the multisensory properties of the neurons recorded we performed a spike count between 0 and 500 ms post stimuli onset (see also Ghose et al., 2014 for a similar approach). Within the multisensory framework, a neuron is said to integrate sensory information if it responds to multisensory stimulation more vigorously than to 1) the sum its unisensory constituents (supra-additivity index > 1; Murray & Wallace, 2012; Ghose et al., 2014) or 2) the maximum of its unisensory constituents (enhancement index > 1; Murray & Wallace, 2012; Ghose et al., 2014). Here we report both indices for completeness, but in the following label neurons demonstrating an enhancement index > 1 as integrative since previous reports (and the current dataset) have indicated that supra-additivity is rare in cortex (e.g., Bizley et al., 2007; Sugihara et al., 2006), while in contrast covert multisensory modulations (i.e., the sub-threshold modulation by part of a sensory modality on a supra-threshold response to another modality) are more commonplace (and increasingly appreciated as central in the process of multisensory integration; Ghazanfar and Schroeder, 2006).

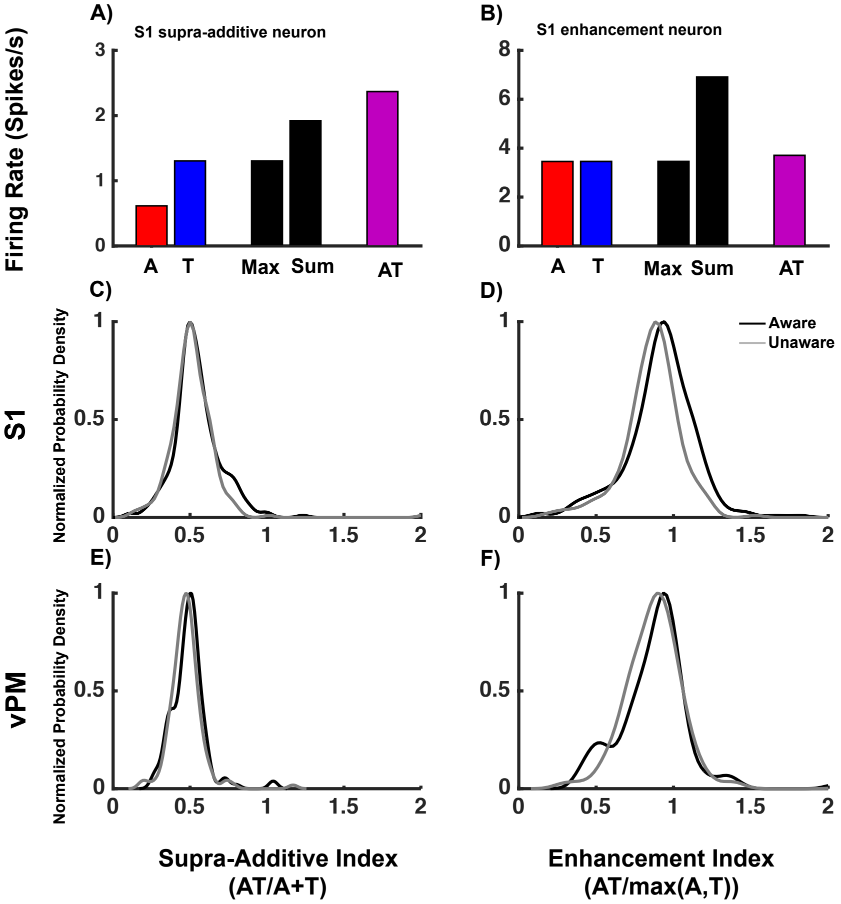


Figure 5.3. Characterizing multisensory neurons. A neuron whose multisensory response is greater than the sum of unisensory responses is said to be supra-additive (see A), while if it's greater than the greatest unisensory response it's considered to demonstrate multisensory enhancement (see B). A and B illustrate firing rates above a spontaneous rate (baseline-correction from -500 to 0ms; y-axis = 0). The distribution of supra-additive indices (left column) and enhancement indices (see Methods for detail) were normally distributed both in S1 (C and D) and vPM (E and F), regardless of whether the animals were aware (black) or unaware (gray).

From the 293 single units recorded in S1, when the animals were aware 2 had a supra-additive index above 1 (supra-additivity index = 1.23 and 1.01, former depicted in Figure 3a), while another 2 (different neurons) had supra-additive responses when the monkeys were rendered unconscious (supra-additivity index = 2.01 and 1.01). Thus, supra-additivity is seemingly rare in S1. On the other hand, 100 neurons had enhancement indices above 1 when the animals were conscious (see Figure 3b, for example), a number that was reduced to 55 when monkeys were rendered unconscious (25 of which indicating an enhancement index greater than 1 in both aware and unaware states). Regarding vPM neurons, of the 140 neurons recorded, when the animals were aware 2 had a supra-additive index above 1 (supra-additivity index = 1.03 and 1.04), while only a single neuron was supra-additive when the animals were unconscious (supra-additivity index = 1.16, distinct neurons in aware and unaware cases). Twenty-nine vPM neurons had enhancement indices above 1 when animals were aware, a number that remained stable at 29 when monkeys were unconscious (2 out of the 29 neurons were the same in aware and unaware states). Hence, multisensory supra-additivity appears equally infrequent in S1 as in vPM, and interestingly there are seemingly more neurons demonstrating multisensory enhancement in S1 than vPM when animals were conscious (S1 = 34%, vPM = 20%) yet approximately equal proportions when the animals are unconscious (S1 = 18%, vPM = 20%). To the best of our knowledge, this is the first simultaneous categorization of supra-additive and enhancement indices in both S1 and vPM, as well as their first characterization as a function of awareness. The large number of S1 neurons exhibiting multisensory enhancement is somewhat surprising, yet not entirely unexpected as this region is known to be the primary sensory area receiving the most non-matched cross-modal inputs from thalamus (Henschke et al., 2015; in fact more than doubling the next, V1) and somatosensation is developmentally the first sense to interact with others (Wallace et al., 2006).

Remarkably, as illustrated in Figure 3 (c-f) the distributions of supra-additive and enhancement indices are seemingly Gaussian, both when monkeys were aware (chi-square goodness-of-fit test, $p = 0.28$ and $p = 0.24$, respectively) and unaware ($p = 0.70$, and $p = 0.90$, respectively; see Bizley et al., 2007 for a similar observation). Thus, in addition to quantifying the frequency with which neurons are supra-additive or demonstrate multisensory enhancement, we can equally estimate the mean supra-additivity and enhancement indices associated with each neural population and consciousness state (see for example Olcese et al., 2013, for an indication that frequency of multisensory neurons and degree to which integration occurs may be dissociated). A 2 (recording area; S1 vs. vPM) x 2 (consciousness state; aware vs. unaware) independent samples ANOVA on supra-additive indices (Figure 3c and e) revealed main effects both of consciousness state ($p = 0.015$) and recording area ($p < 0.01$), where supra-additivity indices were larger under aware (M = 0.52, S.E.M = 0.006) than unaware (M = 0.50, S.E.M = 0.007) states, and surprisingly, larger in S1 (M = 0.52, S.E.M = 0.006) than vPM (M = 0.48, S.E.M = 0.006). There was no interaction between these variables ($p = 0.47$). On the other hand, a similar analysis with regard to enhancement indices suggested no distinction between consciousness states ($p = 0.11$) or recording areas ($p = 0.30$), nor an interaction between these variables ($p = 0.09$). These results, therefore, highlight that the frequency and degree of multisensory integration may be dissociated (e.g., Olcese et al., 2013) and that supra-additive – where both unisensory responses are considered – and enhancement indices – where solely the maximal unisensory response is compared to the multisensory response – may paint vastly different pictures. Further, the findings indicate a vastly heterogeneous population. Taking the example of the enhancement index (from where a representative multisensory integrative pool may be drawn, N = 100 in S1 and 29 in vPM), this metric indicates no overall change in the amount of integration at a population-level and across states of consciousness, yet examination of the particular neurons classified as integrating information reveals a drastic re-shuffling; from 100 to 55 neurons in S1, only 25 of which were classified as integrating information both in aware and unaware states.

Fortunately within the current context aiming at examining theories of consciousness (e.g., IIT) we can leverage this variability to examine the outcome of neurons labeled as either integrative or convergent as monkeys transition across states of consciousness. Figure 4 depicts this non-mutually exclusive compartmentalization (e.g., integration vs. convergence) during consciousness. In more detail, within the time frame from 0ms to 1000ms post-stimuli onset, a neuron that on average (i.e., across trials) responded to both unisensory auditory and tactile information beyond its spontaneous count (-500ms to 0ms) plus 2 standard deviations for at least 10ms was defined as convergent. On the other hand, a neuron was considered to integrate information when it most readily was driven by the simultaneous presence of A and T information than to these sensory stimuli presented in isolation. That is, neurons with an enhancement index greater than 1 were considered to integrate information. Importantly, these definitions are not the same as those employed by a large array of multisensory studies (Murray & Wallace, 2012, but see Hartline et al., 1978), which would likely require "integrative" neurons to equally respond to unisensory stimulation, but best fit the definitions of "XOR" and "AND" gates, and hence are best positioned to probe the IIT. Further, we employed slightly different categorization techniques in Figures 3 and 4 (Figure 3; spike count within the pre-determined window from 0ms to 500ms post-stimuli onset; Figure 4; convolved spike-count exceeding baseline + 2 standard deviations for at least 50ms unrestricted between 0ms and 1000ms) to both mimic prior literature and classical descriptions (Figure 3), but also allow for neuron specific idiosyncrasies (Figure

4). As illustrated in Figure 4, under these definitions and a conscious state, 43% of neurons in S1 converge audio and tactile information, while 44% do so in vPM. In turn, 52% of neurons in S1 integrate auditory and tactile information, i.e., respond to AT + (AT> A+T) and/or respond to AT+(AT> max (A, T), while 33% do so in vPM. Now, importantly, in order to examine how this categorization is changed when animals are rendered unconscious (Prediction #1) and quantify to which extent they exhibit properties of consciousness (Prediction #2), we create mutually exclusive groups. Neurons that respond indiscriminately to sensory stimulation are classified as convergent (as above), but differently only those that exhibit multisensory enhancement without being considered convergent are taken to integrate information. Thus, from the categorization in Figure 4 we discard convergent neurons from the integrative population. This is important from a statistical perspective (in order not to create groups that are partially overlapping and overlapping to different extents across states of consciousness and recordings areas), yet given the initial number of neurons in S1 and vPM, this bifurcation yielded a sufficient number of neurons exclusively categorized as convergent (N = 125) and integrative (N = 64) in S1, but not in vPM (convergent, N = 61; integrative, N = 8) – thus, for the rest of analyses specifically probing the difference between convergent and integrative neurons (Predictions #1 and #2), analyses are restricted to the S1 population.

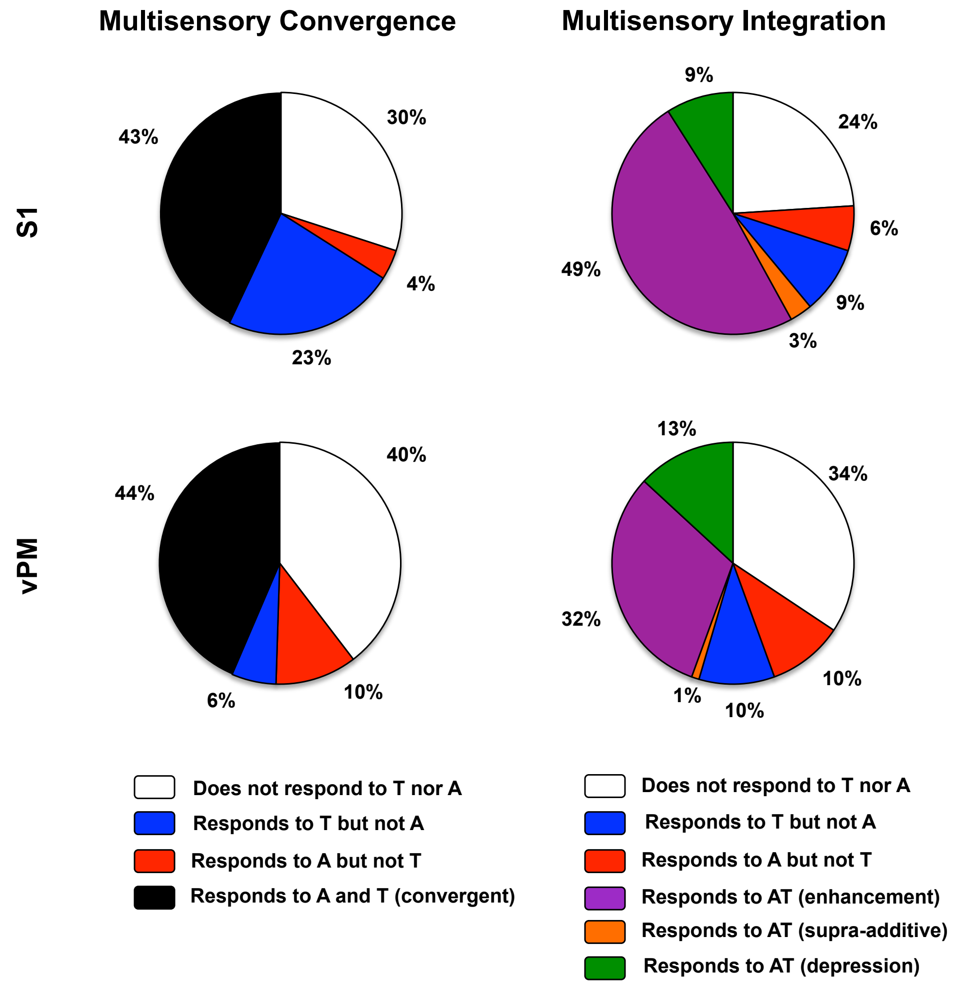


Figure 5.4. Non-mutually exclusive classification of neurons in S1 (top row) and vPM (bottom row) as convergent, integrative, unisensory, or non-responsive. Left column; Neurons whose convolved firing rate excited their spontaneous rate plus 2 standard deviations for at least 10ms between 0ms and 1000ms post-stimuli onset were responsive. If they responded to both tactile (T) and auditory (A) stimulation, they were considered convergent (black). On the other hand, if they responded solely to T or A stimulation, they were respectively labeled as tactile (blue) and auditory (red). Right column; Differently from the case of convergence, in order to characterize a neuron as integrative, their response profile to audio-tactile (AT) stimulation had to be examined.

First, neurons were classified as responsive or not (white; as above). Next, if the neuron was responsive to AT stimulation (defined as above) we queried whether during some epoch between 0ms and 1000ms post-stimuli onset their firing rate to AT stimulation was greater than the sum of A and T firing rates (supra-additivity; orange) or the maximum of A and T firing rates (enhancement; purple). Lastly, if a neuron was responsive to AT stimulation but responded less to AT than to unisensory stimulation, the neuron was classified as demonstrating multisensory depression (green). Lastly, if they neuron did not respond to AT or A stimulation, but did to T, it was labeled as tactile (blue), while if a neuron did not respond to AT or T, but did to A, it was labeled as auditory (red).

A first neurophysiological prediction that may be derived from the IIT, and the fact that it specifies that a network amalgamating on an integrative neuron should bear a greater degree of consciousness than one amalgamating on a convergent one (see Results above), is that as an organism is rendered unconscious, it is the integrative neurons that are most readily impacted. That is, putatively the anesthetic hinders information integration, which degrades conscious-level. In turn here we examined what occurred to integrative and convergent neurons in S1, as the animal was rendered unconscious. As illustrated in Figure 5a, while a significant portion of neurons labeled as convergent when the monkey was conscious became responsive exclusively to touch (42.1%), some were rendered non-responsive (24.1%), a small minority became responsive exclusively to auditory stimulation (2.5%), and 31.0% remained as responsive to both auditory and tactile stimulation. On the other hand, of those neurons labeled as integrative when the animal was conscious, 18.6% became exclusively responsive to tactile stimulation, 2.2% exclusively responsive to auditory stimulation, 16.3% unresponsive, and 62.9% remained as integrating audiotactile information. A Chi-squared test demonstrated that these proportions (62.9% remaining as integrative but only 31.0% remaining as convergent) were significantly different from one another ($p = 0.001$). Thus, contrarily to the prediction derived from IIT seemingly convergent neurons were most impacted by monkeys becoming unaware. It must be noted that this occurred notwithstanding the fact that arguably the threshold for being classified as “integrative” (i.e., responding to AT stimuli beyond their spontaneous and responding to AT stimuli beyond the maximal unisensory response) was more stringent than the bar required to pass in order to classify as “convergent” (i.e., responding to A and T stimuli beyond their spontaneous firing rate).

Further we examined whether the putative resistance to becoming either responsive solely to unisensory stimulation (T or A) or entirely non-responsive as monkeys loss consciousness scaled with the degree to which neurons may be considered to be integrative. While supra-additivity or multisensory enhancement are considered to be the hallmark of multisensory integration, neurons that respond less vigorously to multisensory stimuli than to the maximal unisensory response are considered to exhibit multisensory depression (Murray & Wallace, 2012), and have been shown to play an important role within the process of multisensory integration (Kadunce et al., 1997). Thus, here we examined whether neurons exhibiting multisensory enhancement or depression would be most resistant to the loss of consciousness. As illustrated in Figure 5b, while 56.4% of neurons exhibiting multisensory enhancement during consciousness did so as well during unconsciousness, only 36.8% of neurons that were categorized as exhibiting multisensory depression remained in that category during unawareness. These proportions were significantly different what is expected under the null distribution ($p = 0.04$). In sum, therefore, not only are integrative neurons not most readily impacted during the loss of consciousness, but in fact seemingly the more a neuron is driven by concomitant inputs above and beyond it is driven by sensory stimulation in isolation, the more it retains it's category during unconsciousness.

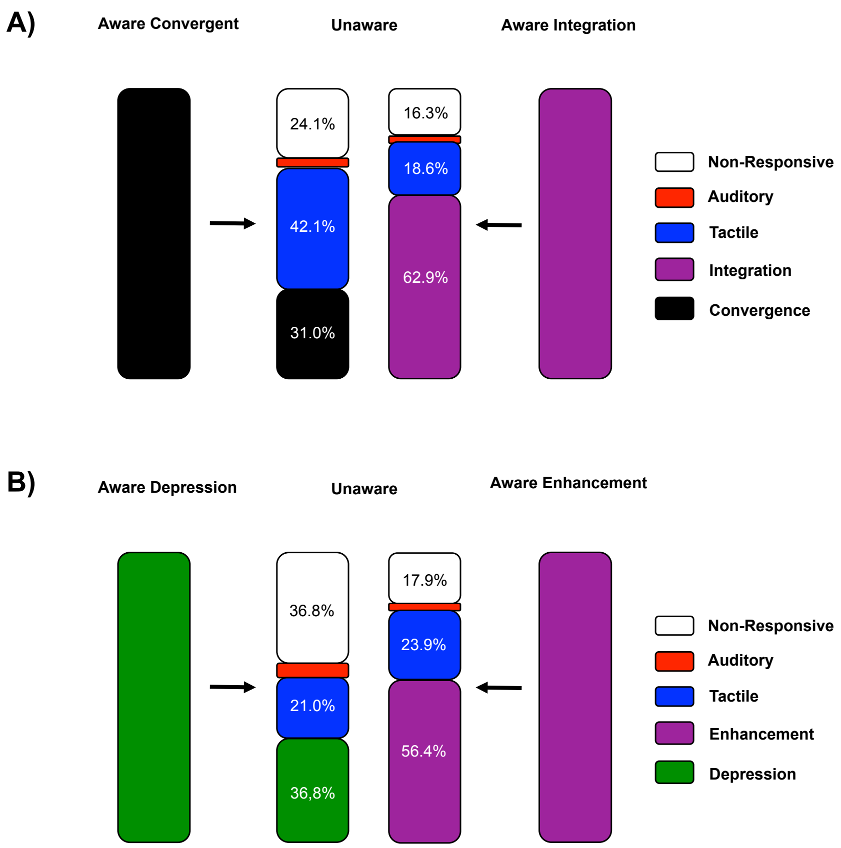


Figure 5.5. Transitions of S1 convergent and integrative neurons into distinct categories as monkeys are anesthetized. A) The largest proportion of convergent neurons when monkeys were aware (black, leftmost) became responsive solely to tactile stimulation (blue) when monkeys were rendered unconscious (second column), while 31.0% remained as convergent (black, second column). On the other hand, the majority of integrative neurons when monkeys were aware (rightmost column) remained as integrative (purple, 3rd column). **B)** Similar to the contrast between convergent and integrative neurons, when contrasting neurons exhibiting multisensory depression (i.e., responds to AT but to a lesser extend than to unisensory stimulation) and enhancement (i.e., responds to AT and to a greater degree than to unisensory stimulation), results

suggests that the larger the multisensory gain, the more neurons remain as integrative (vs. not) when rendered unconscious.

In addition to probing the fate of convergent and integrative neurons as the animals were rendered unconscious, we can also probe the degree to which these neurons exhibit neurophysiological properties of consciousness. The empirical measure most commonly associated with the IIT is the perturbation complexity index (PCI; Casali et al., 2013) and a component thereof, Lempel-Ziv complexity (LZ; Lempel-Ziv, 1976). In short, PCI is calculated by perturbing the cortex via transcranial magnetic stimulation (TMS) in an attempt to engage a distributed brain network, and subsequently compressing via LZ the spatiotemporal patterns generated by the perturbation to measure the algorithmic complexity of the electrocortical response. The further distributed and recurrent the network, the larger should be the spatiotemporal complexity evoked. This measure is directly driven by the IIT (Tononi et al., 2016) and has been shown to successfully differentiate between distinct levels of consciousness (Casali et al., 2013; Sarasso et al., 2015). More simply, LZ has also been directly applied to resting state (Schatner et al., 2015, 2017) and stimuli evoked (Andrillon et al., 2016; Noel et al., 2018) neural activity – scalp EEG most commonly – and has equally been demonstrated to bifurcate between levels of consciousness (Schatner et al., 2015, 2017). Hence, here we first characterize time-resolved LZ complexity in spike trains as a function of consciousness state, and as evoked by AT, T, A, and N stimulation. The analysis is performed both on baseline-corrected values (in order to compare the deflections evoked by sensory stimulation) and on non baseline-corrected values (in order to more generally query the relationship between LZ complexity in spike trains and level of consciousness). Next, we bifurcate S1 neurons into convergent or integrative, and examine their LZ complexity as animals are rendered unconscious.

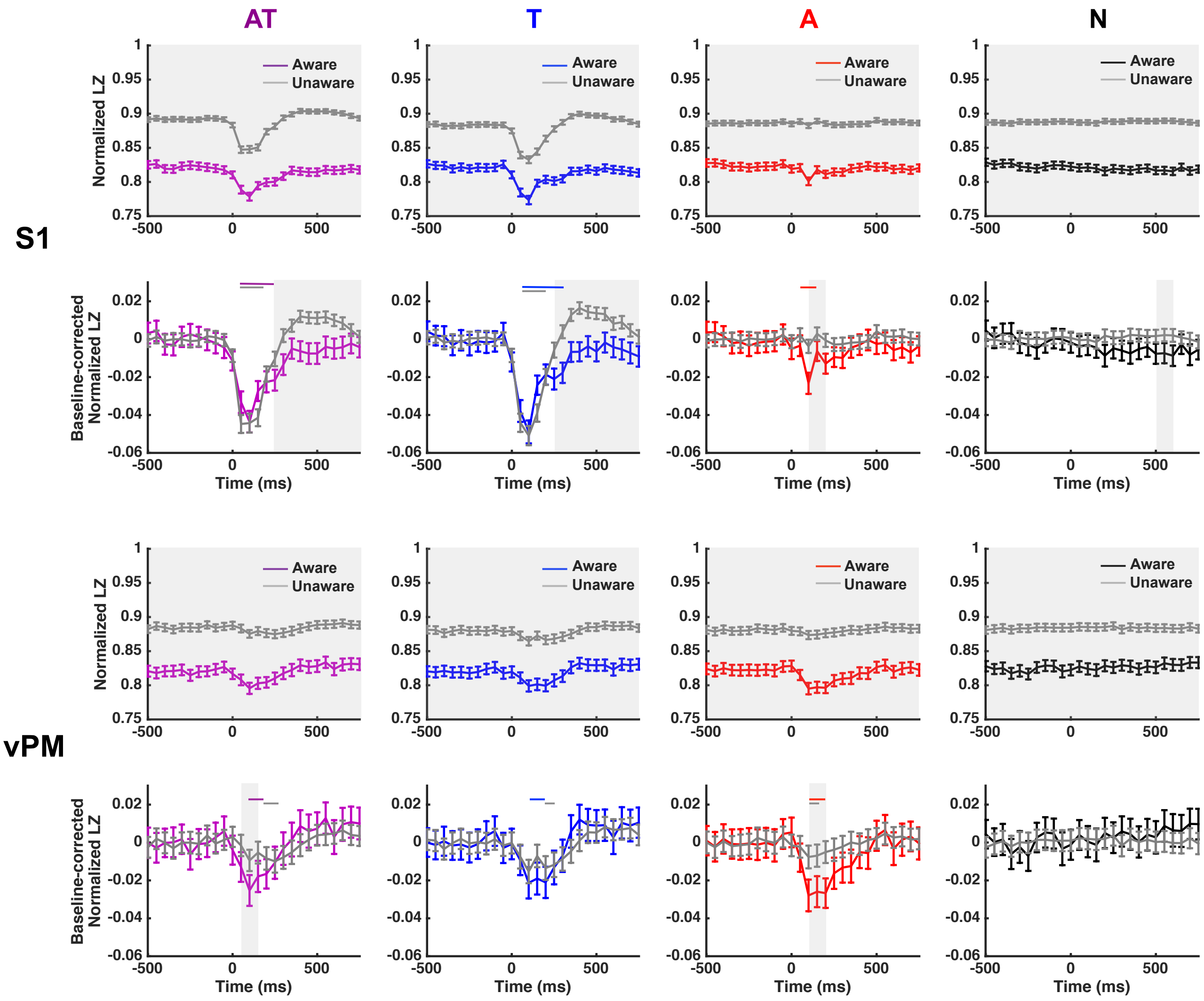


Figure 5.6. Time-resolved evoked Lempel-Ziv Complexity in spiking activity in S1 (top 2 rows) and vPM (bottom 2 rows) neurons as a function of consciousness state (aware = colored; unaware = gray) and sensory stimulation (AT = purple, T = blue; A = red; none = back). Most strikingly as illustrated when time-courses were not corrected for baseline (1st and 3rd rows) results suggest an increase in complexity (y-axis) when monkeys were rendered unconscious. Further, as better exemplified when correcting for baseline (2nd and 4th rows), the evoked complexity (negative deflection) is seemingly more sustained when aware than unaware.

Figure 6 illustrates normalized LZ (see Andrillon et al., 2016; Noel et al., 2018, and Methods), both in its baseline-corrected and non-corrected format, and as a function of consciousness state (aware = colored; unaware = gray) and sensory stimulation. Regarding the non-corrected values, a 2 (consciousness state; aware vs. unaware) x 2 (recording area; S1 vs. vPM) x 4 (stimulation type; AT, T, A, N) ANOVA most strikingly revealed that unaware states (M = 0.88, S.E.M = 0.003) were generally more complex ($p<0.01$ at all time-points) than aware states (M = 0.81, S.E.M = 0.004). This analysis also revealed a main effect of recording area between 50ms and 100ms post-stimuli onset ($p<0.01$), as well as a main effect of stimulation between 50ms and 250ms ($p<0.01$). This analysis equally indicated a significant interaction between recording area and stimulation type ($p<0.01$ between 50ms and 150ms post-stimuli onset). The interaction was driven by a significant main effect of stimulation that lasted longer ($p<0.01$, between 50ms and 250ms post-stimuli onset) in S1 than vPM ($p<0.01$ between 100 and 150ms). Once normalized LZ was corrected for baseline, analyses specified a main effect of consciousness state specifically between 200 and 400ms post-stimuli onset ($p<0.01$), indicating that not only was overall LZ different across consciousness states, but the evoked nature of this measure equally differed. This main effect was driven by the AT and T conditions, where complexity returned to it's baseline value more readily under unaware (AT, and T, return to baseline at 300ms) than aware states (AT and T, return to baseline at 350ms). The rest of statistical contrasts followed the same pattern as for the non-corrected values. The time-periods demonstrating a significant difference in evoked activity as a function of state of consciousness are shaded in gray in Figure 6 separated by area recorded and sensory stimulation, while the time-periods demonstrating a significant response vis-à-vis baseline are indicated by horizontal lines in each panel (see Figure 6). In sum, therefore, the state of awareness is seemingly indexed in spiking activity by an overall lower level of LZ complexity (see Figure 6, non-corrected normalized LZ), as well as by a more sustained negative deflection evoked by sensory stimulation (see Andrillon et al., 2016, for a similar observation). Thus, we next examined these LZ complexity properties in convergent and integrative neurons.

As illustrated in Figure 7, a 2 (consciousness state; aware vs. unaware) x 2 (neuron type; convergent vs. integrative) ANOVA on non-corrected values demonstrated a main effect of awareness (aware; M = 0.80, S.E.M = 0.001; unaware; M = 0.87, S.E.M = 0.002; p<0.01), yet no main effect of neuron type (all p>0.11). Most interestingly, however, there was a significant interaction between these variables (p<0.01), as convergent neurons (M = 0.79, S.E.M. = 0.002) had marginally significantly lower LZ complexity than integrative neurons (M = 0.81, S.E.M. = 0.002) when monkeys were aware (p = 0.052), yet this pattern reversed when monkeys loss consciousness (integrate; M = 0.86, S.E.M. = 0.002; converge; M = 0.88, S.E.M = 0.001, p = 0.045). That is, given the non-corrected for baseline LZ values, seemingly convergent neurons tracked the state of consciousness – in that they exemplified the LZ behavior expected from a given state of consciousness (see Figure 6) – better than integrative neurons did. A similar analysis once normalized LZ was corrected for differential baselines indicated a main effect of consciousness state (p<0.01 between 50ms and 700ms post-stimuli onset), but failed to indicate a difference between neuron types (all p>0.02), or an interaction between these variables (all p>0.09). And hence, while the overall level of LZ complexity appeared to differentiate between convergent and integrative neurons, the duration and/or magnitude of the negative deflection in LZ complexity during stimuli presentation did not. Specific time-periods demonstrating a significant difference in neural complexity as a function of state of consciousness are shaded in gray in Figure 7, while the time-periods demonstrating a significant difference in neural complexity vis-à-vis baseline are indicated by horizontal lines in each panel (see Figure 7).

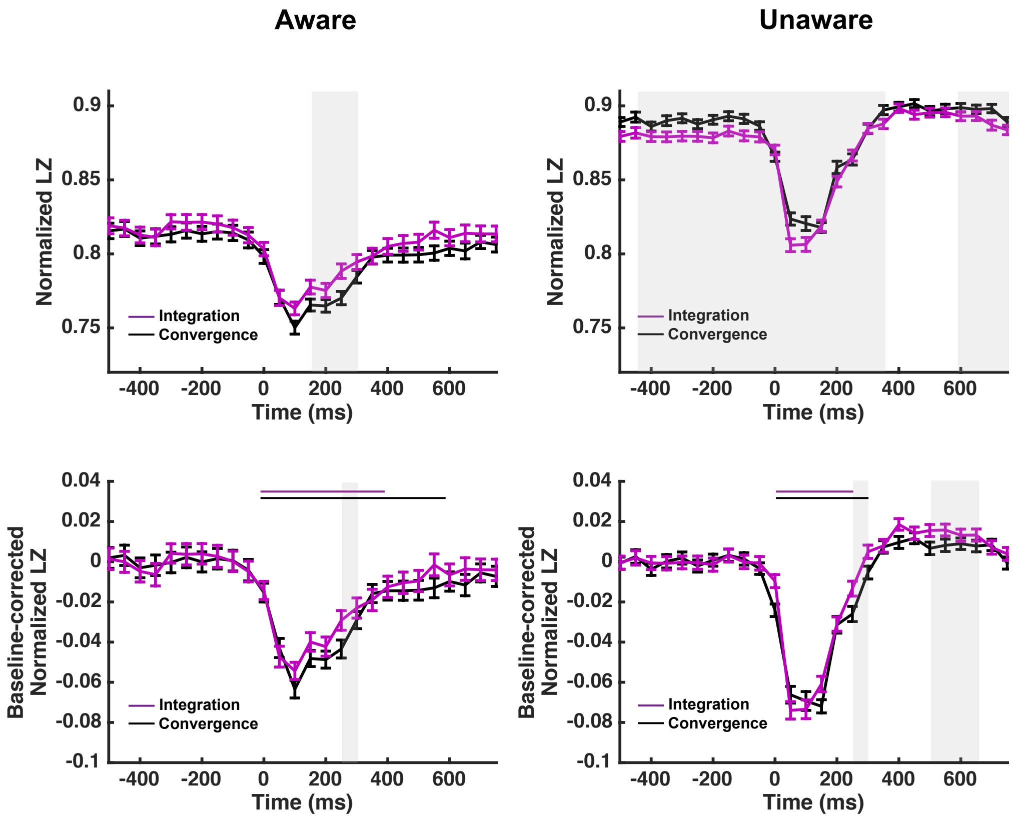


Figure 5.7. Time-resolved evoked Lempel-Ziv Complexity in spiking activity in S1 neurons as a function of consciousness state (aware = 1st column; unaware = 2nd column) and whether the neuron was determine to converge (black) or integrate (purple) sensory information when aware. Results suggest that normalized LZ (top row, y-axis) is higher for integrative than convergent neurons when monkeys are aware (left column) yet this pattern reverses when monkeys are rendered unconscious (right column). Similarly, the evoked nature of LZ complexity due to AT stimulation (bottom row) was similarly more sustained for convergent than integrative neurons (particularly when aware; left column), however there was no significant interaction between consciousness state and neuron type when normalized LZ complexity was corrected for baseline.

These LZ complexity results, just as the analysis of the outcome of convergent/integrative neurons when animals are rendered unconscious (i.e., Prediction #1), are suggestive of the fact that contrarily to our predictions generated from the IIT, the convergent and not the integrative neurons most faithfully exhibit properties of consciousness (i.e., Prediction #2). However, it is equally true that the literature quantifying LZ complexity in spike trains is solely nascent (Amigó et al., 2004; Abasolo et al., 2015), and hence it may be beneficial to apply a similar logic – contrasting convergent and integrative neurons as a function of consciousness – while utilizing a better characterized neurophysiological measure within single unit consciousness studies.

Noise correlations – the degree to which the response of a pair of simultaneously recorded neurons co-vary after accounting for the signal (i.e., mean) – were originally considered to arise due to shared sensory noise arising in afferent sensory pathways (Shadlen and Newsome, 1998). However, more recent studies suggest that they represent meaningful top-down signals generated internally within the central nervous system (Cohen and Newsome, 2008; Ecker et al., 2010). Most interestingly within the current framework, noise correlations have been shown to be a powerful index for awareness; one study demonstrating a six-fold increase under an opioid anesthetic than during wakefulness (unaware = 0.05; aware = 0.008; Ecker et al., 2014). Consequently, in the following we first index noise correlations as a function of recording area (S1 and vPM), type of sensory stimulation (AT, T, A, and N), and consciousness state (aware and unaware). This is important as to the best of our knowledge the impact of propofol on single unit noise correlations is unknown. Subsequently, we query whether neurons that integrate or converge most faithfully follow the pattern established under general conditions. As illustrated in Figure 8, noise correlations demonstrated a striking increase from aware (M = 0.02, S.E.M = 0.001) to unaware (M = 0.11, S.E.M = 0.002) states (F=742.76, p<0.001). This effect was independent of recording area (p = 0.86) and stimulation type (p = 0.33), nor was there an interaction between variables in driving the degree to which noise correlated across single units (all p>0.11). Thus, the current dataset (utilizing propofol) concords with the opioid-derived observation (Ecker et al., 2014) that under anesthesia noise correlations increase by approximately six-fold; specifically, 5.5 within the current dataset.

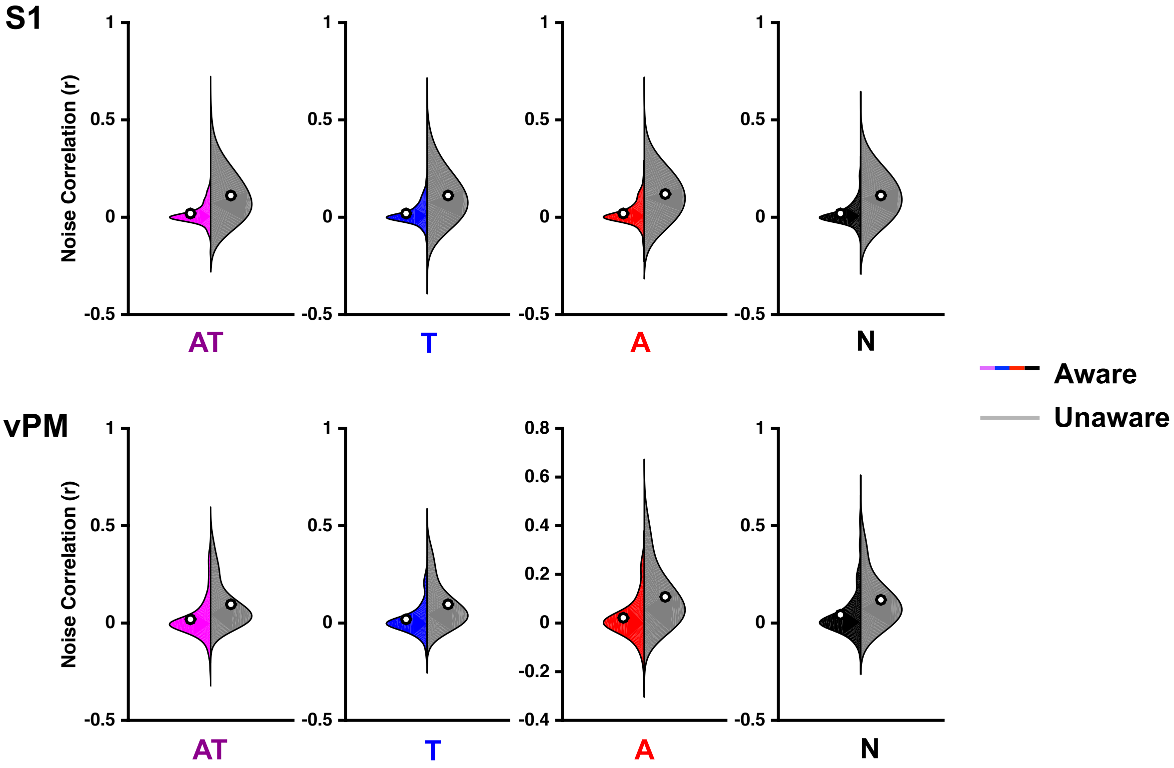


Figure 5.8. Noise correlations in S1 (top) and vPM (bottom) as a function of consciousness state and sensory stimulation. Violin plots colored (purple = AT, blue = T, red = A, black = N) represent conscious states, while their gray counterparts illustrate noise correlations when the monkeys were rendered unconscious. White dots emphasize the mean. Overall, across all sensory modalities, noise correlations are 6-fold greater under unconscious than conscious states.

When restricting noise correlation analysis to the integrative and convergent neurons, results demonstrated significant main effects of consciousness state (F=91.56, $p<0.001$) and neuron type (F=19.59, $p<0.001$), as well as an interaction between these variables (F=29.63, $p<0.001$). The interaction was driven by the fact that while monkeys were aware convergent (M = 0.018, S.E.M = 0.004) neurons exhibited a lower noise correlation (marginally significant at $p = 0.067$) than integrative (M = 0.028, S.E.M = 0.008) neurons, once again this pattern was reversed when monkeys were rendered unaware (convergent; M = 0.16, S.E.M = 0.02; integrative; M = 0.068, S.E.M = 0.008; $p < 0.001$; see Figure 9a). That is, while noise correlations are seemingly low during consciousness, the convergent neurons demonstrate inclusively lower noise correlations. And similarly, while unconsciousness is characterized by a heightened noise correlation, this is particularly apparent in convergent and not integrative neurons.

We considered it was interesting that consciousness was marked by a reduced degree of noise correlations, and that integrative neurons seemingly inadequately tracked consciousness-level of the animals. As if there were a dissociation between the degree of noise correlation that is optimal for consciousness on the one hand, and integration on the other hand. In fact, this results leads to the speculation that perhaps neurons that demonstrate the greatest degree of integration are those that show the greatest degree of noise correlation (when an organism is conscious). We tested this hypothesis, and as illustrated in Figures 9c and d, respectively, both the supra-additivity ($r = 0.15$, $p = 0.02$) and enhancement ($r = 0.12$, $p = 0.05$) indices were positively correlated with the degree to which a neuron exhibited noise correlations.

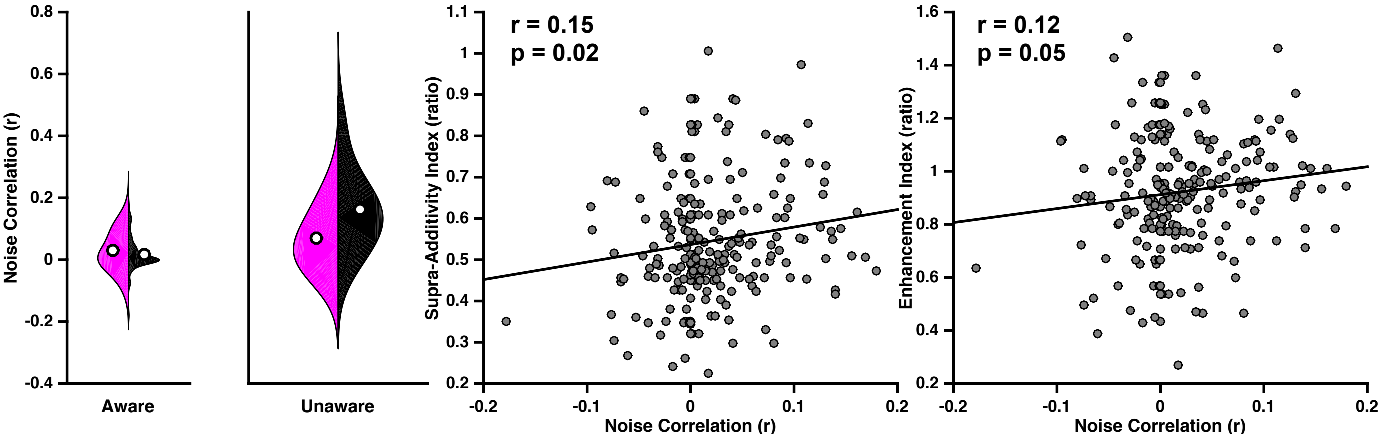


Figure 5.9. Noise correlations in integrative and convergent neurons. When monkeys are aware (leftmost panel) integrative neurons (purple) exhibit a higher degree of noise correlations than neuron that integrate (black), while the contrary is true when monkeys were rendered unaware (2nd column). Further, when monkeys were aware, the more a neuron exhibited noise correlations (3rd and 4th panel, x-axis) the greater it's supra-additive (3rd panel, y-axis) and enhancement (4th panel, y-axis) indices. White dots represent the mean of each distribution.

Testing Consciousness Theory in Multisensory Circuits; Global Neuronal Workspace

Moving past the IIT, it is possible to leverage the fact that neurons both in S1 and vPM – a well studied microcircuit (Romo et al., 2004; de Lafuente & Romo, 2006) – were concurrently recorded in order to test another prominent theory of consciousness; the GNW theory (Dehaene & Changeux, 2011). This theory states that sensory stimuli will elicit a conscious percept if it enlists neural activity within a broad fronto-parietal network. Namely, when a stimulus in the environment is not consciously perceived, it's neural representation remains encapsulated within sensory areas. Contrarily, when the stimulus is consciously perceived, the process of "neural ignition" broadly distributes its neural representation. More specifically within the current experimental design, it may be postulated according to the GNW theory that sensory stimulation will result in both S1 and vPM concurrently firing (at the single trial level) to a greater degree when animals are conscious (and thus capable of conscious content) than when they are unconscious (Prediction #3).

To test this prediction we define a response threshold as exceeding spontaneous firing by two standard deviations (see Methods), and then query the percentage of trials that result in significant firing in S1, vPM, or both S1 and vPM, as a function of consciousness and sensory stimulation type. This approach yields relatively small percentages, which is to be expected given Poisson firing (i.e., the fact that on most trials most neuron's firing rate due to sensory presentation is solely modestly changed with only a few neurons driving global population changes; Churchland et al., 2010) and thus is statistically conservative. As highlighted in Figure 10 (leftmost panel), results revealed that on 1.17% of trials both S1 and vPM were concurrently active (labeled "Neural Ignition") due to AT presentation; a number that is reduced to 0.96% of trials during T stimulation, 0.67% of trials during A stimulation, and 0.28% of catch trials (main effect of stimulation type during awareness; Friedman Test, $\chi^2 = 135$, $p < 0.001$). The percentage of trials in which sensory stimulation resulted in the co-activation of S1 and vPM was significantly smaller when animals under unconscious (vs. conscious; main effect of consciousness state, Wilcoxon Signed Rank Test, $Z = 1135$, $p < 0.001$) and did not differ across stimulation types (Friedman Test during unawareness; $\chi^2 = 14.32$, $p = 0.64$; stimulation type by consciousness state interaction, Friedman Test of the difference between aware vs. unaware as a function of sensory stimulation type, $\chi^2 = 204.78$, $p < 0.001$). A similar pattern of results emergence when examining the number of trials that resulted in activation of S1, with a main effect of consciousness state ($Z = 1294$, $p < 0.001$), stimulation modality ($\chi^2 = 51.52$, $p < 0.001$), and an interaction between these variables ($\chi^2 = 80.99$, $p < 0.001$). The interaction was driven by a significant main effect of stimuli type during consciousness ($\chi^2 = 91.18$, $p < 0.001$), but not unconsciousness ($\chi^2 = 4.07$, $p = 0.19$). Overall, when monkeys were conscious, 13.2% of AT trials resulted in significant firing in S1, a number that was reduced to 10.5% in T trials (Wilcoxon Signed Rank Test, $p = 1.61e-19$), and further reduced to 6.5% in A and 6.1% in N trials (T vs. A, $p = 1.28e-8$; A vs. N t-test, $p = 0.68$). Regarding the pre-frontal cortex, once again results demonstrated further activation consciously ($M = 6.9\%$) than unconsciously ($M = 3.1\%$; $Z = 1319$, $p < 0.001$), a main effect of stimulation type ($\chi^2 = 105.7$, $p < 0.001$), and an interaction between these variables ($\chi^2 = 233.11$, $p < 0.001$). Again, the interaction was driven by differential trial-activation percentages as a function of stimulation type when the monkeys were conscious ($\chi^2 = 133.7$, $p < 0.001$) but not unconscious ($\chi^2 = 7.51$, $p = 0.08$). Interestingly, in vPM the main effect of trial type in the conscious condition resulted from AT, T, and A all being different from N trials (all $p<5.0e-20$), as well as from vPM firing being most likely due to A stimulation ($M = 8.4\%$) than to AT ($M = 7.4\%$) or T ($M = 7.5\%$) stimulation (all $p<2.3e-5$). That is, activation of vPM was more probably due to A stimulation as it was to T or AT stimulation – a stipulation that was not true (in fact opposite) in S1 or when examining co-activation of S1 and vPM. This finding pinpoints that auditory information must arrive to vPM via a route that is not the same as how tactile information arrives in vPM (e.g., via S1), a finding that makes a great deal of sense since vPM is known to be part of the auditory "what" or ventral pathway (Rauschecker et al., 2000). Lastly, on the vast majority of trials sensory stimulation did not result in activity in either S1 or vPM, a finding that is most prominent in unconscious (M = 91.0%) than conscious states (M = 81.3%, Z = 37949, $p < 0.001$).

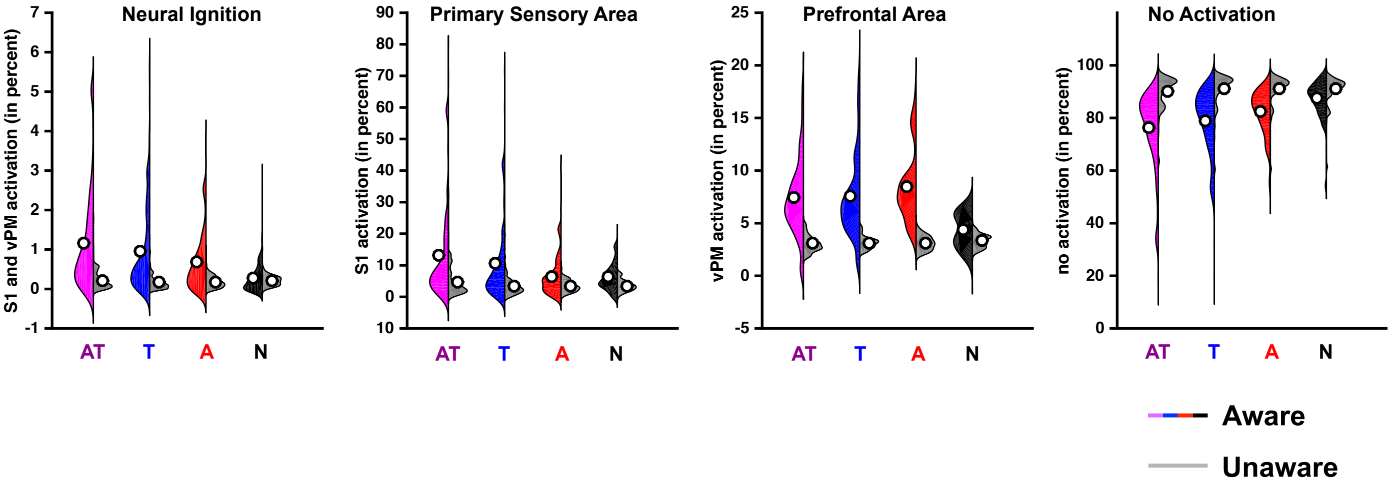


Figure 5.10. Percentage of trials that result in significant activation of S1, vPM, both or neither area, as a function of consciousness state and stimulation type. Neural ignition is defined as the simultaneous co-activation of S1 and vPM (leftmost panel). This phenomenon occurs to a greater degree when animals were conscious than unconscious, during AT (purple), T (blue), or A (red) stimulation, but not during catch trials (no stimulation). 2nd and 3rd panel respectively demonstrate the number of trials that result in significant activation of S1 and vPM. Interestingly, while AT and T stimulation seemingly result in a greater percentage of trial demonstrating neural ignition and S1 activation than A stimulation, this is not the case for activation of vPM. Namely, auditory information seemingly reaches prefrontal areas via other routes. Lastly, rightmost panel illustrates the percentage of trials that do not result in significant activation; here the percentage is greater in unconscious than conscious trials, regardless of type of sensory stimulation. White dots represent the mean of each distribution.

Seemingly, therefore, when monkeys were aware a greater number of trials resulted in co-activation of both primary sensory and “associative” areas than when animals were unaware, and this pattern of results appear to hold for AT, T, and A stimulation. The finding is in line with the GNW theory, yet may equally be trivial, given that a larger number of trials also show exclusive activation in S1 or vPM when the animals were conscious, and hence simply probabilistically co-activation of S1 and vPM is more likely under conscious than unconscious conditions. In turn, in a second step for both conscious and unconscious conditions we multiplied the likelihood of observing activation in S1 by the likelihood of observing activation in vPM and contrasted this predicted value to that observed. As shown in Figure 11, results demonstrated that in both the aware (M = 0.49%, one-sample t-test to zero, $p = 2.79e-22$) and unaware cases (M = 0.08%, one-sample t-test to zero, $p = 2.95e-13$) co-activation of S1 and vPM was more likely than what would be predicted by simply multiplying probabilities (Figure 11, y = 0). More importantly, the degree to which co-activation exceeded its prediction was greater in the aware case than the unaware one ($t = 6.2$, $p = 6.41e-10$).

Lastly, as the previous results (Figures 5-9; testing the IIT) had suggested that convergent neurons exhibited properties of consciousness to a greater degree than integrative ones, we sought to determine whether this was equally true for neural ignition. As illustrated in Figure 11 (center and right-most panels) neural ignition was generally more common when monkeys were aware (M = 1.5%) than unaware (M = 0.3%, Mann-Whitney U, $p < 0.001$), yet this likelihood interacted with neuron type. Indeed neural ignition was not distinct in convergent and integrative neuron when the animals were aware (convergent, M = 1.6%; integrative, M = 1.2%, $p = 0.37$), while the convergent neurons demonstrated less neural ignition than the integrative ones when the animals were aware (convergent, M = 0.26%; integrative, M = 0.31%, $p = 0.004$).

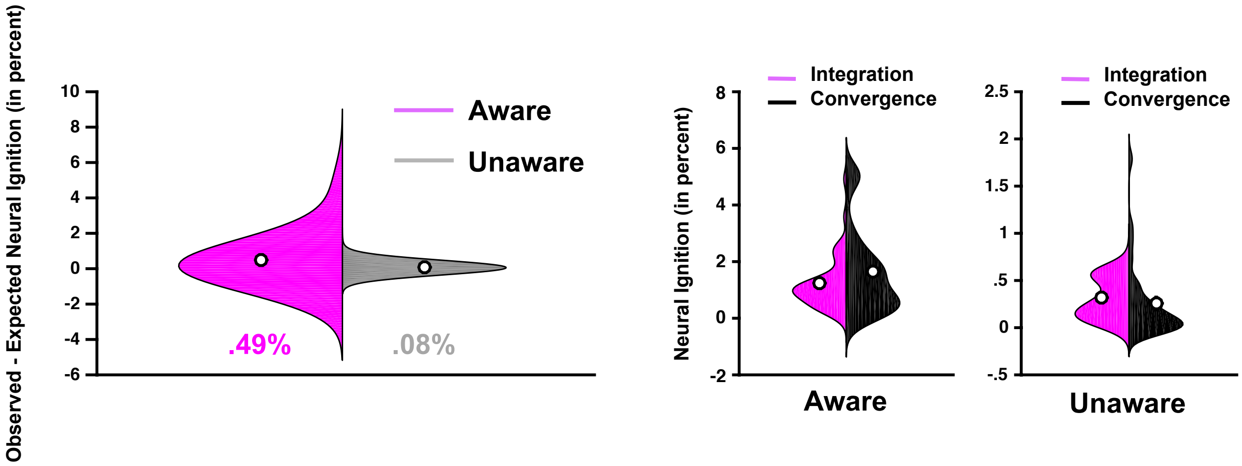


Figure 5.11. Neural ignition as a function of conscious state. A) Difference in the observed percentage of trials resulting in neural ignition due to AT stimulation from the percentage of trials that would be predicted based on S1 and vPM activation alone (y = 0), as a function of conscious state (aware = purple; unaware = gray). **B)** Neural ignition due to AT stimulation in integrative (purple) and convergent (black) neurons as a function of consciousness state (aware = left; unaware = right). White dots represent means of the distribution.

Discussion

Detailing the neural mechanisms enabling wakefulness and conscious experiences is a central question within systems neurosciences (Dehaene et al., 2018). Further, it is a question we not only do not have an answer for, but also one we are just recently learning how to pose. As such, a number of competing – yet at times compatible – theories exist; two of the frontrunners being Tononi's IIT (Tononi et al., 2016; Tononi & Koch, 2015) and Dehaene's GNW (Dehaene et al., 2006; Dehaene & Changeux, 2011). Consequently, here we sought to arbitrate between these two theories by generating a set of neurophysiological predictions derived from these theories, and testing them.

Arguably the IIT would predict that as organisms are rendered unconscious, it is likely the central integrative hubs of a neural network that are most readily impacted. Indeed, this theory states that the greater the information possessed by a network above and beyond its constituent parts, the more conscious the system is (Tononi et al., 2016; Tononi & Koch, 2015). This consciousness level may be calculated and represented in a variable denominated phi (Φ), and here we demonstrate that within a three-node network, if the central node is replaced from an indiscriminant node (i.e., convergent or XOR gate) to an integrative one (i.e., AND gate), Φ triples. Subsequently, we categorized neurons as being either convergent or integrative and examined which class was most readily impacted by propofol administration. Contrarily our predictions derived from the IIT, the integrative neurons remained relatively unaltered by the administration of anesthesia, which seemingly most readily impacted convergent neurons. To further put predictions derived from IIT to the test, we reasoned that when organisms were conscious, neurons sustaining consciousness should exhibit neurophysiological properties of consciousness, and vice-versa for unconsciousness. Hence, we examined Lempel-Ziv complexity and noise correlations as a function of stimulation type and conscious state. It is important to note that we do not aim at explaining why neural complexity or noise correlations are altered by consciousness state, but simply to use these facts as "features of consciousness" and index how these properties are modulated in integrative vs. convergent neurons as a function of consciousness. The former was utilized as it is the measure most often used within the IIT framework (e.g., Schatner et al., 2015, 2017) – though arguably the relation between Φ, Lempel-Ziv complexity, TMS-evoked complexity (PCI) and stimuli-evoked complexity is far from clear – while the latter was employed as it is a measure with a stronger tradition within neurophysiology, and prior studies (Ecker et al., 2014) have shown a six-fold increase in noise correlations after administration of an opioid anesthetic. Here again, findings indicated that the convergent neurons and not the integrative ones most faithfully mimicked the animals' consciousness state. Namely, neural complexity at the single unit level seemingly is greater under unconscious than conscious states and when monkeys were aware the complexity associated with convergent neurons was smaller than that associated with integrative neurons, and conversely when the animals were unaware, the convergent neurons were more complex than the integrative ones. Similarly regarding noise correlations; we novelty demonstrate that under propofol – a GABA_A potentiator (Brown et al., 2010, 2011) – noise correlations are approximately six-fold greater than during wakefulness. This finding is both in line with previous single unit recordings under a different kind of anesthetic (opioid; Ecker et al., 2014) and concordant with graph theory analysis of electrophysiology data showing that increased local efficiency could differentiate between distinct levels of responsiveness due to propofol administration (Lee et al., 2017). Next, we demonstrate that as for the complexity measure, convergent neurons most readily exhibited properties of consciousness when the animals were conscious, and of unconsciousness when the animals were unconscious. Taken together, our results do not support the IIT.

The second theory put to the test was Dehaene's GNW theory (Dehaene et al., 2006; Dehaene & Changeux, 2011); the basic idea being that during wakefulness a conscious experience is plausible and this occurrence should results in neural ignition, i.e., sensory evidence being broadly broadcasted throughout the brain. Our results here suggest that indeed the co-activation of primary sensory areas and higher-order levels on a single trial is more likely under conscious than unconscious conditions. Importantly, this occurrence was equally true above and beyond the expected values derived from the probability of noting S1 and vPM activations alone. In addition to these co-activation findings, we analyzed firing rates in a time-resolved fashion (as opposed spike counting within an arbitrarily time period), which granted us the possibility of examining whether firing rates to sensory stimulation during consciousness were further sustained than during unconsciousness. As predicted by the GNW and well established in electroencephalography and electrocorticography (Del Cul et al., 2006, 2007; Gaillard et al., 2009), neural activity was in fact generally further sustained when animals were conscious (vs. unconscious). Taken together, our results support the GNW theory.

In addition to providing empirical neurophysiological evidence attempting to falsify distinct theories of consciousness, our results make a number of contributions to the study of multisensory integration. First, to the best of our knowledge this is the first report to detail that supra-additivity and enhancement indices are normally distributed both in vPM and S1 in non-human primates (see Bieler et al., 2017, for a categorization of S1 neurons demonstrating enhancement and supra-additivity in rats). Further, we observed a remarkable number of neurons exhibiting multisensory enhancement in S1 and vPM, yet interestingly supra-additivity was quasi-nonexistent. These results are well in line with known multisensory convergence in vPM (Fogassi et al., 1996; Graziano et al., 1997), yet importantly highlight that not solely convergence occurs in this area, but also frank integration. Further, these results are in line with the observation that S1 receives numerous non-matched sensory afferents from thalamus (Henschke et al., 2015) and the fact that the somatosensory system is the first to demonstrate cross-modal associations developmentally (Wallace et al., 2006). Second, we equally detail the dispersion tendencies associated with (multi)sensory neurons in S1 and vPM. Variance in firing responses may emanate from a variety of causes (Churchland et al., 2010), both internal to the neuron or as a property of a network of neurons. Interestingly, while fano factors are likely impacted by both these sources, an elevation in noise correlations likely reflects a source of co-modulation. Thus, the current results demonstrating an increase in both fano factors and noise correlations during unconsciousness suggests an interesting dynamical system wherein individual neurons are becoming more chaotic yet the population as a whole is co-modulating synchronously; an observation that is in line with reports suggesting a potentiation of slow oscillations and a reduction of high-frequencies during unawareness (Ishizawa et al., 2016). Lastly, from the observations that a conscious state seemingly benefits from low noise correlations and that neurons showing multisensory convergence as opposed to integration most faithfully track consciousness according to this metric, we reasoned that perhaps a high degree of noise correlation is beneficial to multisensory integration. In fact, our results suggest a positive correlation between the amount of a neuron shares noise with its neighbors, and the degree to which it exhibits multisensory enhancement and/or supra-additivity. We find this result particularly interesting, as multisensory integration is arguably a special form of integration – a form that has minimal shared variance at the periphery, since information is transduced at different organs. Thus, this relation between shared noise and greater multisensory integration may putatively reflect larger dendritic arborizations in neurons that integrate more (see Meredith et al., 2016, 2017; Clemo et al., 2017 for recent work demonstrating alterations in dendritic arborizations of multisensory neurons in auditory cortex), and may be the neural underpinning of the postulation that (stimuli) correlation detection subserves the synthesis across the senses (Parise et al., 2012, 2016).

In conclusion, we started from the IIT (Tononi et al., 2016) and GNW theory (Dehaene & Changeux, 2011) to derive neurophysiological predictions relating to consciousness. Then, we leveraged multisensory neurons and circuits, where am established definition of information integration exists at the neurophysiological level, to attempt to falsify these theories. Results generally support the GNW and not the IIT. Of course, nonetheless, it is possible that the predictions we generated according to the IIT represented a higher bar to clear than those we generated from the GNW – this is in fact a strength of the IIT (i.e., making strong prediction) – and thus future work should aim at continuing translating theoretical postulates into concrete hypotheses, and subsequently testing these hypotheses. The study of multisensory processes may offer an important leverage in this endeavor (e.g., Noel et al., 2015, 2018; Sanchez et al., 2017; Dykstra et al., 2017).

Methods

Animal Model

Animals were handled according to the institutional standards of the National Institutes of Health (NIH) and an approved protocol by the institutional animal care and use committee at the Massachusetts General Hospital. Two adult male monkeys (*Macaca mulatta*, 10 –12 kg) were used.

Behavioral Task and Experimental Procedure

The animals were trained in a behavioral task wherein following the onset of a start tone (1000 Hz, 100 ms, see Figure 12A, first row) they were required to initiate each trial by holding down a button with their hand ipsilateral to the recording hemisphere. In order to successfully launch a trial, the animals were required to hold the button within 1.5 seconds of the trial onset tone (Figure 12A, second row). Then, following button press, within a uniform random delay between 1 and 3 seconds (Figure 12, blue shaded area with dashed contour representing a variable delay) one of four sensory stimulus sets was delivered (tactile air puffs, T; auditory stimuli, A; simultaneous auditory and tactile, AT; no stimuli, N; Figure 12A depicts an AT trial, and hence T, A, and N trials are shaded). Air puffs during T trials were delivered at 12 psi to the lower part of the face contralateral to the recording hemisphere via a computer-controlled regulator with a solenoid valve (AirStim; San Diego Instruments). The eye area was avoided. Auditory stimuli during A trials were pure tones at 4000 Hz and at 80 dB SPL generated by a computer and delivered using two speakers 40 cm from the animal. Audiotactile (AT) trials were simply the joint and simultaneous presentation of A and T trials. N trials were catch trials were no stimulus was presented. White noise (50 dB SPL) was applied throughout the trial to mask inherent noise derived from air puff and mechanical apparatus. All of the stimulus sets were presented randomly to the animal regardless of their behavioral response throughout the recording session. Following the presentation of the sensory stimulus the animals were required to keep holding the button down until the presentation of liquid reward (3 seconds post stimuli onset, Figure 12A bottom row and second blue interval). The monkeys were trained to perform a correct response on <90% of the trials consistently for longer than 1.5 hours in an alert condition. The animal's performance during the session was monitored and simultaneously recorded using a MATLAB-based behavior control system (Asaad and Eskandar, 2008a, 2008b). Trial-by-trial behavioral responses were binned as a correct response (button holding until the trial end and release), failed attempt (early release, late touch, or no release of the button), or no response (Fig. 1C). Loss of consciousness was defined as the first no-response trial that was consistently followed by a lack of responses for the rest of anesthesia (see Figure 12B for an exemplar session where the cumulative sum of trials categorized as correct responses raises quickly initially and then saturates, while the cumulative sum of trials categorized as no-response is initially stagnant at zero and subsequently raises rapidly following approximately 280 trials).

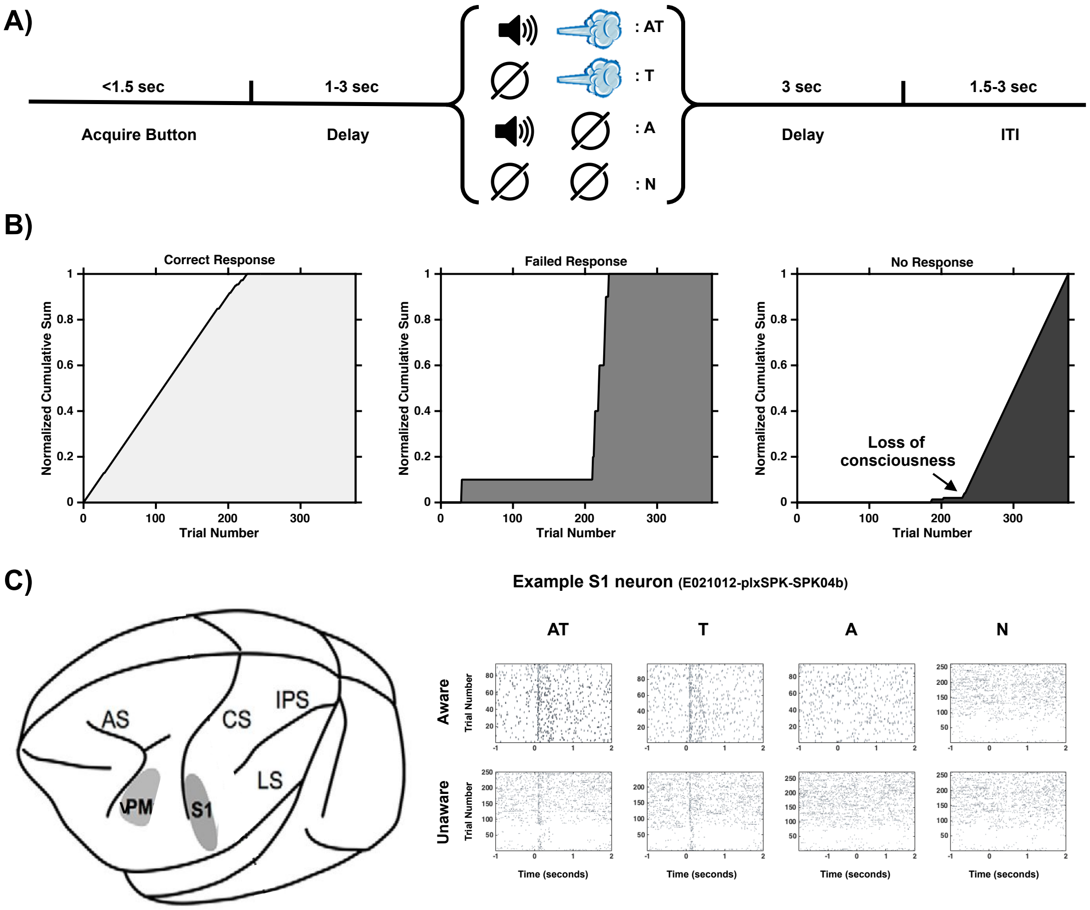


Figure 5.12. Experimental Procedure, Methods, and Neurophysiology Preprocessing. A) Experimental task; animals were required to press a button within 1.5 seconds following a start tone. Subsequently, following a random delay between 1 and 3 seconds post button press (dashed blue area) they were presented with a sensory stimulus (audiotactile, AT (purple); tactile, T (blue); or auditory, A (red)) or not (faded black, N). In this case an AT trial is illustrated, and hence represented in a continuous line, while T, A, and N are dashed and shaded. After a fixed delay of 3 seconds post stimulus onset, if the monkey was still holding the button, it was given a liquid reward

and allowed to stop pressing the button. The trial depicted is a correct response trial, but a trial could also be categorized as failed response (e.g., released the button too soon) or a no-response trial (e.g., the monkey never executed button press). **B)** Cumulative sum of trial categories (leftmost; light gray = correct response; center, dark gray = failed response; rightmost, black = no response). Initially all trials are correct, but as propofol is administered, the animal falls unconscious and does not execute the button press. Unawareness is defined as the period between the first no-response trial that is consistently followed by a lack of responses for the rest of anesthesia. **C)** A schematic of a monkey brain depicting areas S1 and vPM, where neurons were recorded and example raster plots from a neuron in S1. Responses during an aware period are depicted on the top row, while the bottom row illustrates activity during unawareness. The first column shows audiotactile trials, the second illustrates tactile trials, the third shows audio trials, and the last column shows spiking activity during trials with no sensory stimuli. On the x-axis is time (in seconds, centered at stimuli onset) and on the y-axis is trial number.

Anesthesia

Thirty minutes after initiating each recording session, propofol was infused for 60 minutes at a fixed rate (200 g/kg/min for Monkey E, and 230 or 270 g/kg/min for Monkey H) through a vascular access port. The infusion rate of propofol was a priori determined to induce loss of consciousness in approximately 10 minutes for each animal. No other sedatives or anesthetics were used during the experiment. The animal's heart rate and oxygen saturation were monitored continuously throughout the session (CANL-425SV-A Pulse Oximeter; Med Associates). The animals maintained >94% oxygen saturation throughout the experiments.

Neurophysiology Data Recording and Preprocessing

Before starting the study, a titanium head post was surgically implanted on each of the two animals. A vascular access port was equally surgically implanted in the internal jugular vein (Model CP6; Access Technologies). Once the animals had mastered the behavioral task described above, extracellular microelectrode arrays (Floating Microelectrode Arrays; MicroProbes) were implanted into S1 and vPM through a craniotomy (see Figure 12C). Microelectrodes were also implanted in S2, but due to insufficient recorded neurons caused by a technical malfunction, here we focus our report on recordings from S1 and vPM. Each array (1.95x2.50 mm) contained 16 platinum–iridium recording microelectrodes (0.5 MΩ, 1.5– 4.5 mm staggered length) separated by 400 μm. Landmarks on cortical surface and stereotaxic coordinates (Saleem and Logothetis, 2012) guided the placement of arrays. A total of five arrays were implanted in Monkey E (two arrays in S1, one in S2, and two in vPM, all in the left hemisphere) and four arrays in Monkey H (two arrays in S1, one in S2, and one and vPM; all in the right hemisphere). The recording experiments were performed after 2 weeks of recovery following the array surgery. All experiments were conducted in a radio frequency shielded recording enclosure.

Neural activity was recorded continuously and simultaneously from S1 and vPM through the microelectrode arrays while the animals were performing the behavioral task. Analog data were amplified, band-pass filtered between 0.5 and 8 kHz, and sampled at 40 kHz (OmniPlex; Plexon). The spiking activity (see Figure 12C) was obtained by high-pass filtering at 300 kHz and applying a minimum threshold of 3 standard deviations in order to exclude background noise from the raw voltage tracings on each channel. Subsequently all action potentials were sorted using waveform principal component analysis (Offline Sorter; Plexon) and binned into 1 ms bins, effectively rendering the sampling rate 1kHz.

Rationale and Computation of Integrated Information (Φ)

From an information-theoretic perspective information is the reduction of uncertainty (Shannon, 1948). In turn, information may be quantified by considering how a system in its current state S_0 constrains the system's potential past and future states. Figure 13 illustrates this principle form within the purview of C at time t for the system with an XOR gate. Under this scenario, if C is currently active, then at time t-1 by necessity either A was active, B was active, A and C were active, or B and C were active (Figure 13, left panel). The probability distribution of past states that could have been causes of $C = 1$ is its cause repertoire $p(ABC^{past}|C = 1)$. On the other hand, if it is unknown in what state C is in, t-1 is unconstrained $p^{uc}(ABC^{past})$. A similar rationale applies to future states wherein the current state of C constrains its future potential states, and the effect repertoire is thus the probability of being in any given state given that C is current active, or $p\left(ABC^{future}\middle|C=1\right)$. The amount of information that $C=1$ specifies about the past is its cause information (CI) and the amount it specifies about the future is its effect information (EI). CI and EI are respectively measured as follows,

$$CI = EMD(p(ABC^{t-1}|C^{t}=1)\ ||\ p^{uc}(ABC^{t-1}) \qquad Eq.1$$

$$EI = EMD(p(ABC^{t+1}|C^{t}=1)\ ||\ p^{uc}(ABC^{t+1}) \qquad Eq.2$$

where EMD refers to earth mover's distance (Rubner et al., 2000), the minimal cost of reshaping one distribution (e.g., unconstrained) into the other (e.g., constrained) or area of distribution moved times the distance moved. Finally, the total amount of cause-effect information (CEI) specified by $C=1$ is the minimum value between CI and EI. This results from the fact that both CI and EI may act as limiting cases – an information bottleneck – and hence minimize the CEI of the system as a whole (see Oizumi et al., 2014 for detail). Finally, while CEI measures information, the IIT conjectures that consciousness is *integrated* information. That is, information generated by the system above and beyond that generated by its constituent parts. Hence, the system as a whole is iteratively partioned into all possible subsystems or purviews and the process delineated above is evaluated for each of these components. Similar to CEI, integrated information is calculated as the EMD between the cause-effect repertoire specified by the system as a whole and the cause-effect repertoire of the partitioned system. Φ is the distance between the system as a whole and the system-partitioned that makes the least difference; the minimum information partition. That is, Φ is the degree to which the cause effect repertoire for the system as a whole differs from the next most informative partition.

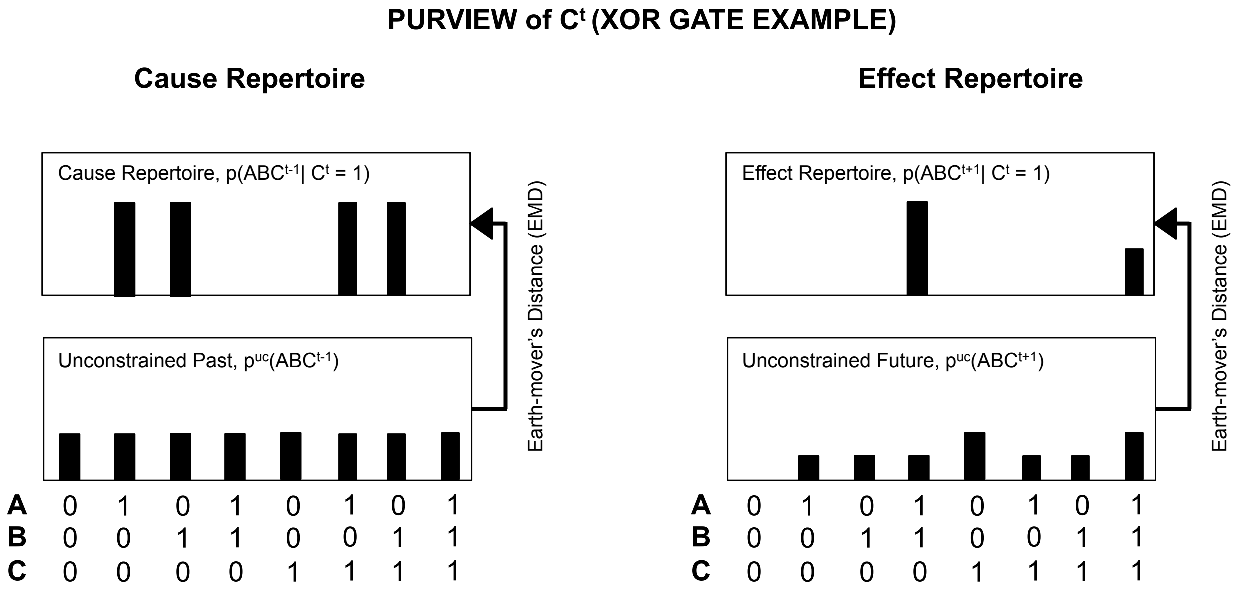


Figure 5.13. Illustration of cause and effect repertoires and the constraints imposed on potential probability distributions by the fact that C=1. Cause (left) and effect (right) repertoires for a system with three nodes as the one illustrated in Figure 1, and as a function of whether the past-future is constrained to C=1 (top) or not (bottom).

Information integration (phi, Φ) was calculated for the multisensory convergent and integrative networks using the transitions probability matrices illustrated in Figure 1 and as implemented in *PyPhi* (Mayner et al., 2017) with Python 3.4.

Neurophysiology Data Analyses

Firing Rate and Fano Factor

Both central and dispersion tendencies of single-unit spiking activity in S1 and vPM were quantified as a function of stimulus modality as it is well-established that mean firing rates alone do not fully characterize the properties of neural activity (Churchland et al., 2010), in particular within a multisensory context (Kording et al., 2007). Regarding firing rates, spikes were first binned in 1ms intervals, and epochs were centered on stimuli onset, ranging from 2000ms prior to stimuli onset (i.e., -2000ms), to 2000ms after stimuli onset. Subsequently spike counts were effectuated within a 100ms window, between -500ms and 1000ms, and in steps of 10ms. It must be noted that this analysis essentially low-passes time, and hence the exact timing of reported effects should not be emphasized. Analyses of firing rates were conducted both on baseline-corrected and non-corrected rates. The contrast of non-corrected rates allows for determining the impact of propofol on baseline firing, while the analysis on baseline-corrected rates allows specifically querying the evoked-responses to stimuli onset. That is, for the baseline-corrected rates, every spike count function was centered along the y-axis (i.e., spikes/s) to zero according to their own baseline firing (-500 to 0ms post-stimuli onset). In this manner, positive deviations from 0 indicate an increased in firing rate, while negative deflections indicate a silencing in spiking activity post-stimuli onset with respect to baseline. Spike counts were first averaged within a cell and across trials, and subsequently across neurons. In terms of statistical analyses, as the temporal dynamics of spiking activity was of interest, in particular within the GNW theory (Dehaene et al., 2006; Dehaene & Changeux, 2011) emphasizing sustained activity in aware and not unaware states, we conducted a time-resolved (at each 10ms time-point, 151 in total) 2 (State; Aware vs. Unaware) x 2 (Area; S1 vs. vPM) x 4 (Stimulation; AT, T, A, N) independent samples analysis of variance (ANOVA). As spiking rates were not normally distributed (i.e., presence of a true floor, in that negative spikes are not possible), the ANOVAs for non-baseline corrected rates were conducted on log-transformed data. On the other hand, the subtraction of evoked activity to baseline activity did yield normal distributions, and hence this data is analyzed without log-transform. The inter-dependence of observations is difficult to ascertain within a neural network composed of neurons whose precise connections are unknown, and thus independent as opposed to dependent ANOVAs were conducted in order to adopt the most conservative approach (i.e., within-samples ANOVAs are statistically stronger than between-samples analyses). Similarly, in order to protect against Type I error (i.e., false positives) significant effects were only considered at $\alpha < 0.01$ for at least 3 consecutive windows (i.e., 30 time-points; see Noel et al., 2018, for a similar approach with time-series data).

Regarding the inter-trial variance in evoked responses associated with the distinct states of consciousness, stimuli modalities, and brain areas, fano factors (i.e., ratio of spike-count variance to spike-count mean) were calculated (Fano, 1947). Indeed, repeated trials do not yield identical responses, and this variance is associated both with cellular and molecular processes involved in spike generation at the axon hillock (e.g., refractory periods) and network-level properties (van Vreeswijk & Sompolinsky, 1996). Conveniently the neuron-specific variance is largely considered to be well accounted by a Poisson point process (i.e., mean and variance scale linearly), and hence a fano factor of 1 (Churchland et al., 2010; Mainen & Seinowski, 1995). Fano factors in excess of 1, thus, may be considered to index variability that is associated with network-level properties and this variability is typically reduced at stimuli onset (Churchland et al., 2010). Here, therefore, we report time-resolved fano factor both corrected for baseline (in order to examine putative network-level decreases in inter-trial variability as a function of stimuli onset, awareness state and sensory modality), and not corrected for baseline (in order to assess basal cell-specific and network level inter-trial variability as a function of awareness state). Statistical analysis is conducted as described above for firing rates.

Neural Index of Multisensory Integration

The hallmark for multisensory integration at the single unit level is an evoked response to multisensory stimuli (.e., AT) that may not be linearly predicted by responses to the constituent unisensory stimuli (e.g., A and T; Stein & Stanford, 2008; Murray & Wallace, 2012). Thus, given the time-resolved results demonstrating sustained activity to sensory stimulation until approximately 500ms post-stimuli onset, mean spike counts to AT, T, A, and N trials were executed within this time period (see Ghose et al., 2014 for a similar approach). Subsequently, the i) supra-additivity and ii) enhancement index of each neuron was computed (according to Eq. 3 and Eq. 4, respectively). Historically, supra-additivity – the degree to which a multisensory response exceeds the sum of unisensory responses (see Eq. 3) - was considered the clearest indication of multisensory facilitation (Stein & Stanford, 2008); nonetheless this feature is not as prominent in cortex as it is in sub-cortex (Kadunce et al., 1997; Stein & Stanford, 2008). Thus, we supplement the supra-additivity index with the enhancement index – the degree to which a multisensory response is greater than the maximal response to unisensory stimuli (see Eq. 4). An enhancement index above 1 indicates a neuron that is further driven by multisensory than unisensory stimulation. Supra-additivity (Eq. 3) and enhancement (Eq. 4) indices were computed as follows;

$$Supra - Additivity\ Index = \frac{AT_{FR}}{(A_{FR} + T_{FR})} \qquad Eq. 3$$

$$Enhancement\ Index = \frac{AT_{FR}}{max(A_{FR}, T_{FR})} \qquad Eq. 4$$

where AT_{FR} is the mean baseline-corrected firing rate for a particular neuron to audiotactile stimulation, T_{FR} is the mean baseline-corrected firing rate for the particular neuron to tactile stimulation, and finally A_{FR} is the mean baseline-corrected firing rate for the particular neuron to auditory stimulation.

Bifurcation Into Convergence and Integration

The IIT specifies that a network converging on a neuron that integrates information, as opposed to responding indiscriminately, ought to bear a greater degree to consciousness. Hence, here we aim at testing two predictions that may follow from the IIT; i) as an organism falls into unconsciousness, the neurons that are most impacted are those that integrate information (i.e., putatively anesthetics act on these neurons preferentially), and ii) neurons that integrate information exhibit the properties of consciousness when the organism is conscious. To test these predictions, we divide our population of neurons into those that integrate vs. converge (Figure 5 and beyond). However, initially we simply describe the proportion of neurons that fit within each category (Figure 4) in a non-mutually exclusive fashion. A neuron that converges information is defined as a neuron that on average (i.e., across trials) responds – spike count from 0 to 500ms - to both unisensory auditory and tactile information beyond its baseline firing rate (-500ms to 0ms) plus 2 standard deviations. That is, in order to qualify as convergent, the spiking count of a neuron to AT stimulation does not need to be examined. On the other hand, a neuron that integrates information is defined as a neuron that is most readily driven by the simultaneous presence of A and T information. Thus, neurons that respond to AT stimulation (as defined above) and do so to a greater degree than their maximal unisensory response (i.e., enhancement index above 1) were initially classified as integrative. Importantly, beyond Figure 4 (e.g., to categorize the fate of neurons when the animal becomes unconscious and quantify neural complexity, noise correlations, and neural ignition) two mutually exclusive classes are created. Neurons that respond indiscriminately to sensory stimulation are classified as convergent, while those that exhibit multisensory enhancement without being considered convergent are taken to integrate information. Given the initial number of neurons in S1 and vPM, this bifurcation yielded a sufficient quantity of neurons exclusively categorized as convergent (N = 125) and integrative (N = 64) in S1, but not in vPM (convergent, N = 61; integrative, N = 8) – thus, for the analyses specifically probing the difference between convergent and integrative neurons, analyses are restricted to S1. Further, given the heterogeneity of neuron's spike trains (see Figures 2-4) for Figure 4 and beyond we considered a neuron as fitting within a particular category (e.g., A, T, AT convergent, AT integrative) if at some point between 0ms and 1000ms post-stimuli onset they met the particular criteria for at least 50 consecutive ms.

Equally of note, in Figure 4 neurons that are labeled to integrate auditory and tactile information (purple, orange, and green) are not first indexed for their unisensory responses. That is, while in S1, 49% of neurons are classified as responding to a greater extent to AT stimulation than to the maximum unisensory stimulation, this latter unisensory response is not necessarily different from baseline activity. We consider this approach appropriate within the current aim of leveraging multisensory responses in querying consciousness theories, but it must be highlighted that multisensory enhancement may be more strictly considered to apply only when tactile, auditory, and audiotactile responses are different from baseline, and the latter responses is greater than the maximal of the former two (Murray & Wallace, 2012). Indeed, the categorization here is more in line with the recent emphasis within the study of multisensory integration to index covert multisensory processes (Bizley et al., 2007), in particular within classically considered primary sensory areas (Ghazanfar & Schroeder, 2006), than with the original description of multisensory integration in the late eighteens and early nineties (Stein & Meredith, 1993).

Lempel-Ziv Complexity

Categorizing the complexity of neural representations – operationalized as the number of distinct patterns present in data – has become of increasing popularity as of late (e.g., Koch et al., 2016a,b), in particular due to its ability to differentiate between states of consciousness given scalp electrophysiological data (Casali et al., 2013) and the belief that complexity is at least indirectly related to functional differentiation/integration, paramount notions with the IIT (Tononi et al., 2016). In order to quantify neural complexity, here we measure the Lempel-Ziv (LZ) complexity (Lempel & Ziv, 1978) associated with each spike train evoked as a consequence of AT, T, A, or N trials, and as a function of the animals' consciousness state. LZ complexity measures the approximate quantity of non-redundant information contained within a string by estimating the minimal size of the " vocabulary" necessary to describe the entirety of the information contained within the string in a lossless manner (Lempel & Ziv, 1978). That is, it is a lossless compression algorithm (routinely used in ZIP files and TIFF images), and it is utilized to measure the number of distinct patterns in symbolic sequences, in particular within binary signals. LZ is impacted by the overall entropy within a signal (Amigo et al., 2004; i.e., a binary string composed almost exclusively of '0' will not have a high LZ, not due to the arrangement of those '1', but simply because there are not many of them). Thus, here, to equate entropy across conditions we first converted spike trains into a continuous measure by convolving each trial with a Gaussian kernel with σ=50ms, and then binarized each time-point within this trial by assigning a '1' to time-points above the trial mean, and '0' to time-points below the trial mean. Next, LZ was computed (Lempel-Ziv, 1978) in MATLAB within a sliding window moving between -500ms and 750ms post-stimuli onset, a length of 100ms, and step size of 50ms. Lastly, the same procedure was executed while randomly shuffling the binary sequence before calculating LZ. This shuffled LZ time-series represents a theoretical upper bound (i.e., random data has a higher LZ) and was used to normalize the calculated LZ from the non-shuffled data. Hence, a normalized LZ of 1 indicates 'as complex as random noise', while lower values indicate the presence of structure in the data (see Andrillon et al., 2016; Noel et al., 2018, for a similar approach). Statistical analysis largely followed that of firing rates and fano factors, which exception that data were never log-transformed as they were normally distributed. Analysis was effectuated both on baseline-corrected values, in order to compare the negative deflection present during stimulus onset (see Andrillon et al., 2016 for a similar findings) and most importantly, on non-corrected values, in order to examine the basal complexity in spiking activity as a function of consciousness and whether neurons were categorized as convergent or integrative.

Noise Correlations

While LZ complexity is arguably the most often utilized measure within the IIT framework (Tononi et al., 2016), it is not a traditional measure within neurophysiology. Thus, we sought to further probe the properties of convergent and integrative neurons – and their correspondence with the alteration in the particular measure as a function of consciousness state – with a neurophysiological measure that is well established to alter with consciousness state. Noise correlations (Shadlen and Newsome, 1998; Ecker et al., 2014) express the amount of covariability in the trial-to-trial fluctuations of responses of two neurons to repeated presentations of the same stimuli, are central to questions of coding accuracy and efficiency (Averbeck et al., 2006), and are well-established to be altered by consciousness state (Ecker et al., 2014). Thus, this measure was computed both in S1 and vPM neurons, as a function of consciousness state and stimuli modality. Noise correlations where computed as the Pearson correlation between all pairs of neurons recorded simultaneously within the same session (see Ecker et al., 2014 for a similar approach). Spike counts were effectuated for each trial on the 500ms immediately following stimuli presentation (defined above as the average time-period of neural response, and in concert with Ecker et al., 2014). We considered the noise correlation for a particular neuron it's average correlation with all other neurons recorded in the same session.

Neural Ignition

The GNW model points to the late amplification of relevant sensory activity, long-distance cortico-cortical synchronization at beta and gamma frequencies, and ignition of large-scale fronto-parietal networks as neural measures of consciousness (Dehaene and Changeux, 2011). To test this prediction, we query at the single trial level whether sensory stimulation leads to co-activation of both primary sensory areas (i.e., S1) and frontal regions (i.e., vPM) more commonly during conscious than unconscious states. For each neuron (both in S1 and vPM) we specify a threshold benchmarking reliable neural activity as the average spike count between -500 and 0 ms post-stimuli onset plus 2 standard deviations. Similarly, the neural response is considered to be the spike-count between 0 and 500 post-stimuli onset. Then, iteratively we pick a neuron from S1 and a neuron from vPM and query whether on a particular trial did neither area respond, did solely S1 respond, did solely vPM respond, or did both S1 and vPM respond. A particular S1 neuron is subsequently paired with all neurons in vPM recorded during the same session, and finally it's mean activation patterns (e.g., S1 and vPM active, vPM active, S1 active, or none) as a function of consciousness state and sensory stimulation are quantified. The same procedure is applied to vPM neurons. It must be highlighted that routinely mean firing rates are largely driven by strong responses in a few trials (Churchland et al., 2010, for example), and hence demanding a response within a particular trial to exceed baseline plus 2 standard deviations is a conservative approach yielding a great number of no-response trials. Nonparametric statistics are used in this analysis as data did not confirm to the assumptions made by parametric inference statistics.

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PART II: CONSCIOUSNESS FROM THE INSIDE-OUT

CHAPTER VI

AUDIO-TACTILE AND PERI-PERSONAL SPACE PROCESSING AROUND THE TRUNK IN HUMAN PARIETAL AND TEMPORAL CORTEX; AN INTRACRANIAL EEG STUDY

The contents of this chapter are adapted from

Bernasconi, F., Noel, J.P., Park, H.D., Faivre, N., Seeck, M., Spinelli, L., Schaller, K., Blanke, O., Serino, A. (in press). Audio-tactile and peri-personal space processing around the trunk in human parietal and temporal cortex: an intracranial EEG study. Cerebral Cortex.

Abstract

Interactions with the environment happen within one’s peripersonal space (PPS) - the space surrounding the body. Studies in monkeys and humans have highlighted a multisensory distributed cortical network representing the PPS. However, the temporal dynamics of PPS processing on the trunk is lacking. Here, we recorded intracranial electroencephalography (iEEG) in humans while administering tactile stimulation (T),

approaching auditory stimuli (A), and the two combined (AT). To map PPS, tactile stimulation was delivered when the sound was far, intermediate or close to the body. 19% of the electrodes showed AT multisensory integration. Among those, 30% showed a PPS effect; a modulation of the response as a function of the distance between the sound and body. AT multisensory integration and PPS effects had similar spatiotemporal characteristics, with an early response (~50ms) in the insular cortex, and later responses (~200ms) in pre- and post-central gyri. Superior temporal cortex showed a different response pattern with AT multisensory integration at ~100ms without PPS effect. These results, representing the first iEEG delineation of PPS processing in humans and show that PPS and multisensory integration happen at similar neural sites and time periods, suggesting that PPS representation is based on a spatial modulation of multisensory integration.'

Introduction

The space immediately adjacent to and surrounding the body - defined as peripersonal space (PPS; di Pellegrino et al., 1997; Rizzolatti et al., 1981, 1997) - is particularly relevant for behavior, as it is where physical interactions with the environment occur (Graziano and Cooke, 2006; Làdavas and Serino, 2008). The ecological significance of the PPS is evidenced in that the primate brain has developed a fronto-parietal network encoding preferentially multisensory stimuli occurring near to (as opposed to far from) the body. That is, neurons located in monkey posterior parietal cortex (i.e., intra-parietal sulcus (IPS) (Duhamel et al., 1997, 1998)), parietal area 7b (Leinonen and Nyman, 1979; Fogassi et al., 1996; Graziano et al., 1997), and ventral premotor cortex (vPM; (Fogassi et al., 1996; Graziano et al., 1997)) have been reported to respond to tactile stimuli applied to different body parts. These regions also respond to visual (Schlack et al., 2005) or auditory cues (Graziano et al., 1999; Schlack et al., 2005) if they occur in similar spatial position with respect to the tactile simuli.

A homologous PPS neural network is postulated to exist in humans, supported by numerous psychophysical (Salomon et al., 2017; Spence et al., 2004) and neuropsychological (Farnè and Làdavas, 2000; Maravita and Iriki, 2004) studies demonstrating enhanced processing of tactile stimulation when a task-irrelevant visual or auditory object is present near vs. far from the body. These studies rely on the congruent presentation of multisensory stimuli in the environment (Serino et al., 2015; Canzoneri et al., 2012) are body part centered (hand: (Canzoneri et al., 2012); face: (Teneggi et al., 2013); Trunk: (Galli et al., 2015; Noel et al., 2015, 2015b, 2018)). The existence of a homologous PPS neural network in humans is further supported by fMRI studies, which have demonstrated a close association between the areas encoding for PPS in non-human primates and humans (e.g., Bremmer et al., 2001; Brozzoli et al., 2011, 2012; Ferri et al., 2016; Gentile et al., 2011; Grivaz et al., 2017; Makin et al., 2009). In addition to the above mentioned PPS areas described in monkeys, human fMRI has equally revealed primary somatosensory cortex (S1), parietal operculum (e.g., Tyll et al., 2013), insula (e.g., Schaefer et al., 2012), cingulate cortex (e.g., Holt et al., 2014) and the lateral occipital cortex (Gentile et al., 2013) as brain regions encoding PPS (for a review see Grivaz et al., 2017).

The characterization of the areas encoding PPS in humans, however, has quasi-exclusively mapped the peri-hand representation (Brozzoli et al., 2011, 2012; Gentile et al., 2011; Makin et al., 2007), with only a few studies investigating the peri-face space (Bremmer et al., 2001; Holt et al., 2014; Sereno and Huang, 2006 for exceptions) and even fewer on the peri-trunk space (see Huang et al., 2012 for an exception). Moreover, while the encoding of PPS is largely taken to be subsumed by multisensory networks, most of the evidence on PPS-related neural response is based on the finding that PPS neurons or regions respond both to tactile and visual (or auditory) stimulation. Yet, only one single electrophysiological study (Avillac et al., 2007) has demonstrated clear multisensory integration (i.e., a non-linear integration of stimuli, leading to a multisensory supra- or sub-additivity, see below) (see Gentile et al., 2011 for fMRI evidence). Surprisingly, this non-linear multisensory integration for the PPS effect (around the trunk) has not been shown in electrophisiological studies in humans. Finally, evidence on the PPS system in humans mainly comes from fMRI studies. Thus, the existing literature has left several open questions such as the characterization of the spatio-temporal brain dynamics of the PPS processing (on the trunk), to what extent regions showing a PPS effect are also multisensory, and whether multisensory integration and PPS processing occur at similar time periods. Answering these questions would provide insight on whether the spatial modulation of multisensory processing characterizing PPS representation occurs in parallel with multisensory integration or follows it in a hierarchical way.

Answering these questions would provide insight on whether the spatial modulation of multisensory processing characterising PPS representation occurs in parallel with multisensory integration or follows it in a hierarchical way.

Here, we address the issues raised above, by recording intracranial electrical brain activity in humans, via surgically implanted electrodes in six patients with pharmacoresistant epilepsy. By combining high temporal and spatial resolution, intracranial recordings overcome some of the limitations of the techniques used in previous PPS experiments. Patients received tactile stimuli on the trunk while a task-irrelevant auditory stimulus approached the body. Because of the novelty of the study (and therefore limited evidence to generate hypothesis-driven analysis), and to avoid biases induced by prior assumptions, we used a data-driven methodology. To test multisensory PPS processing, we adopted a 2-step analysis approach , in which we first identified electrodes demonstrating multisensory integration – defined as showing non-linear sensory summation of response to multisensory stimuli (i.e., A+T vs. AT; Giard and Peronnet, 1999, for a review see Besle et al., 2004) – and then, within the resulting set of multisensory sensors, we search for electrodes showing a neural response that is modulated by the distance between the location of tactile and auditory stimulation (see Quinn et al., 2014 for a similar analytic approach in the visuo-tactile domain). By comparing the sites and the timing of multisensory integration and PPS processing, we investigated whether multisensory brain areas also encode for PPS. As additional analysis, we also investigated whether other brain regions (not showing a non-linear multisensory integration) also encode for PPS.

Methods

Participants

Intracranial EEG data (i.e., local field potentials; LFP) were recorded from 6 epileptic patients (3 females, 2 left-handed, mean age: 33±4.8 (mean ± sem), see Supplementary Table 1 for age, gender, handedness, and epilepsy focus of each patient) who were either implanted stereotactically with depth electrodes and/or grid electrodes were placed on the cortical surface (P-1, P2 and P-5) for clinical purposes (i.e., pre-surgical evaluation in pharmacoresistant epilepsy, see Table 1 for details). Written informed consent was obtained from all patients to take part in the procedures, which were approved by the local ethics committee.

Material and apparatus

Tactile and auditory stimuli were administered during the task (see Procedures below). Tactile stimulations were applied to the patient's chest, on the upper part of the sternum, by activation of a vibro-tactile motor (Precision MicroDrives, shaftless vibration motors, model 312-101, 3 V, 60 mA, 9000 rpm, 150 Hz, 5g, 113 mm2 surface area, maximal rotation speed reached in 50ms). Tactile stimulation lasted 100ms and was controlled via a purpose-made microcontroller (Arduino^{TM}, http://arduino.cc, refresh rate 10 kHz) and driven by in-house experimental software (ExpyVR, http://lnco.epfl.ch/expyvr, direct serial port communication with microcontroller). The auditory stimulus consisted of a white noise sound, which was approaching from the front, and centred on the patient's body, presented via insert earphones (model ER-4P; Etymotic Research). To give the impression that the sound was approaching from the front, sounds were pre-recorded from two arrays of 8 speakers (2m length in total) and head model binaural microphones (Omni Binaural Microphone, http://3diosound.com, see Serino et al., 2015, 2017 for detail regarding the external auditory setup).

Procedures

During the experiment, the patient was comfortably lying in bed, with the upper part of the body reclined forming approximately a 135° angle with the rest of their body. The patient was asked to keep their eyes closed for the duration of the experiment, and they were equally instructed to be attentive to the approaching sound and tactile vibrations. No overt task was requested from the patients.

The experiment consisted in three different types of trials: i) Auditory trials (unisensory audio; A), which consisted of an approaching sound, with a maximal simulated distance from the body of 2m (and lasted a total of 3 seconds; speed: 0.66 m/s), ii) vibro-tactile trials (unisensory tactile; T), which consisted of three successive stimulations, administrated 500ms, 1500ms and 2500m after the onset of the trial, and iii) audio-tactile trials (multisensory; AT), in which the tactile stimulation were administrated 500ms (Far distance, equivalent to 1.7m from the body), 1500ms (Middle distance, equivalent to 1m), and 2500m (Close distance, equivalent to 0.3m) after the initiation of the trial and auditory stimulus onset. To prevent anticipation effects on the vibro-tactile stimulation, a jitter of 0-200ms (steps of 50ms) was used for each delay of stimulation. This small temporal jitter allowed us to induce some variability in the timing of tactile stimulation, while not altering the spatial position of the sound when tactile stimulation was administered. A total of 85 trials for each condition were presented, in a randomized manner. The inter-trial interval was shuffled randomly between 1.4s, 1.7s, or 1.9s. In total, the experiment lasted approximately 20 minutes.

Electrode implantation, intracranial EEG recordings, and pre-processing

In total, 500 electrodes (depth & grid) were implanted in 6 patients, covering diverse cortical and subcortical areas including the post- and pre-central gyrus, insula, temporal and parietal operculum, amygdala, hippocampus, frontal and temporal cortex (see Figure 1 for the location of all recording sites). All implantation sites were determined purely based on clinical requirements. Three different types of electrodes were used for the recording: standard electrodes (contact size: 2.4mm, inter-electrode spacing: 10mm) ‘short spacing’ electrodes (contact size: 1.32mm, inter-electrode spacing: 2.2mm), and ‘micro’ electrodes (contact size: 1.6mm, inter-electrode spacing: 5.0mm).

For each patient, intracranial EEG signals were simultaneously recorded across all sites (Micromed System PLUS, Micromed, Mogliano Veneto, Italy) with a sampling rate of 2048 Hz, and an online high-pass filtered at 0.02 Hz. The external reference electrode was located at position Cz (i.e., vertex). Continuous intracranial EEG data were down-sampled to 512 Hz for analyses. Signals were filtered with a band-pass filter between 1Hz and 40Hz. Initial peri-stimulus EEG epochs were generated (800ms pre-trial onset – auditory stimulus in the case of A and AT trials - to 3000ms post-trial onset), and each epoch was centred to zero. Data were further re-epoched to 100ms pre-stimulus onset to 300ms post-stimulus onset. Baseline correction on the 100 ms pre-stimulus onset was applied, only on the electrodes that were identified as responsive vs. baseline (see Statistical analysis below for details).

In each patient, electrodes and trials showing excessive noise (i.e., > 6 interquartile range) were excluded, and thus 480 clean electrodes out of 500 implanted electrodes were used for further analysis. On stripes and depth electrodes, bipolar signals were computed by subtracting intracranial EEG signals from two adjacent electrodes (e.g., A1 – A2, A2 – A3…) from within each electrode shaft, to eliminate the influence of the common external reference and remote sources (Lachaux et al., 2003). In the case of grid electrodes, as bipolar referencing is not suitable (Lachaux et al., 2012, but see Mercier et al., 2017 for other procedures), we computed the average of the grid as a reference (i.e., local reference). After preprocessing the number of trials for the tactile conditions was 80.3 ± 1.2 (mean ± sem), 79.7 ± 1.7 (mean ± sem) for the auditory conditions, and 77.5 ± 1.5 (mean ± sem) for the audio-tactile condition. The number of trials retained per condition was not significantly different ($F(2,15) = 0.97$; $p = 0.39$).

To compute the Montreal Neurological Institute (MNI) coordinates for each electrode, a post-implant computed tomography (CT) image was co-registered to the normalised preoperative magnetic resonance imaging (MRI) using Cartool Software (Brunet et al., 2011). The midpoint between two depth electrodes was considered as the location of the corresponding bipolar derivation, and for the grid electrodes, the exact position was used. Then, locations of the electrodes were visualized on the Colin27 MRI brain template using the BrainStorm toolbox (Tadel et al., 2011). The anatomical description was assessed using Talairach coordinates (http://talairach.org/; Lancaster et al., 1997, 2000), with a 1mm cube around the coordinates defined above.

Statistical analysis

With the current experiment, we wanted to assess whether (non-linear) multisensory integration is mandatory for a PPS effect. Therefore, we conducted two distinct analysis. The first analysis was conducted based on the classic approach to study PPS in non-human primates, in which PPS is defined as a multisensory modulation of tactile processing due to an external sensory stimulation, as a function of the distance of these stimuli from the body in space (see introduction). Therefore, to identify PPS electrodes, we used a three-step statistical approach. First, we first identified electrodes responding to multisensory AT stimuli (vs. baseline), and among those electrodes. Second, among those AT electrodes, we investigated which responded in a manner suggesting multisensory integration (AT vs. A+T; see below). Third, among the electrodes showing a multisensory integration effect, we characterized those that had a PPS effect – a multisensory response that is dependent on the distance of exteroceptive signals (e.g., auditory information) to the body (see below for more details; a similar approach has been previously used in iEEG studies, e.g., Quinn et al., 2014). A second analysis aimed at identifying whether electrodes not showing a multisensory integration, did show a PPS effect. First, we first identified electrodes responding to the AT stimuli (vs. baseline). Second, among the electrodes showing a response, we identified those that had a PPS effect. For each of the above mentioned steps, statistical significance within each electrode was assessed through (temporal) cluster-based permutation statistics (Maris and Oostenveld, 2007) as implemented in the Fieldtrip toolbox (Oostenveld et al., 2011). The advantage of this test is that differences between conditions can be identified without prior assumptions about the temporal distribution of effects. Therefore, it is a data-driven approach. The cluster-level statistic was calculated as the maximum sum (maxsum) of the t-values within the cluster. Statistical significance at the cluster level was determined by computing a Monte Carlo estimate of the permutation distribution of cluster statistics, using 5000 resampling of the original data, yielding a distribution of cluster-level statistics under the null hypothesis that any differences between conditions are due to chance. Within a single electrode, a cluster was taken to be significant if it fell outside the 95% confidence interval of the permutation distribution for that electrode. The determination of significant temporal clusters was performed independently for each electrode. This method controlled for false alarms within an electrode across time points.

Active (unisensory and multisensory) electrodes

To evaluate and select active electrodes for latter between-conditions testing, we applied the cluster-based, nonparametric statistical procedure (see above for details). Electrodes demonstrating a significant response (post-stimulus period 0-300ms) relative to a baseline (-100ms to 0ms) during the post-stimuli onset to A, T and/or AT trials were considered as active electrodes (no baseline correction was applied for this analysis).

Audio-tactile multisensory integration

Among the active AT electrodes, we first selected those showing a response revealing significant multisensory integration (i.e., demonstrating either a supra or subadditivity effect., A+T vs. AT), and then among the electrodes evidencing multisensory integration we investigate which had a “PPS effect” – i.e., a non-linear modulation of tactile response depending on the distance of the sounds from the body. To identify both the “multisensory” and “PPS” electrodes a modified version of the cluster-based, nonparametric statistical procedure outlined by Maris and Oostenveld (2007) was applied. To assess statistically a multisensory integration effect, we applied a cluster-based permutation statistic individually to each electrode (which showed to be active in comparison to baseline), with the contrast AT vs. A+T.

PPS effect

To investigate the PPS effect we conducted to distinct analysis (see statistical analysis above). One the one hand, we first selected the electrodes showing an AT multisensory integration. Then among those electrodes, we selected those showing a PPS effect. To identify a PPS effect (i.e., a modulation according to the distance of the sound from the body) the following procedure was applied: i) we first computed the difference AT-A, providing us with the LFPs for the PPS in response to the tactile stimulus, ii) to assess a statistically PPS effect we applied a cluster-based permutation statistic individually on the PPS-LFPs, and we computed a one-way ANOVA (with the contrast Far vs. Middle vs. Close). These analysis steps were applied to each electrode, independently.

This two-step approach was chosen for several reasons. First, it provides the possibility to compare the PPS effect with the condition in which only the T stimulus was administered (our control condition), and therefore assess that the PPS processing effect is different from the T stimulation effect (i.e., which may indicate habituation/expectation effect). Second, this approach allows us to control for an eventual effect due to a change in sound intensity as a function of the distance from the body. That is, with this approach we can certify that putative PPS effects are not purely due to a change in sound intensity (at the stimulus is closer to the body), and that it is different from a simple tactile habituation.

On the other hand, to provide a characterization of the PPS effect as detailed as possible, we conducted additional analysis in which we assessed whether any PPS effect may be present also in electrodes that do not show multisensory integration. For this complementary analysis, we applied the cluster-based, nonparametric statistical procedure (p-val<0.01, see above for details). Electrodes demonstrating a significant response (post-stimulus period 0-300ms) relative to a baseline (-100ms to 0ms) during the post-stimuli onset to AT trials were considered as active electrodes. Among those electrodes, we assess which electrodes also showed a PPS effect. That is, to assess a statistically PPS effect we applied a cluster-based permutation statistic (p-val<0.01) individually on the PPS-LFPs, and we computed a one-way ANOVA (with the contrast Far vs. Middle vs. Close) for each electrodes/condition.

Control analysis

To investigate if any anticipation/habituation effect had occurred and could account for the PPS effect, we computed a similar analysis as for the “PPS effect” on the condition in which only the tactile stimulus was presented. Electrodes demonstrating both a multisensory integration and PPS effect but no (or at least with different response pattern) tactile habituation effect can arguably be safely considered electrodes evidencing a multisensory effect that is space-dependent, i.e., putatively recording activities from “PPS brain areas.

Results

Active unisensory and multisensory electrodes

We first investigated which electrodes showed a significant response vs. baseline period, across the 480 implanted electrodes (Figure 1, 480 out of 500 electrodes were included after pre-processing), from all 6 patients, in any of the tested conditions. Our data show that 75 electrodes (~16% out of 480) were responsive to T stimulation, 61 electrodes (13% out of 480) were responsive to A stimulation, and 99 (~21% out of 480) were responsive to AT stimulation (for a summary of activation see Figure 1 and Figure S2, that show which electrode is responding and to which condition). It should be noted that some of the electrodes responding to one condition can also be responsive to one of the other conditions.

Table 6.1. Patient Demographics and Electrodes Detail.

Patient	Age	Gender	Handedness	Epilepsy Focus	Comorbidity	Medication	Number of implanted electrodes	Number of electrodes with Multisensory integration	Number of PPS electrodes
P-1	33	Male	Left	Right post central epilepsy	Migraine, anxiety	No antiepileptic drugs	88 (Grid 64e + 3x8e deepth)	6	2 (Right hemisphere)
P-2	29	Female	Left	Left parietal opercular epilepsy	None	Trileptal; Vimpat Urbanyl	108 (Grid 64e + 5x8e deepth + 1x4 strip)	2	0
P-3	55	Female	Right	Right temporal epilepsy	None	Trileptal	48 (6x8e deepth)	3	2 (Right hemisphere)
P-4	33	Male	Right	Left temporal epilepsy	Migraine	Carbamazepine	76 (8x8e deepth + 2x6 strip)	2	0
P-5	33	Male	Right	Right post central epilepsy	None	Topiramate; Benzodiazepines	60 (Grid 32e + 3x8e deepth + 1x4 strip)	6	1 (Right hemisphere)
P-6	19	Female	Right	Right temporal epilepsy	Mild anorexia (not comfirmed by DSM-IV), depression	Valproate acid Lamotrigine	120 (15x8e deepth)	1	1 (Right hemisphere)

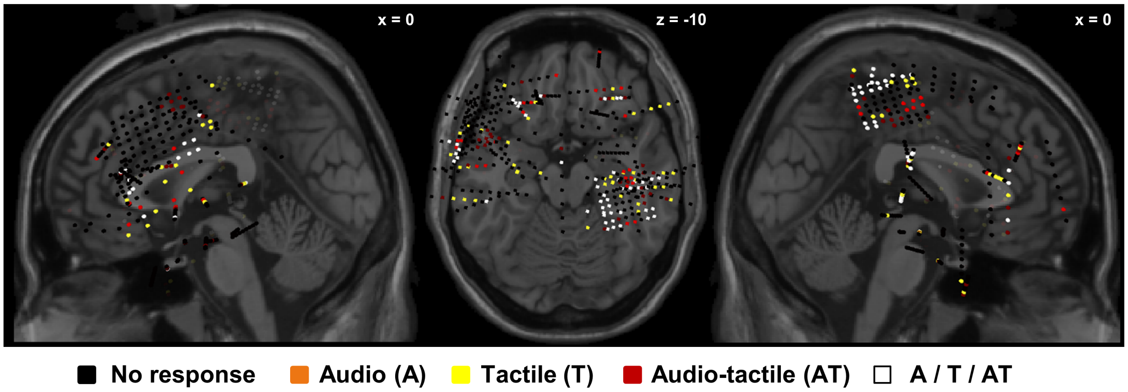

Figure 6.1. Locations of all recording sites in 3D MNI space. MNI coordinates of electrodes from all 6 patients (500 electrodes in total) plotted on the Colin27 MRI template (on selected sagittal and axial planes). Note that locations are in 3D MNI space, and not located on the surface of MRI slice shown (thus, recording sites behind the depicted MRI slice are marked with faded color). In black, the implanted electrodes not showing a response (vs. baseline, cluster-corrected) to stimuli, in red, the electrodes showing a response to audio stimuli only, in yellow, the electrodes showing a response to tactile stimuli only, in dark red, the electrodes showing a response to audio-tactile stimuli, and in white the electrodes showing a response to at least two conditions.

Location of unisensory and multisensory electrodes

Among the responsive electrode, we assessed the distribution of unisensory (T and A) and multisensory (AT) responses. The electrodes responding to the T stimulus were predominantly located in the postcentral gyrus (PCG), but also in the insula and inferior frontal gyrus (IFG). The electrodes responding to the A stimulus were predominantly located in the superior and inferior temporal gyrus (STG and ITG). The electrodes responding to the AT stimuli were in the PCG, the precentral gyrus (PreCG), the mid-temporal gyrus (MTG) and STG, IFG, insula and parahippocampal gyrus (PHG) (Figure 1 & 2 for a summary). Next, to give an overview of the distribution of the electrode location (and quantify the proportion of electrodes), we grouped them into larger brain regions. 42% (213 electrodes) of the electrodes were implanted in frontal areas, among those electrodes ~11% (23 electrodes) showed a response to A, ~11% (24 electrodes) to T and ~12% (26 electrodes) to AT, the rest of the electrodes were not responsive electrodes. 18% (86 electrodes) of the electrodes were implanted in the temporal areas, among those electrodes ~17% (15 electrodes) showed a response to A, ~8% (7 electrodes) to T and ~23% (20 electrodes) to AT. 12% (56 electrodes) of the total number of electrodes in the current study were implanted in the parietal areas, among those electrodes ~9% (5 electrodes) showed a response to A, ~43% (24 electrodes) to T and ~46% (26 electrodes) to AT. Finally, 2% (13 electrodes) of all electrodes implanted in the current study were implanted in the insula, among those electrodes ~23% (3 electrodes) showed a response to A, ~31% (4 electrodes) to T and ~46% (6 electrodes) to AT (for additional details see Figure 1, and Figure S1).

Location of the electrodes showing audio-tactile multisensory integration

Among the responsive AT multisensory electrodes (99), 20 electrodes (~19% of active electrodes) showed significant multisensory integration (i.e., AT vs. A+T). This multisensory integration occurred principally within the PCG (7 electrodes, 35% of the AT multisensory electrodes), but also within the STG (3 electrodes, 15% of the AT multisensory electrodes), within the PHG (3 electrodes, 15% of the AT multisensory electrodes), within the Pre-CG (1 electrode, 5% of the AT electrodes), IFG (1 electrode, 5% of the AT electrodes), and the insula (1 electrodes, 5% of the AT electrodes). 4 electrodes were situated in the white matter (Figure 2 and see Table 2 for more details). The closest cortical brain regions which could have have generated the responses at these 4 electrodes are: insula (1 electrode), STG (1 electrode) and IFG (2 electrodes).

Timing of audio-tactile multisensory integration

On average, across the 20 electrodes showing AT multisensory integration, the effect occurred from 151ms ± 18ms (mean ± sem) to 244ms ± 15ms (mean ± sem) post-stimulus onset (i.e., tactile). Within the insula the effect occurred from 63ms to 296ms post-stimulus onset, and a supra-additive non-linear (AT > A+T) neural response was observed. Within the STG the response occurred from 100ms ± 40ms (mean ± sem) to 210ms ± 57ms (mean ± sem), and supra-additive non-linear (AT > A+T; neural response interactions between multisensory and the sum of the constituent unisensory stimuli) was observed. Within the PHG the effect occurred from 112ms± 39ms (mean ± sem) to 239ms ± 25ms (mean ± sem) and a supra-additive non-linear (AT > A+T) neural response was observed between the multisensory response and the sum of the constituent unisensory stimuli. Within the pre- and post-central gyri and IFG the effect occurred from 181 ± 25ms (mean ± sem) to 254 ± 22ms (mean ± sem) (see Table 2 for a summary of the timing). In the pre- and post-central gyri the multisensory integration occurred as a supra-additive non-linear neural response (AT > A+T) (Figure 3, for an exemplary LFP for AT multisensory integration). In the IFG the multisensory integration occurred as a sub-additive non-linear neural response (AT < A+T).

Table 6.2. Number, Location, and Timing of Multisensory Electrodes

Region	Number of AT Multisensory electrodes	Timing of AT multisensory integration (mean ± sem)
Postcentral Gyrus	7	228ms ± 18ms to 279ms ± 6ms
Superior Temporal Gyrus	3	100ms ± 40ms to 210ms ± 57ms
Parahippocampal Gyrus	3	112ms± 39ms to 239ms ± 25ms
Inferior Frontal Gyrus	1	245ms to 291ms
Precentral Gyrus	1	222ms to 299ms
Insula	1	63ms to 296ms

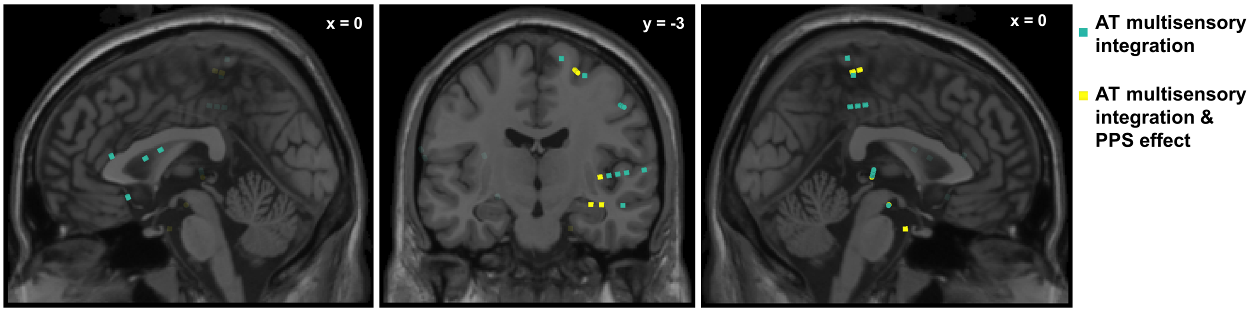

Figure 6.2. Locations of electrodes showing an AT multisensory integration and peripersonal space (PPS) effect, in 3D MNI space. MNI coordinates of electrodes from all 6 patients, electrodes showing specifically a significant multisensory integration profile are highlighted in green (20 electrodes, see Table 1 for the position), electrodes showing both an AT multisensory integration and PPS effect are highlighted in yellow (6 electrodes, see Table 1 for electrodes positions). Note that locations are in 3D MNI space, and not located on the surface of selected MRI slice (thus, recording sites behind the depicted MRI slice are marked with faded color).

Location of the electrodes showing a PPS effect

Among the 20 electrodes showing AT multisensory integration, 6 electrodes (30% of AT multisensory electrodes, and 6% of active AT electrodes) showed a PPS effect. From the electrodes characterized as coding for PPS, 3 electrodes were located in the PHG (50% of the PPS electrodes), 2 electrodes were found in the PCG (34% of the PPS electrodes), and 1 electrodes in the insula (17% of the PPS electrodes; see Figure 2, Table 3 for details). Importantly, for all the locations where a PPS effect was observed, the response profile differed as a function of the distance from the trunk in such a way that PPS-dependent multisensory integration does not linearly decrease with distance, but is more similar to a step-function (see Figure 4, right panel).

In addition to the electrodes showing AT multisensory integration and a PPS effect, we also observed 4 electrodes showing a PPS effect, without showing a non-linear AT multisensory integration effect. Among those electrodes, 3 were located in the IFG, 1 electrode was located in the STG.

Timing of the PPS effect

On average, across the 6 electrodes, the PPS effect occurred from 139ms ± 26ms (mean ± sem) to 226ms ± 31ms (mean ± sem) post-stimulus onset. Within the insula the effect occurred from 39ms to 129ms and from 141ms to 296ms. Within the PCG the PPS effect occurred from 44ms ± 3ms (mean ± sem) to 92ms ± 12ms (mean ± sem) and from 202ms ± 18ms (mean ± sem) to 265ms ± 7ms (mean ± sem). Within the PHG the PPS effect occurred from 193ms ± 23ms (mean ± sem) to 299ms ± 1ms (mean ± sem) (see table 3 for a summary of the timing).

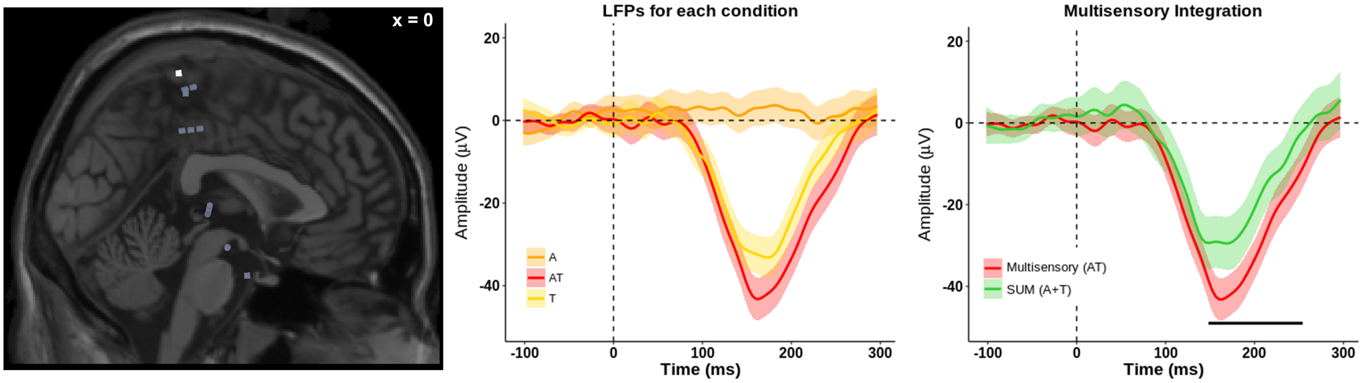

Figure 6.3. Exemplar LFP for AT multisensory integration. The left panel shows the position of the electrode, on a selected plane. The electrode was located in the postcentral gyrus (PCG). The middle panel shows the LFPs responses for three conditions: A (orange), T (yellow) and AT (red). The right panel shows the LFPs for the AT (red) and the SUM of A+T (green), with a multisensory integration at 148-253ms after the stimulus onset. The lines indicate the average over trials; the shaded areas indicate the 95% C.I., and the black lines indicate the time period with a significant AT multisensory integration (p-value < 0.05, cluster-corrected).

Tactile habituation (control analysis)

To ascertain that the above-described PPS effect was not simply due to tactile habituation, we investigated if a 'time-dependent' effect (i.e., a significant difference on unisensory tactile responses as a function of the delay of tactile stimulation) was observed with the T stimulus alone. Among the 20 AT multisensory integration electrodes, 2 electrodes showed a possible anticipation/habituation effect in the tactile condition. These effects occurred within the PHG. Here, two distinct time periods showed a tactile habituation effect, on average the first time period occurred from 143ms ± 16ms (mean ± sem) to 213ms ± 35ms (mean ± sem) post-stimuli onset, and the second time period occurred from 188ms to 281 (only on one electrode – Figure S2). No other electrode showed a modulation in response to the T stimulus as a function of time.

These tactile habituation effects occurred during (at least partially) different time-points than the PPS effects, and the modulation was "linearly" dependent on the temporal order of the stimuli presentation. That is, the effect on the T condition showed a modulation of the LFPs for the 1st vs. 2nd administrated tactile stimulus (over both time significant time periods), and for the 2nd vs. 3rd (over the second significant time period) administrated tactile stimulus. This modulation pattern was different from what was observed for the PPS effect, where we see a difference, for instance, between the far and the middle/close distance (conceptually similar to a step-function, see Figure S2).

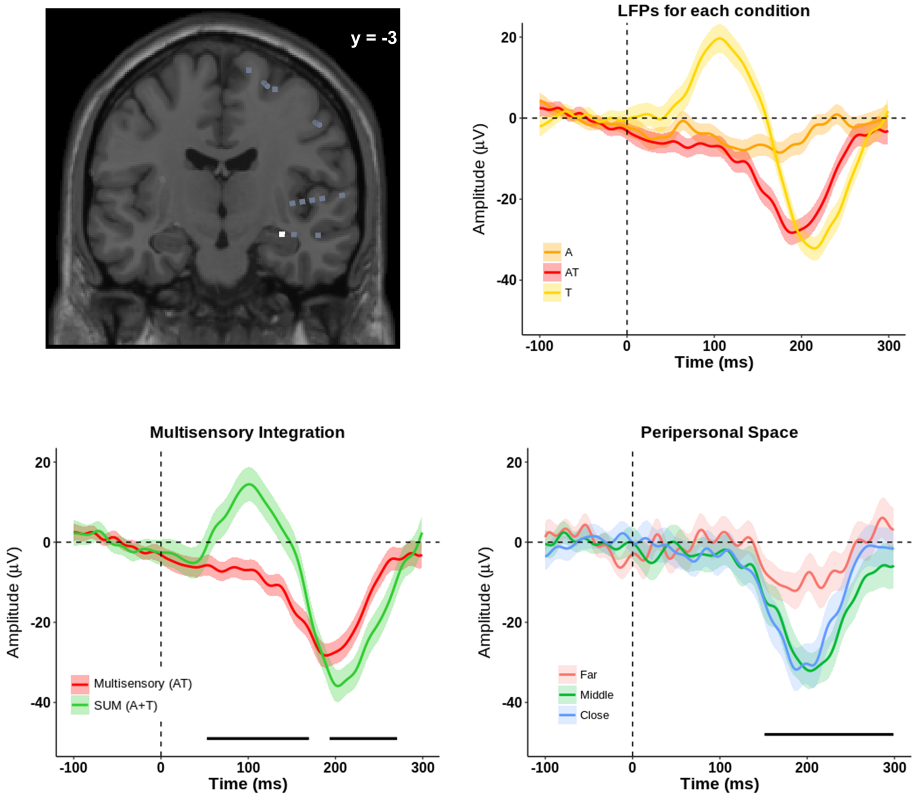

Figure 6.4. Exemplar LFP for AT multisensory integration & PPS effect. The top left panel shows the position of the electrode, on a selected plane. The electrode was located in the parahippocampal gyrus (PHG). The top right panel shows the LFPs responses for three conditions: A (orange), T (yellow) and AT (red). The bottom left panel shows the LFPs for the AT (red) and the SUM of A+T (green), with a multisensory integration at 52-170ms and 193-270ms after stimulus onset. The bottom right panel shows the LFPs for the PPS effect at 151-298ms after stimulus onset. The bottom right. The lines indicate the average over trials; the shaded areas indicate the 95% C.I., and the black lines indicate the time period with a significant PPS effect (p-value < 0.05, cluster-corrected).

Discussion

Intracranial EEG human recordings were performed in six patients suffering from pharmacoresistant epilepsy, who were presented with vibrotactile stimulation and concurrent sounds approaching their trunk in an effort to unravel the neurophysiological substrates of audio-tactile peripersonal space (PPS) surrounding the trunk. Crucially, and overlooked in most previous studies, PPS is defined as a multisensory spatial extent (e.g., Ferri et al., 2016; Graziano et al., 1997; Serino et al., 2015). Therefore, here we first identified brain responses that exhibited AT multisensory integration, indexed by non-linearity compared to the sum of the unisensory constituents of the multisensory stimuli (i.e., A+T vs. AT). Subsequently, within this subset of multisensory integration responses, we identified those that showed a modulation of the response as a function of distance from the body – that is, a PPS response. Broadly, results demonstrated that 99 (21%) of the 500 electrodes, implanted for clinical purposes, were responsive to the multisensory AT stimulation, with 75electrodes (21%) and 65 (16%) being only responsive to T or the A unisensory stimulation, respectively. In addition, 19% (20 electrodes from the 104 electrodes showing an AT multisensory response) of these active electrodes specifically exhibited multisensory integration (defined as a non-linear summation of the response to AT stimuli, differently from the sum of A+T stimuli). These were located predominantly in the PCG, STG, insula and PHG. The AT multisensory response occurred, respectively, on average from 181ms, 100ms, 63ms, and 112ms post-stimuli onset. Among these 20 AT multisensory integration electrodes, 30% (6 electrodes) also showed a PPS effect - i.e., a non-linear modulation of the response to tactile stimuli as a function of the distance of the sounds from the body. Crucially, the spatial modulation of the responses did not linearly decrease with distance from the body (as it may be the case for responses related to tactile anticipation), but differentiated between the far vs. middle and/or near positions, suggestive of the presence of an electrophysiologically defined boundary between PPS and the far space (between 30cm and 100 cm from the body), in agreement with behavioral data in humans (Noel et al., 2015; Serino et al., 2015; Pfeiffer et al., 2018). The brain regions demonstrating a multisensory PPS effect were located most prominently in the PCG, but also within other cortical structures, namely the insula and the PHG (see Grivaz et al., 2017 for independent corroborative evidence). The PPS effect in those brain regions occurred, respectively, on average at 44ms, 39ms and 193ms post-stimuli onset. Hence, we present neurophysiological evidence, for the first time in humans, for the encoding of audio-tactile multisensory PPS in an extended cortical network. These human findings corroborate and extend those described in non-human primate studies, which demonstrated PPS processing mostly tested around the face and the hand in the parietal lobe (Duhamel et al., 1997, 1998; Graziano et al., 1997, 1999; Schlack et al., 2005) and fMRI studies in humans showing specific processing for stimuli presented close to the hand and face (parietal lobe, primary somatosensory cortex and insula; Grivaz et al., 2017). The present results describe neural mechanisms of the human *trunk* PPS that has been suggested to also be of particular importance for bodily self-consciousness (Noel et al., 2015; Serino et al., 2015; Blanke et al., 2015) and also reveal evidence for trunk PPS coding within the limbic system (i.e., PHG). In the following, we discuss our results with respect to multisensory integration, PPS and the conjunction between the two processes, in terms of brain location and timing of the effects.

Location of audio-tactile multisensory integration

Our results corroborate and extend previous literature, by showing multisensory neural processing in response to audio-tactile multisensory pairings (vs. visuotactile in Avillac et al., 2007), in humans (vs. monkeys) and in LFP recordings (vs. single units). Research regarding multisensory integration – in particular, electrophysiological studies in non-primary sensory areas - have focused mostly on audio-visual and visuo-tactile integration. Much less is known about AT multisensory integration. Classically, multisensory integration has been considered to occur in higher-order temporal, parietal and occipital regions (Jones and Powell, 1970, more recently Quinn et al., 2014). However, this view has been challenged by studies, in both monkeys and humans alike, that provided evidence for early multisensory neural modulations (Lakatos et al., 2007; Schroeder and Foxe, 2002) occurring in regions traditionally considered purely unisensory cortices. Many of these modulatory effects in primary sensory areas have been demonstrated via somatosensory or visual effects in the primary auditory areas (Besle et al., 2008; Lakatos et al., 2007; Schroeder and Foxe, 2002). However, both fMRI and EEG experiments have highlighted the posterior superior temporal plane (Foxe et al., 2002; Murray et al., 2005), and not primary sensory areas, as brain regions implicated in veritable, overt or supra-threshold, audio-tactile multisensory integration. Other studies localized AT multisensory integration in the posterior parietal cortex, the somatosensory area SII and insula, rather than auditory association cortices (Gobbelé et al., 2003; Lütkenhöner et al., 2002; Renier et al., 2009). Thus, despite the fact that brain coverage in our study was limited by clinical purposes, the location of the electrodes showing stronger AT multisensory integration responses in our data corroborate and extend previous literature. That is, most of the electrodes demonstrating multisensory integration in our study were located in PCG, but also in the STG and insula. Despite, most of the multisensory electrodes being located in the PCG and thus anterior to the VIP region studied in monkeys (Avillac et al., 2007), this difference might be partially due to a different location of VIP in humans (more anterior and ventral) than in monkeys (Sereno and Huang, 2014).

The timing of audio-tactile multisensory integration

A key advantage of recording intracranial LFPs as opposed to the BOLD response is that the former allows for indexing and characterizing time-resolved computations, in combination with high spatial resolution. In monkeys, AT multisensory integration has been reported to occur at early latencies (< 100ms) (e.g., Schroeder and Foxe, 2002; Schroeder et al., 2001, 2003). In humans, AT multisensory integration has been reported to occur both at early latencies (e.g., Murray et al., 2005) and at later latencies > 100ms (Lütkenhöner et al., 2002; Gobbelé et al., 2003). Late multisensory integration is supported by Quinn et al. (2014), who reported multisensory responses to visuo-tactile stimulation from iEEG recordings at latencies ranging from 145ms to 313ms post-stimulus onset. Multisensory integration at later latencies is also consistent with Valdés-Conroy et al., (2014), who performed an ERP study as a function of visual depth and reported a significant amplitude modulation in evoked responses within 150-200ms from stimulus onset. At first, our results show that the latency of the AT multisensory integration responses occurs on average between 151ms and 244ms, which is in agreement with later processes of multisensory integration. However, it is important to note that our results show three distinct temporal response patterns. That is, we also found an early AT multisensory integration occurring at ~60ms after the stimulus onset, within the insula and PHG, and a later effect occurring at ~100ms within the STG, followed by the even later PCG and IFG responses, suggesting that AT multisensory integration occurs over two (at least partially) distinct time periods, over more ventral (earlier effects) and more dorsal (later effect) regions (e.g., Reiner et al., 2009).

Location of PPS effect

The present results extend the findings of a recent fMRI meta-analysis (Grivaz et al., 2017) study in humans, that aimed at identifying areas that consistently coded for PPS. This later study identified a portion of the PCG, including regions of area 1, 2 and 3b, as well as areas 5 and 40, as crucial PPS areas. Similarly, the present (and other) studies found PPS-like responses in the insula (Cappe et al., 2012; Schaefer et al., 2012) in humans. Thus, locating the bulk of multisensory PPS neural responses to the PCG (present study) is corroborated by recent functional neuroimaging literature on PPS processing.

We also found multisensory PPS responses in the insula and PHG. Regarding the insula, although it is a known area of multisensory convergence (Bushara et al., 2001; Calvert et al., 2001; Renier et al., 2009; Rodgers et al., 2008), its direct electrophysiological implication in the multisensory mapping of PPS has not been previously established. However, the insula has been linked to changes in body ownership, self-identification and self-location after multisensory illusions, such as the rubber hand illusion (Blefari et al., 2017; Brozzoli et al., 2012; Grivaz et al., 2017; Tsakiris et al., 2007), the enfacement illusion (Apps et al., 2015), and the full body illusion. It is therefore considered a key area for the processing of multisensory cues underlying bodily self-consciousness (Blanke, 2012; Salomon et al., 2016; Seth, 2013). Notably, the illusions often used to study bodily self-consciousness rely on the manipulation of the spatiotemporal congruency of tactile cues on the body and visual cues from the external space, and have been shown to induce remapping of the PPS around the hand (Brozzoli et al., 2012), face (Maister et al., 2015) and trunk (Noel et al., 2015; Park et al., 2017). The present finding of PPS-related activity in the insula, hence, reinforces theoretical postulations (Blanke, 2012; Blanke et al., 2015; Serino et al., 2013) and psychophysical results (Noel et al., 2015; Salomon et al., 2017) highlighting the association between bodily self-consciousness and PPS representation. Lastly, the PHG has previously been categorized as a multisensory region (Tanabe et al., 2005), and a number of studies have suggested that the PHG is part of a network involved in processes relating to bodily self-consciousness (Tsakiris et al., 2007; Forget et al., 2015) as well as spatial navigation and self-location (Guterstam et al., 2015a, 2015b). The present data underline the PHGs involvement in multisensory PPS processing. This finding deserves further research concerning the potential role of this region as a hub between multisensory PPS processing, self-related processing, and its well-described role in memory and spatial navigation (Guterstam et al., 2015a, b). Interestingly, experimental alterations of bodily self-consciousness have been suggested to alter memory formation through activation of the hippocampal formation (Bergouignan et al., 2014). Thus, it may be proposed that the PHG serves as a gateway between the lower-level (multisensory) aspects of PPS and the implication of trunk-centered PPS in higher-order level of cognition such as egocentric processing (Canzoneri et al., 2016). A speculation that remains to be further tested (see Berthoz, 2000, for similar speculation).

The timing of PPS effect

Evidence on the timing of AT PPS effect is currently lacking based both animal and humans studies. The only evidence concerning the timing of the PPS effect is provided by studies investigating visuo-tactile PPS. At first, our PPS results may appear somewhat late compared to previous electrophysiological findings of visuo-tactile PPS, as the present PPS responses occurred on average between 129ms and 226ms. For instance, evidence from single cell recording in monkeys (Avillac et al., 2007) show visuo-tactile, PPS-related responses occurring already at 68ms. In humans, Sambo and Forster, (2009) performed a visuo-tactile ERP study as a function of the spatial disparity of visuo-tactile stimuli in depth and observed a modulation in ERP amplitude at electrodes over the superior temporal lobe already at 100ms post-stimulus onset. Similarly, Cappe et al., (2012) showed an effect of distance for audio-visual stimuli starting at ~75ms post-stimuli onset. Although the average of our PPS effect occurred somewhat later compared to previous evidence, it is worth noting that our results show distinct response patterns. That is, the insula and PCG show a first response at ~40ms after stimulus onset, which is compatible with an early visuo-tactile PPS response. In addition, we also found a later response (~150ms after stimulus onset) in the insula, PCG, and PHG, in line with later responses observed in previous studies. These results suggest that the PPS responses (on the trunk) occur during at least two distinct time periods, and can occur simultaneously over different brain areas, largely overlapping with AT responses (see next section).

Audio-tactile multisensory integration and PPS effect

Another finding worth highlighting regarding AT multisensory integration and the PPS effect is that both these processes appear to co-exist spatially and temporally (i.e., in the same electrodes and during similar time periods). AT multisensory integration is apparent on average from 151ms to 244ms post-stimuli onset, while PPS effect is discernable on average from 139ms to 226ms post-stimuli onset. If we look in greater detail into the different regions where both multisensory integration and PPS effect occurred, the timing of the two processes also overlapped. This observation hence provides – for the first time - evidence speaking in favour of a PPS representation, which is not yielded after a series of processes whereby multisensory integration occurs first and in different brain regions and then forwarded to different regions forming a PPS representation of the space surrounding a body. On the contrary, our results show that AT multisensory integration and PPS effect are concurrent during two time periods and across several brain regions. These electrophysiological findings suggest that PPS processing is based on a form of multisensory integration which, in addition, shows a clear spatial modulation of the response, in agreement with previous suggestions from neuropsychology (Farnè and Làdavas, 2000) or psychophysical (e.g., Noel et al., 2015; Serino et al., 2015) studies. Our data add critical insight by demonstrating that the representation of the space near (vs. far) from one's body results from the processing of events/objects in the world involving the response of multisensory brain regions located in the PCG, but also in deeper and more medial areas (such as the insula and the PHG), likely harboring multisensory neurons with bodily-anchored and depth-restricted RFs (Fogassi et al., 1996; Graziano et al., 1997, Avillac et al., 2007; see Magosso, 2010 for a computational model of multisensory PPS representation). Our results also indicate that some electrodes, located in the IFG, STG and CG, show a PPS effect without showing a multisensory integration. However, it should be noted that those electrodes were spatially adjacent (or at least in the same brain regions) to electrodes showing multisensory integration and PPS effect.

Our results also show that the PPS effect is not due to a mere habituation and/or anticipation effect. First, because of the experimental design used included a randomized order of conditions (Audio (A), Tactile (T), and Audio-tactile (AT)) across trials. Therefore, despite the onset of a sound for the A and AT, the participant could not predict if a tactile stimulation would occur or not. Second, if indeed our results had been biased by some form of warning cue, we would have expected that the response to the first tactile stimulation (i.e., far condition for the AT) to be stronger compared to the two other tactile stimulation conditions (i.e., middle, close for the AT). This, however, was not the case. Our results rather show a stronger effect for tactile stimuli in the middle and close (vs. far) position (see figure 4). Third, there was a 500 msec between the onset of the auditory stimulus and the occurrence of the first tactile stimulus in the AT conditions. Thus, more than a warning stimulus, the auditory stimulation might act as a cue to expect the occurrence of the tactile stimulation at the far location. However, given the design of our task, this was also the case for the AT middle and near locations. The expectation is therefore equivalent between the 3 time points/distances, or eventually should increase linearly. This was the reason why we added the control analysis on the T condition, which actually showed a very different pattern of modulation of the response as compared to the AT condition.

As a last note, the experimental design used in the current study was aimed at studying multisensory processing involving a tactile response, and more precisely a modulation of tactile processing due to the presence of an auditory cue within the PPS, in line with the neurophysiological mechanisms of PPS as suggested by previous animal research. This may have biased our results towards finding PPS effects more likely within tactile rather than auditory areas. Despite this, we observed results in both tactile and auditory areas. Nevertheless, because the electrodes were exclusively implanted for clinical purpose, the current dataset does not allow us to clearly state for or against such bias, nor to make any specific claim about the prevalence of our effect in any specific region of the brain.

Conclusion

We describe electrophysiological responses linked to the multisensory integration of AT events and distinguished them from unimodal A or unimodal T responses as well as from simple AT summation responses. In addition, we showed that among these AT multisensory responses, LFPs from specific sites were modulated by the distance between the A and T component in a way that distinguishes near, peripersonal or bodily space (the trunk PPS) from spatial compartments far from the body. AT multisensory integration was first observed in the insula and during later phases in the STG, PCG, PHG, and IFG. A similar spatiotemporal response pattern was observed for the PPS effect but limited to insula, PHG, and PCG. Taken together, the present findings show – for the first time – that AT multisensory integration and PPS effect share common spatial and temporal processes, which go beyond previous single unit reports of multisensory integration in putative PPS neurons in area VIP (Avillac et al., 2007) to a number of other cortical areas, while also indexing multisensory PPS in humans, via audio-tactile, as opposed to visuotactile integration, and around the trunk as opposed to the hand or face.

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Supplementary Materials

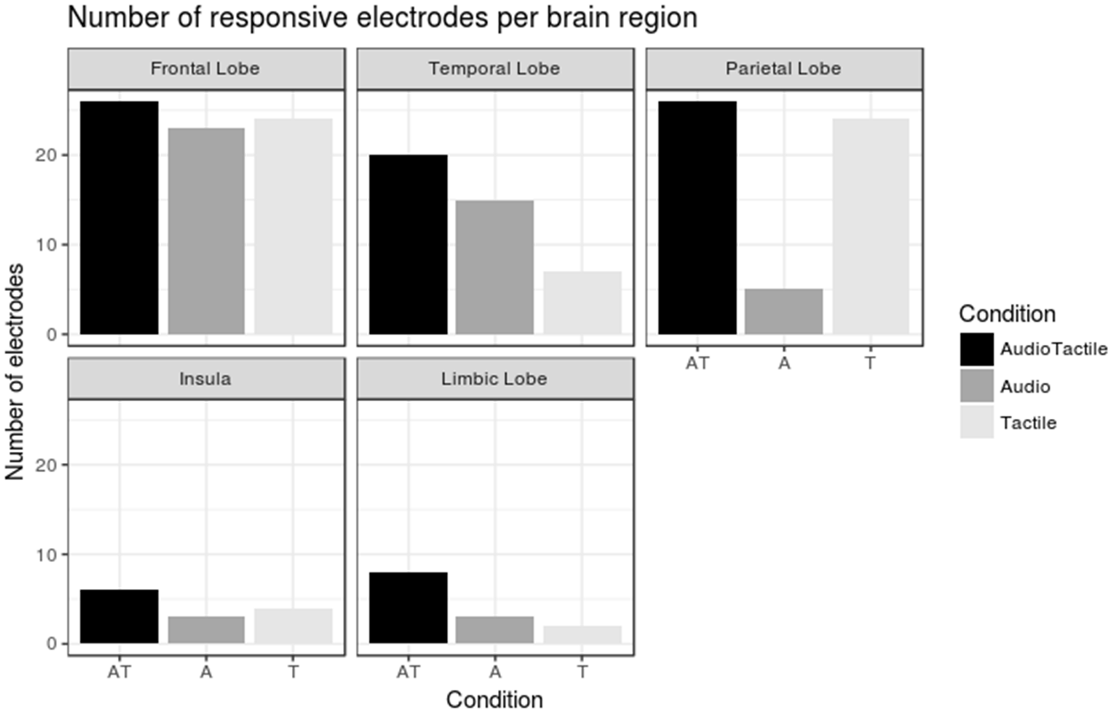

Figure 6.5. Number of electrodes responding per brain region. We show the number of electrodes responding per brain region and for the different conditions: auditory, tactile and audio-tactile stimuli.

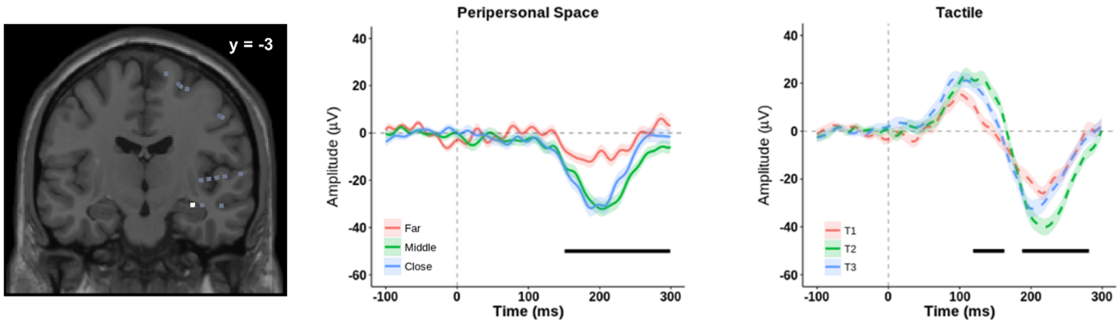

Figure 6.6. Exemplar LFP waveforms from one patient (control condition). This electrode showed an audio-tactile multisensory integration (i.e., AT vs. A+T; middle panel) effect at 52-170ms and 193-270ms after stimulus onset, a PPS effect (i.e., modulation of the LFPs response depending on the distance of the sound from the body; third panel from the left) at 151-298ms after stimulus onset. An effect was observed for the unisensory tactile condition (i.e., a modulation of the response according to the order of presentation; fourth panel from the left) at 120-163ms and 188-281ms after the stimulus onset. The electrode was located in the parahippocampal gyrus. The lines indicate the average over trials; the shaded areas indicate the 95% C.I., and the black lines indicate the time period significant (p-value < 0.05, cluster-corrected).

CHAPTER VII

PERIPERSONAL SPACE AS THE SPACE OF THE BODILY SELF

The contents of this chapter are adapted from

Noel, J.P., Pfeiffer, C., Blanke, O., Serino, A. (2015). Peripersonal Space as the space of the bodily self. Cognition, 114, 49-57. doi:10.1016/j.cognition.2015.07.12

Abstract

Bodily self-consciousness (BSC) refers to experience of our self as located within an owned body (self-identification) and as occupying a specific location in space (self-location). BSC can be altered through multisensory stimulation, as in the Full Body Illusion (FBI). If participants view a virtual body from a distance being stroked, while receiving synchronous tactile stroking on their physical body, they feel such as the virtual body were their own and they experience, subjectively, to drift toward the virtual body. Here we hypothesized that - while normally the experience of the body in space depends on the integration of multisensory body-related signals within a limited space surrounding the body (i.e. peripersonal space, PPS) - during the FBI the boundaries of PPS would shift toward the virtual body that is toward the position of self-location. To test this hypothesis, we used synchronous visuo-tactile stroking to induce the FBI, as contrasted with a control condition of asynchronous stroking. Concurrently, we applied an audio-tactile interaction paradigm to estimate the boundaries of PPS. PPS was measured in front of and behind the participants' body as the distance where tactile information interacted with auditory stimuli looming in space toward the participant's physical body. We found that during synchronous stroking, i.e. when participants experienced the FBI, PPS boundaries extended in the front-space, toward the avatar, and concurrently shrunk in the back-space, as compared to the asynchronous stroking control condition, where no FBI was induced. These findings support the view that during the FBI, PPS boundaries translate toward the virtual body, such that the PPS representation shifts from being centered at the location of the physical body to being now centered at the subjectively experienced location of the self.

Introduction

A fundamental aspect of our sense of self as subject of conscious experience is the experience of the bodily self, that is, the feeling of being located within a body we own and control (Blanke & Metzinger, 2009; Gallagher, 2005; Jeannerod, 2006). Empirical data demonstrate that the feeling of owning a body (self-identification), as well as the sense of being located within the boundaries of that body (self-location), are fundamentally rooted in the congruent and cohesive integration of multiple sensory modalities within the spatio-temporal dimensions of the physical body (Blanke, 2012). In fact, manipulating the spatio-temporal congruency of different sensory modalities can induce different bodily illusions, such as the Rubber Hand Illusion (RHI: Botvinick & Cohen, 1998), the Full Body Illusion (FBI: Lenggenhager, Tadi, Metzinger, & Blanke, 2007) and Out-of-Body illusions (Ehrsson, 2007). During the FBI subjects see a virtual body (avatar), placed 2 meters in front them, being stroked, while synchronously receiving a congruent tactile stimulation on their physical body. Under such circumstances participants report to identify with the virtual body (change in self-identification), and feel displaced toward the virtual body (change in self-location). These effects are absent, or reduced, when tactile and visual stimulation are asynchronously administered. Bodily illusions such as the RHI and the FBI reveal that both body-part and full-body representations are malleable in that a sense of ownership can be induced for physical or virtual replacements of our body and that the spatial limits of self-experience can go beyond those of our physical body.

While similar findings have been repetitively reported for different multisensory manipulations (see Blanke, 2012; Ehrsson, 2012; Serino et al., 2013 for reviews), the brain mechanisms underlying these effects are not yet known. It has been proposed that, during the FBI, synchronous tactile stimulation on the participants' body and visual stimulation from the avatar seen at an extracorporeal location might enlarge the visual and receptive fields of neurons coding for peripersonal space (PPS) (Blanke, 2012). Multisensory PPS neurons integrate tactile, visual, and auditory stimuli when presented at a limited distance from the body (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997; Graziano & Cooke, 2006; Bremmer at al, 2002; Makin et al., 2007; Gentile et al., 2011), but not when further away. This limit defines the boundary of PPS, that have also been reported to be plastic in that the space where multisensory stimuli are integrated extends when individuals interact with far locations, for instance, by using tools (Maravita & Iriki, 2004; Làdavas & Serino, 2008). It is possible that feeling touch on one's own body, while viewing tactile stimulation administered on a virtual body at a distance may also alter the boundaries of the PPS representation. Accordingly, previous studies have shown that the spatial constraints of multisensory integration between vision and touch vary during the FBI (Aspell, Lenggenhager, & Blanke, 2009) or the RHI (Pavani, Spence, & Driver, 2000; Zopf, Savage, & Williams, 2010). Here we describe how the boundaries of PPS shape during the FBI. In particular, we test the hypothesis that, while normally the PPS representation is bound to the physical body, during the FBI PPS becomes referenced at the illusory perceived self-location.

To test that hypothesis, we induced the FBI (Lenggenhager et al., 2007), while we concurrently measured the spatial extent of PPS representation by means of a dynamic audio-tactile interaction task (Canzoneri et al., 2012, Noel et al., 2014, Galli et al., 2015). In order to experimentally induce a change in BSC, we administered tactile stimulation on the participant's physical body, while synchronously showing (visual stimuli) spatially conflicting tactile stimulation on a virtual body. Change in BSC was reported through a questionnaire. In the control condition, tactile and visual stimulation were administered asynchronously. Concurrently, in order to define the boundary of PPS representation, participants were asked to respond as fast as possible to vibro-tactile stimuli administered on their trunk, while task-irrelevant sounds loomed toward their trunk. Based on previous findings (Canzoneri et al., 2012; 2013a; 2013b; Teneggi et al., 2013), we predicted that reaction times to tactile stimuli would decrease once the sound overcame a particular distance from the body, which can be taken as a proxy for the boundary of PPS. In Experiment 1, dynamic sounds were presented in the participants' front space. In this way, we tested whether during synchronous visuo-tactile stroking inducing the FBI, the PPS boundary extends in the front, toward the virtual body, as compared to the asynchronous control condition. In Experiment 2, moving sounds were presented in the participants' back-space, to test whether the extension of PPS toward the virtual body in the front-space (as predicted in Experiment 1) was associated with a concurrent shrinkage of PPS in the back-space (or whether it was rather associated with no change). Such findings would indicate a shift of PPS representation from the physical body to the illusory perceived location of the self. We predicted no changes in PPS boundaries (either in the front or in the back) during the asynchronous stroking condition, where no FBI was induced.

Material and Methods

Participants

Nineteen and fifteen students from the Ecole Polytechnique Federale de Lausanne participated in Experiment 1 (9 females, mean age = 23.0 years, range 18-29) and in Experiment 2 (4 females, mean age 24.2 years, range 19 – 31), respectively. Sample size for Experiment 1 was derived from power analysis of prior studies (Leggenhager et al., 2007, 2009) and for Experiment 2 based on the effect size in Experiment 1. All participants were right-handed, had normal or corrected-to-normal eyesight, normal hearing, and no history of neurological or psychiatric disease. The study was approved by Brain Mind Institute Ethics Committee for Human Behavioral Research of the EPFL and conducted in line with the Declaration of Helsinki. All participants gave informed consent prior to participation and were remunerated with 20 Swiss Francs for their time.

Stimuli and Apparatus

Figure 1A shows the experimental setup. In order to measure the boundaries of PPS representation, participants stood in the middle of two arrays of 8 speakers each, placed besides their chest, one on the right and one on the left, at 50 cm distance from their midline. Four speakers on each side were placed in the participant's front space, and were utilized in Experiment 1 to map the front PPS, and 4 speakers on each side were placed in the participant's backspace and were utilized in Experiment 2 to map their back space PPS. The loudspeakers extended from 100 cm in front of the subjects to 100 cm in the back. The sounds were perceived as if coming from the center (in between the two arrays). A control experiment (i.e., sound localization, n = 7) validated the paradigm demonstrating that participants perceived the sounds as dynamically approaching their body (see further detail in Supplementary Material).

In addition, participants were outfitted with a vibro-tactile device (Precision MicroDrives shaftless vibration motors, model 312–101), which was placed on the participant's chest in Experiment 1 and on his/her back in Experiment 2, at stern level. Participants were handed a wireless gamepad (XBOX 360 controller, Microsoft, Redmond, WA), which they held in their right hand and used to respond to vibro-tactile stimulation.

In order to induce the FBI, two video cameras (Logitech HD Webcam C270, 1280x720 pixels, Logitech Fluid Crystal Technology) recorded the participant from a distance of 200 cm (in the back), and this signal was relayed stereoscopically to a Head Mounted Display (HMD, Oculus Rift SDK, Oculus VR, 100° field of view, 60Hz) worn by the subject. Synchronous visuo-tactile stroking was achieved by direct real-time (<50 ms delay) display of visual signals from the cameras to the HMD. During asynchronous visuo-tactile stimulation the camera signal was delayed by 500 ms before feeding it to the HMD.

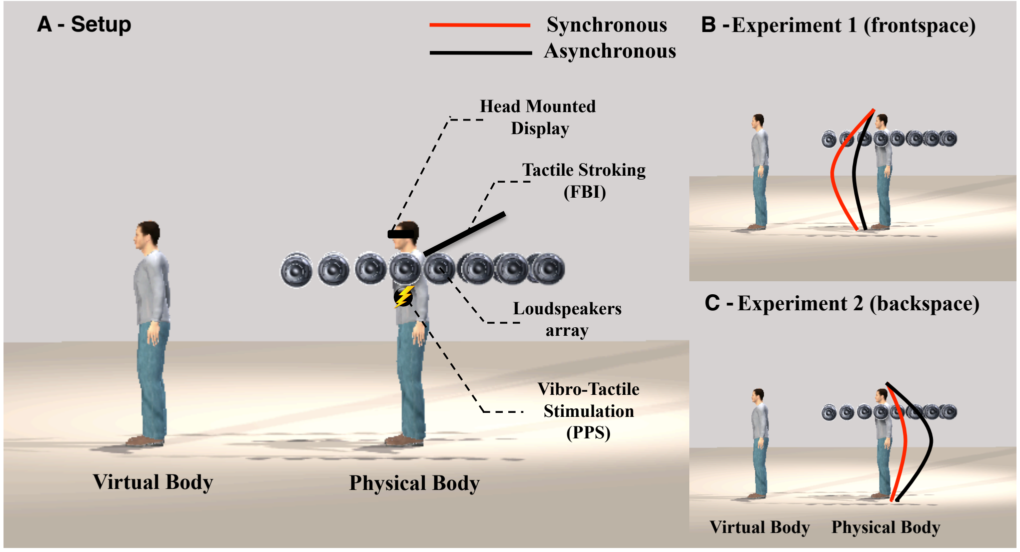

Figure 7.1. ***Experimental Setup and hypothesis.*** (A). In order to induce the Full Body Illusion (FBI), the participant viewed on a head-mounted display a virtual body in front. Tactile stroking was administered to the participant's back while synchronous or asynchronous visual stroking was seen on the back of the virtual body. Peripersonal Space (PPS) representation was measured by recording response times to vibrotactile stimuli applied to the participant's chest while concurrent task-irrelevant looming sounds were administered from a loudspeaker array placed beside the participant. We hypothesized that during synchronous stroking, i.e., when the FBI is induced, PPS representation extends toward the virtual body in the front-space (B, red line), and concurrently shrinks in the back-space (C, red line), as compared to the asynchronous stroking control condition (B and C, black lines).

Experimental Manipulations and Outcome Measures

Full Body Illusion Manipulations

For each experiment, synchronous and asynchronous visuo-tactile stroking were presented in separate blocks, whose order was counterbalanced between participants. These conditions differed in the temporal Synchrony between felt and seen touch (synchronous: <50 ms delay; asynchronous: 500 ms delay, where tactile stimulus preceded the visual stimulus). Participants stood straight and, through a video feed relayed to the HMD, passively watched a virtual body, i.e. a video recording of their own body from 200 cm behind their actual location. The experimenter randomly stroked the participants' upper back at approximately 2Hz. At the end of each condition, the FBI questionnaire (adapted from Lenggenhager et al., 2007)) was administered to quantify the subjective experience associated with the FBI. Questions were: Q1. How strong was the feeling that the rod you saw was directly touching you? Q2. How strong was the feeling that the touch you felt was where you saw the stroking? Q3. How strong was the feeling that you were drifting forward? Q4. How strong was the feeling that you were drifting backward? Q5. How strong did you feel the touch simultaneously at two locations in space? Q6. How strong was the feeling that the visual image you saw was really you? Q7. How strong was the feeling that you had more than one body? Q8. How strong was the feeling that you were floating in the air? Q9. How strong was the feeling that you were dissociated from your body (as if yourself and your body were in different locations)? Q10. How strong was the feeling that you were located at some distance behind the visual image of the body you saw? And Q11. How strong was the feeling that you were looking at someone else? Questions were computerized and presented in random order. Participants responded on a visual horizontal 11-point scale ranging from 0 (lowest) to 10 (highest)".

We did not include in our design a proper concurrent behavioral measure of changes in self-location to show a drift toward the avatar induced by the FBI, as employed by other studies (e.g., Lenggenhager et al., 2007). Thus, we assessed only subjective changes in BSC by means of questionnaires.

Peripersonal Space Measurement

In order to measure changes in PPS during the FBI, visuo-tactile stimulation was intermingled with audio-tactile trials. In those PPS trials, a looming sound approached the participant (in the front, for Experiment 1, and in the back, for Experiment 2) at a velocity of 75 cm/sec. On each trial, after one out of six possible delays from sound onset (SOA; T1 = 190 ms to T6 = 1.14 seconds in increments of 190 ms), a tactile vibration (100 ms duration) was delivered. SOAs correspond in the spatial dimension to audio-tactile distances of 15 (.190 x 75), 30, 45, 60, 75, and 90 cm. Participants were instructed to respond by button press as fast as possible upon perceiving the vibro-tactile stimulus on their chest (for Experiment 1) or back (for Experiment 2) and their reaction times (RT) were measured. As sounds loomed from far to close, the sooner a tactile vibration was given (e.g. at T1), the further away was the sound located in space (e.g. D6) when participants received tactile stimulation. We define, hence, T1 through T6 as corresponding in the spatial dimension to D6 (far from the participant) through D1 (close to the participant). In addition to experimental trials, baseline and catch trials were included. Baseline trials were unimodal tactile trials in which participants responded to touch (at the temporal equivalent to either D1 or D6), but no auditory stimulus was delivered. Catch trials were unimodal auditory trials in which participants had to withhold response (as there was no tactile stimuli).

Procedure

After an initial 60 second visuo-tactile stroking induction-phase to the FBI, three trials of the PPS task were administered. Interstimulus interval between these consecutive PPS trials was set to 0.5 seconds. Then, 10 seconds of merely FBI inducement followed, before the next round of three PPS trials. The FBI stroking continued throughout the experiment, and this pattern (three PPS trials followed by 10 seconds of solely FBI stroking) was repeated until the end of the block. Each block (and therefore, each stroking condition) consisted of 72 PPS experimental trials (12 repetitions X 6 Sound Distances), 24 baseline trials (12 repetitions X 2 baseline Sound Distances, D1 and D6), and 12 catch trials.

Results

Experiment 1 (front-space)

Full Body Illusion: Questionnaire

We analyzed whether Synchronous, as contrasted with the Asynchronous, visuo-tactile stimulation was effective in inducing the FBI. To this aim, for each question, we run a series of paired-sample t-test between the two conditions. Results are reported in Figure 2 (left panel) and demonstrated that participants scored higher in Question 1 (how strong was the feeling that the rod you saw was directly touching you?; $t(18) = 3.45$, $p < 0.01$), Question 2 (how strong was the feeling that the touch you felt was where you saw the stroking?; $t(18) = 13.54$, $p < 0.001$), and Question 3 (how strong was the feeling that you were drifting forward?; $t(18) = 2.75$, $p < 0.05$) during the Synchronous visuo-tactile condition than during the Asynchronous condition. These findings suggest that our set-up allowed for inducing the FBI illusion in the Synchronous condition, at least inasmuch as to provoke participants to more strongly agree with the statement that they felt as if drifting forward. The significant difference between Synchronous and Asynchronous conditions with regard to the self-location question, and the lack thereof in the self-identification one, contrasts with prior findings within our group (see Lenggenhager et al., 2007) and may emanate from a number of methodological differences between these studies (e.g., particular setup of the FBI, the addition of the PPS testing, and/or the wording of the questions).

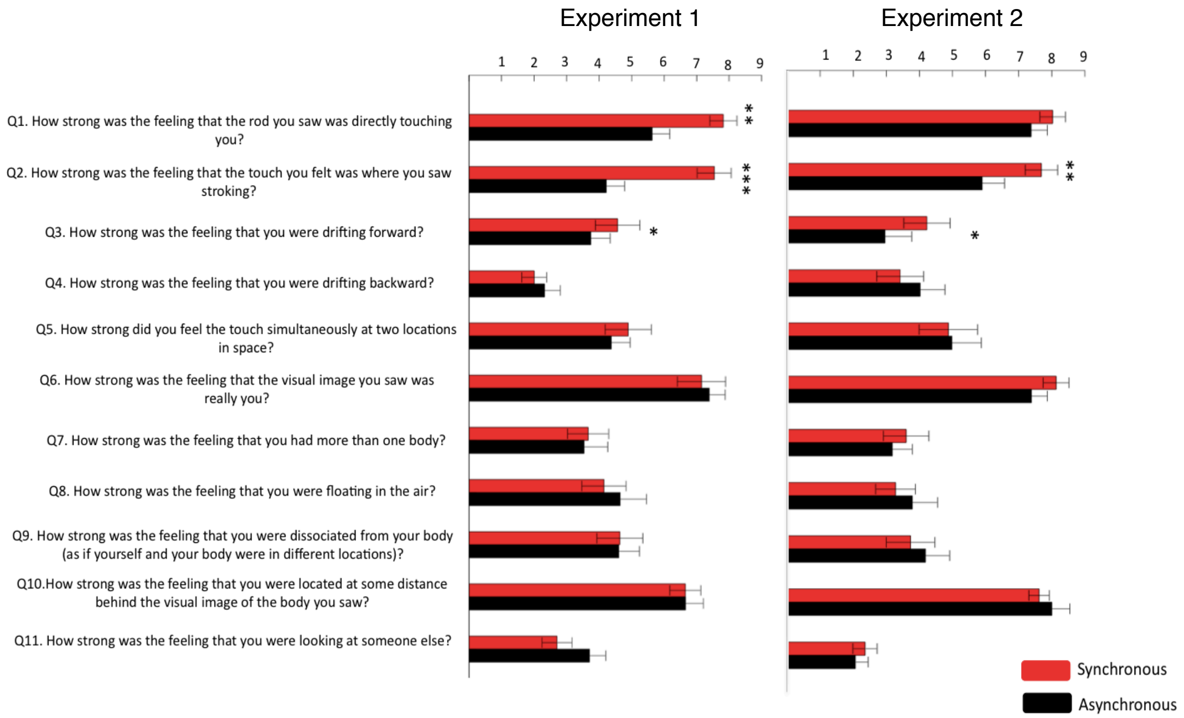

Figure 7.2*. Body Illusion questionnaire results from Experiment 1 (Left Panel) and Experiment 2 (Right Panel).* Average responses (Error bars represent S.E.M.) are plotted as a function of visuo-tactile stroking condition (synchronous in red; asynchronous in black).

Peripersonal Space: audio-tactile interaction task

Subsequently we analyzed whether the visuo-tactile synchrony manipulation, inducing the FBI, also altered audio-tactile interaction in PPS. A Paired-Samples *t*-test ran on the catch trials showed Synchronous (M = 98.2%, S.E.M = 3%) and Asynchronous (M = 97.2%, S.E.M = 4%) stroking conditions did not differ ($t(18) = .741$, $p > 0.05$). Participants were very accurate at the task.

Mean reaction times (RT) to tactile stimuli at the different sound distances were computed, after trimming responses exceeding 2.5 the RT standard deviation (< 3% of total trials). A 2 (Synchrony: Synchronous vs. Asynchronous) x 6 (Sound Distance: D1 through D6) within-subjects ANOVA was performed on participants' RT to vibro-tactile stimulation. Results, shown in Figure 3, highlighted a significant main effect both for Synchrony ($F(1, 18) = 12.24$, $p < 0.01$, $\eta^2 = 0.40$) and for Sound Distance ($F(5, 90) = 22.88$, $p < 0.001$, $\eta^2 = .56$). The main effect of Synchrony suggests a general boost of multisensory processing after synchronous stimulation in the front space, i.e. in the space where the virtual body was presented. More importantly for the purpose of the present study, the two-way Synchrony X Sound Distance interaction was also significant ($F(5, 90) = 2.51$, $p < 0.05$, $\eta^2 = 0.12$), implying that such multisensory boosting effect was not homogenous in the front space, but it was stronger at some specific distances from the body. Thus, to study the source of the significant two-way interaction, we ran two separate ANOVAs, one per Synchrony condition, with Sound Distance as main factor. The aim of these analyses was to identify, for the Synchronous and the Asynchronous conditions, the critical distance at which looming sounds speeded up tactile RT, which can be considered as a proxy of the boundary of PPS, and to test whether this distance varied between the two conditions. The main effect of distance in the Synchronous condition was significant ($F(5, 90) = 21.65$, $p < 0.001$, $\eta^2 = .54$) and post-hoc comparisons (paired t-test) showed that RT at D1 through D5 were equivalent to each other, and significantly faster than RT at D6 ($p < 0.05$, Bonferroni-corrected – alpha set at 0.05/6 – number of comparisons, all Cohen's $d > 0.32$). In the case of the Asynchronous condition the main effect of Sound Distance ($F(5, 90) = 12.68$, $p < 0.001$, $\eta^2 = .41$) was also significant; however as expected and differently to the Synchronous condition, results revealed that now only D1 through D4 exhibited similar reaction times, while these were significantly different from D5 and D6 ($p < 0.05$, Bonferroni-corrected, all Cohen's $d > 0.24$). These results imply that the PPS boundary under Asynchronous visuo-tactile stimulation was placed between D4 and D5, whereas it enlarged to be placed between D5 and D6, i.e. at a farther location of space, toward the virtual body, under Synchronous visuo-tactile stimulation. Indeed, multiple comparisons at each sound distance between Synchronous and Asynchronous conditions showed that RT was statistically significant only at D5 ($t(18) = -3.64$, $p < 0.01$, Bonferroni-corrected, Cohen's $d = 0.61$), with faster RTs in the Synchronous (M = 343 ms; S.E.M= 12 ms) than in the Asynchronous condition (M = 387 ms; S.E.M =16 ms).

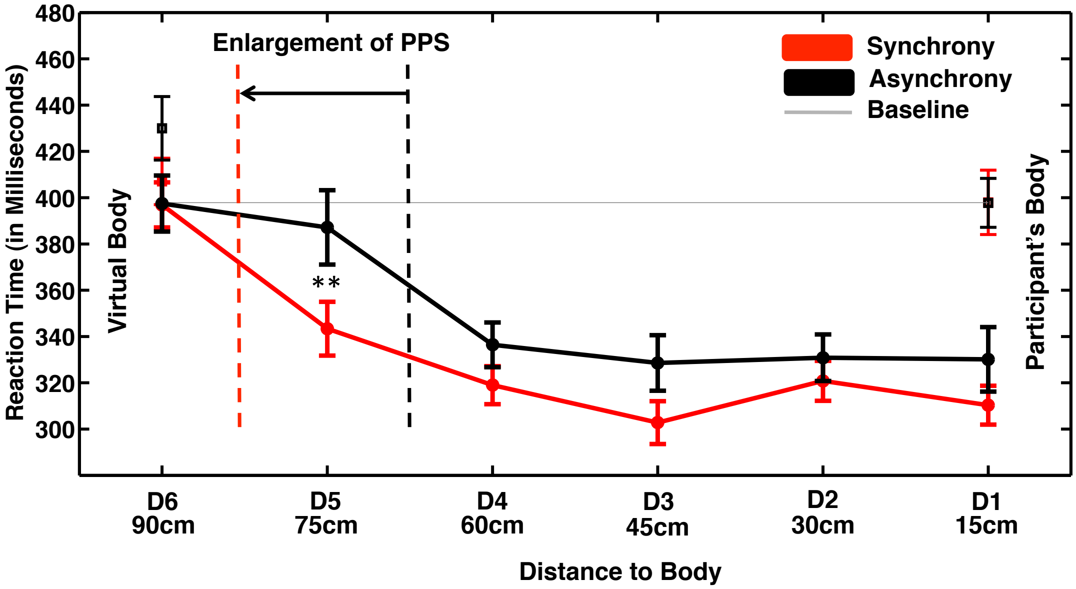

Figure 7.3. PPS representation in the front-space (Experiment 1) for the synchronous and the asynchronous stroking condition*. Reaction times (RT) to the tactile stimulus on the chest are plotted as a function of Stroking condition and the distance between the auditory stimuli and the tactile stimulation. Error bars represent S.E.M and ** indicate difference between Synchronous and Asynchronous condition, $p < 0.01$ (Bonferroni-corrected): The grey horizontal line indicates RT in baseline, unimodal tactile trials.*

Finally, in order to assure that the aforementioned results were due to a facilitation of tactile processing due to multisensory integration of audio-tactile signals, we compared tactile RT when the looming sound was perceived at the different distances with RT in unimodal tactile baseline trials, when no sounds were administered. Faster RT in audio-tactile conditions as compared to unimodal tactile conditions can be considered a facilitation effect due to multisensory integration within the PPS. To this aim we compared RT to audio-tactile trials for each Sound Distance with the average (across synchrony conditions) of the fastest baseline condition (T1 or T6), that is, the fastest unimodal tactile RT condition calculated for each participant individually. In this way we adopted the most conservative approach to detect facilitation of tactile processing due to sound presentation as compared to unimodal tactile processing. This analysis allows for correcting for potential expectancy effects and to compare across experiments with different participants, however, it must be noted that it also tends to underestimate the expansion of PPS representation, as the comparison is always to the fastest unimodal condition. In Experiment 1, 12 out of the 19 participants showed numerically faster RTs for unimodal tactile stimulation at T6 than T1.

Comparison to baseline demonstrated that in the case of the Synchronous stroking stimulation, RT at D1 through D5 were significantly faster from baseline ($p < 0.05$, corrected, all Cohen's $d > 0.34$), but not RT at D6 ($p=0.63$). For the Asynchronous condition, only RT at D1 through D4 were significantly faster from baseline ($p < 0.05$, Bonferroni corrected, all Cohen's $d > 0.27$), but not RT and D5 and D6 (both p-values > 0.41). These comparisons confirm that the limit of audio-tactile interaction, i.e. the PPS boundary, was located between D4 and D5 in the Asynchronous stroking condition, and between D5 and D6, i.e. further away from the physical body and closer to the avatar, during the Synchronous condition.

Experiment 2 (back-space)

Full Body Illusion: Questionnaire

As for Experiment 1, we examined whether Synchronous, as contrasted with the Asynchronous, visuo-tactile stimulation was effective in inducing the FBI by comparing, for each question, participants' responses between the two conditions by means of paired-sample t-tests. Results are reported in Figure 2 (right panel) and demonstrated that participants scored higher in Question 2 (how strong was the feeling that the touch you felt was where you saw the stroking?; $t(14) = 2.88$, $p < 0.01$), and critically, on Question 3 (how strong was the feeling that you were drifting forward?; $t(14) = 1.99$, $p < 0.05$) during the Synchronous visuo-tactile condition than during the Asynchronous condition. A similar trend was found for Question 1 (how strong was the feeling that the rod you saw was directly touching you?; $t(14) = 1.37$, $p= 0.04$, one-tailed), which exhibited a significant difference between Synchronous and Asynchronous stroking conditions in Experiment 1.

Peripersonal Space: audio-tactile interaction task

A Paired-Samples *t*-test ran on the auditory unimodal trials revealed that, as for Experiment 1, participants were generally very accurate at withholding response when it was demanded from them (Synchronous condition: M = 96.4%, S.E.M = 1.5%; Asynchronous condition: M = 93.5%, S.E.M = 2.6%), and this did not differ between stroking conditions ($t(14) < 1$, ns).

Mean RT to vibro-tactile stimulation (trimmed for 2.5 standard deviations, < 2% total trials) was entered into a 2 (Synchrony) x 6 (Sound Distance) within-subjects

ANOVA. Results, shown in Figure 3, demonstrated a significant main effect of Sound Distance ($F(5,70) = 12.54$, $p < 0.001$, $\eta^2 = 0.47$), as well as a Sound Distance X Synchrony interaction ($F(5, 70) = 5.97$, $p < 0.001$, $\eta^2 = 0.29$). In order to interpret the source of the two-way interaction, we ran two separate ANOVAs, one per Synchrony condition. The main effect of Sound Distance in the Synchronous condition was significant ($F(5, 70) = 9.57$, $p < 0.001$, $\eta^2 = .40$) and post-hoc comparisons showed that RT at D1 through D4 were equivalent to each other, and significantly faster than RT at D5 and D6 ($p < 0.05$, Bonferroni-corrected, all Cohen's $d > 0.19$). In the case of the Asynchronous condition the main effect of Sound Distance ($F(5, 70) = 11.82$, $p < 0.001$, $\eta^2 = .45$) was again significant; however, post-hoc comparisons revealed that D1 through D5 exhibited similar reaction times, while these were significantly different from D6 ($p < 0.05$, Bonferroni-corrected, all Cohen's $d > 0.25$). These results imply that the PPS boundary under Asynchronous visuo-tactile stimulation was placed between D5 and D6, whereas it shrank to be placed between D4 and D5, i.e. at a closer location of space, under Synchronous visuo-tactile stimulation.

Multiple comparisons at each sound distance revealed that only the comparison between Synchronous and Asynchronous conditions at D5 was statistically significant ($t(14) = 4.12$, $p < 0.01$, Bonferroni-corrected, Cohen's $d = 0.70$), with slower RTs in the Synchronous condition (Mean RT= 352 ms; S.E.M =15 ms) than in the Asynchronous condition (Mean RT = 310 ms; S.E.M= 17ms). Note that the location at which audio-tactile RT differed in space (namely, D5) was the same as in Experiment 1, however, the direction of the effect is inversed here. While in Experiment 1, at D5 participants were faster in the Synchronous condition, now they are faster in the Asynchronous condition.

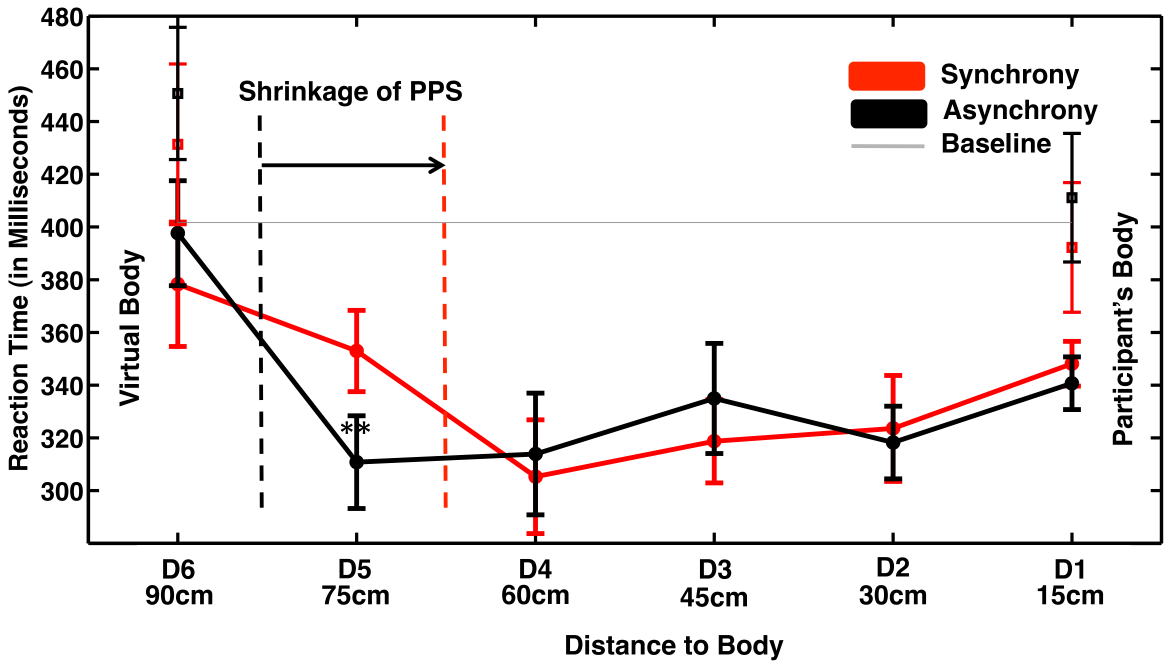

Figure 7.4. PPS representation in the back-space (Experiment 2) during Synchronous and Asynchronous stroking. *RT to the tactile stimulus on the back is plotted as a function of Synchrony during the Full Body Illusion and the distance between the auditory stimuli and the tactile stimulation. Error bars represent S.E.M and ** indicate difference between Synchronous and Asynchronous condition, $p < 0.01$ (Bonferroni-corrected): The grey horizontal line indicates RT in baseline, unimodal tactile trials.*

Lastly, we compared tactile RT when the looming sounds were perceived at the different distances with RT in unimodal tactile baseline trials in order to assure that the above-mentioned distance effects were in fact a space-dependent multisensory facilitation effect. To this aim, as in experiment 1, we compared RT to audio-tactile trials for each Sound Distance with the average of the fastest RT at the baseline (In Experiment 2, 10 out of 15 participants showed numerically faster unimodal tactile RTs at T6 than T1). Comparison to baseline demonstrated that in the case of the Synchronous stroking stimulation, RT at D1 through D4 were significantly faster from baseline ($p < 0.05$, corrected, all Cohen's $d > 0.21$), but not RT at D5 and D6. For the Asynchronous condition RT at D1 through D5 were significantly faster from baseline ($p < 0.05$, Bonferroni corrected, Cohen's $d > 0.27$). These comparisons confirm that the limits of audio-tactile interaction, i.e. the PPS boundary, was located between D5 and D6 in the Asynchronous stroking condition, and between D4 and D5 in the Synchronous one.

Comparison between front-space and back-space PPS during synchronous and asynchronous visuo-tactile stroking

In order to compare the effect of synchronous visuo-tactile stimulation, inducing the FBI, on PPS representation in the front and back space, we ran a final analysis using a mixed-model ANOVA with Synchrony (Synchronous or Asynchronous) and Sound Distance (D1 through D6) as within-subjects variables, and with Experiment (Exp 1, front-space; Exp 2, back-space) as the between-subjects variable. Results demonstrated a main effect of Sound Distance ($F(5, 160) = 30.173$, $p < 0.001$, $\eta^2 = .485$), yet no main effect of Synchrony ($F(1, 32) = 3.609$, $p = .076$), nor Experiment ($F(1, 32) = 0.095$, $p = 0.760$). Findings did show a Sound Distance X Experiment interaction (F(5, 160) =

3.996, $p = .007$) – steeper decrease in the front-space than in the back-space – yet did not reveal a Synchrony X Experiment interaction ($F(1, 32) = 2.198$, $p = .092$). Most importantly, however, and as expected from the aforementioned results, findings did revealed a significant three way interaction ($F(5, 160) = 6.97$, $p < 0.001$, $\eta^2 = 17$). This results is explained by the significant enlargement of PPS in the front-space in the Synchronous condition as opposed to the Asynchronous condition (section 3.1.2), and to a significant reduction of PPS in the backspace in the Synchronous condition as opposed to the Asynchronous one (section 3.2.2). For illustration purposes, this result is displayed in Figure 4 as the absolute value of the difference between multimodal audio-tactile trials at each spatial distance (B6 corresponding to the furthest distance in the back, and F6 corresponding to the furthest distance in the front) and the fastest unimodal tactile baseline condition. Thus, positive values represent a multisensory facilitation effect induced by sounds within the PPS on tactile processing.

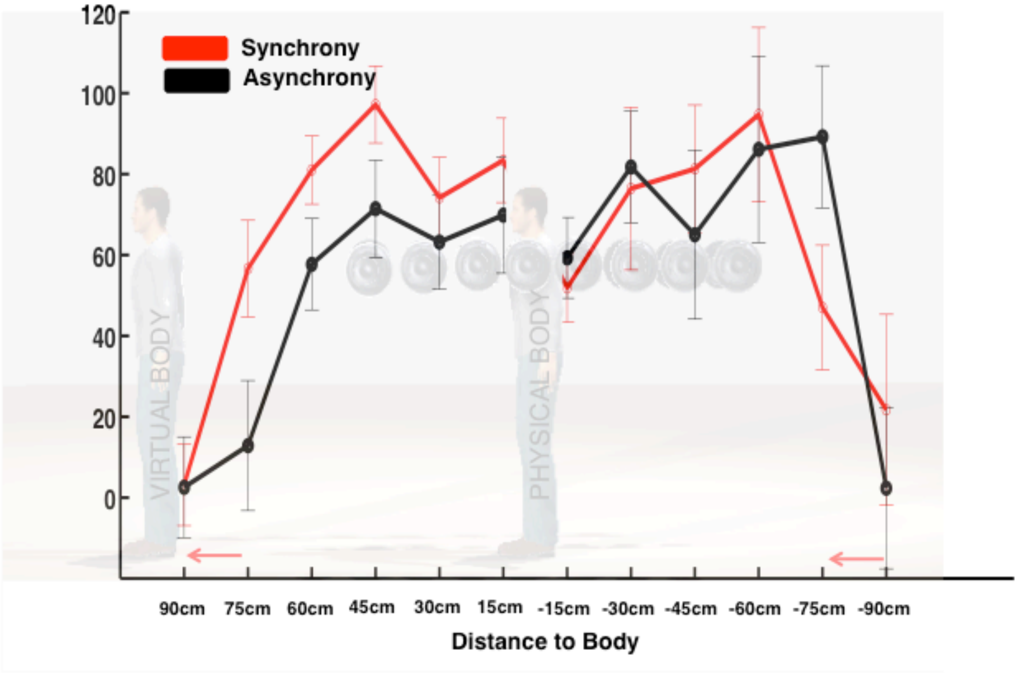

Figure 7.5*. *PPS representation in the front- and back-space during Synchronous and Asynchronous stroking. *RT difference between unimodal tactile stimulus on the trunk and multimodal audio-tactile stimuli is plotted as a function of Synchrony of visuo-tactile stimulation during the Full Body Illusion and the distance between the auditory stimuli and the body. Error bars represent S.E.M. Higher values imply higher facilitation on tactile processing due to audio-tactile interaction.*

Discussion

In the present study we induced the Full-Body Illusion (FBI) in order to manipulate the experience of one's own bodily self in space. When participants received a tactile stimulation on their physical body while viewing a synchronous stimulation administered to a virtual body seen at a distance, they reported a greater feeling of being directly touched by the stimulus touching the virtual body, of feeling touch at the location of the virtual body (Q1 and Q2), and of feeling to drift forward toward the virtual body (Q3), indicating a shift in the experienced location of the self from one's own physical body toward a virtual replacement of it. In line with previous findings, these effects were more weakly induced during asynchronous visuo-tactile stimulation (see Lenggenhager et al., 2007; Blanke et al., 2012; Serino et al., 2013). The focus and main new finding from the present study is that the FBI was associated with a shift in the representation of the PPS. We used an audio-tactile interaction task to identify the point in space where a looming sound speeded up tactile processing as a proxy of the boundaries of multisensory PPS (see Canzoneri et al., 2012; Canzoneri et al., 2013a; Canzoneri et al., 2013b; Teneggi et al., 2013, Noel et al., 2014).

In Experiment 1, when we measured the extension of PPS in the front-space, between the participant's physical body and the avatar, we found, as predicted, that the PPS boundary enlarged toward the location of the avatar in the synchronous visuo-tactile stroking condition inducing the FBI, as compared to the asynchronous control condition (boundary of PPS initially between 60 and 75 cm, and then enlarged to be located between 75 and 90 cm). In Experiment 2, mapping PPS on the participant's back, we found that the PPS boundary shrunk in the synchronous as compared to the asynchronous condition (initially located 75 to 90 cm away, and then shrunk to be placed 60 to 75 cm away). Taken together, these two new findings support the view that during the FBI, PPS boundaries translate toward the virtual body, such that the PPS representation shifts from being centered at the location of the physical body to being now centered at the subjectively experienced location of the self.

Previous studies suggest that multisensory receptive fields of PPS neurons can react to artificial copies of the body. In patients with cross-modal extinction, Farnè and colleagues (2000) showed that visual stimuli presented close to a prosthetic hand interacted with tactile stimuli at the patient’s contralesional hand as much as visual stimuli presented close to the patient’s real hand did. In close analogy, in monkeys, stimuli applied to a fake arm triggered responses from PPS neurons, suggesting that PPS receptive fields can incorporate a fake limb (Graziano, Cooke, & Taylor, 2000). More recently, Brozzoli et al. (2012) showed in humans that brain areas likely representing PPS around the hand, such as the ventral premotor cortex and the posterior parietal cortex, which normally process visual stimuli presented in a limited peri-hand space, responded to visual stimuli presented close to a rubber hand after synchronous visuo-tactile stimulation of the participants’ and of the rubber hand. These findings generally show that some response properties, which normally apply to one’s own real hand, transfer to an artificial replacement of the hand. Similar effects have also been shown after individuals use a tool to extend the physical limits of their own body (see e.g., Iriki et al., 1996; Farne & Ladavas, 2000; Canzoneri et al., 2013a), and those findings have been advocated to suggest that tools can be included into one’s own body representation (Iriki & Maravita, 2004; Maravita, Spence, Kennett, & Driver, 2002). Results from our study are different from those previous ones at least in one critical respect. Contrarily to the cases of rubber hand and tool-use, during the FBI, we did not find only an extension of PPS in the direction of the avatar’s location, but also a concurrent contraction of the back PPS. The combination of these effects suggest a genuine spatial shift of PPS representation, centered on the location of the physical body prior to the FBI, toward the subjectively perceived location of the self during the FBI (as assessed by responses to questionnaire). While normally integration of tactile stimuli at the body and of external stimuli in the environment (in this case sounds) is maximal around the location of the physical body, when participants experienced a forward drift of their perceived self location (see Question 3), due to the FBI, the spatial gradient of multisensory integration congruently shifted in the direction of self-location as induced by the FBI. These findings confirm that the center of the PPS representation is not bound to the physical body and shows that not only arm-related PPS representations are malleable. Importantly, we show that the PPS is centered at the experienced location of the self. Normally self-location and body location coincide, and so does PPS. However, if body location and self-location are dissociated, for instance by means of conflicting multisensory stimulation, PPS representation shapes congruently with the change in self-experience. More generally, the present findings suggest that PPS can be considered as a representation of the self in space, which may mediate interactions between the individual and the environment. This proposal fits with previous results showing that the size of PPS varies across individuals not only depending on the dimension of their bodies (Longo & Lourenco, 2007), but also, more interestingly, depending on individual personality traits (e.g., claustrophobia and anxiety; Lourenco et al., 2011; Sambo & Iannetti, 2013). Our data also corroborate recent reports showing that PPS shapes not only during physical body-objects interactions, such as those mediated by tool-use, but also during virtual interactions with far objects, mediated by a computer mouse (Bassolino et al., 2010) or surgical robots (Rognini et al., 2013; Sengül et al., 2012), and even after social interactions with other persons, depending on the positive or negative value of those interactions (Teneggi et al., 2013).

An interesting question arising from the present results and from other previous studies is whether there is a spatial limit in extending PPS representation and altering bodily processing. Moreover, where would this spatial limit be for shifting one's self-location? For instance, Aspell et al., (2009b), demonstrated that synchronous stroking inducing the FBI modulated multisensory interactions between visual and tactile stimuli in the so-called crossmodal congruency effect (CCE) using a spatial disparity (between visual and tactile stimuli) of 2 meters (between virtual and physical body), thus suggesting that multisensory effects, and thus PPS changes, induced by the FBI might extend well beyond the modulation shown in the present study within 1 meter. The present results cannot answer this question because in this study the avatar was presented at a distance of 2 meters, and PPS was only mapped for up to 1 meter. Future studies may test changes in PPS along a continuous range between the physical body and the virtual body, and even beyond it, to identify a spatial limit in potential PPS extension. Other studies might also measure the effectiveness of the FBI illusion and the related changes in multisensory integration with the virtual body being placed at variable distances from the participant's body to identify a limit in the possibility of incorporating a virtual body (as done for the related rubber hand illusion; i.e. Lloyd, 2006). Such research might have important application in the study of embodiment and presence in virtual reality and tele-presence (see Sanchez-Vives & Slater, 2005).

Two other issues need clarification before concluding. First, it is important to mention an alternative explanation for the present results, namely that synchronous visuo-tactile stimulation may have also resulted in a reallocation of spatial attention, rather than in shifting PPS representation (see Holmes, Sanabria, Calvert, & Spence, 2007, for relevant discussion). In order to exclude that a shift in attention per se explains the present findings, we conducted a control experiment, which is fully described as Supplementary Material online. We run the same experimental protocol, as in Experiment 1, with the exception that receding, instead than looming sounds were used. Previous data show that receding sounds do not induce a spatial dependent modulation of tactile processing for trunk and face stimulation (Noel et al., 2014; Teneggi et al., 2013), and therefore they cannot capture any change in PPS representation due to the FBI illusion. On the contrary, any effect due to a shift of spatial attention should equally affect the interaction of tactile stimuli with both looming (as in Experiment 1) and receding (as in the supplemental experiment) sounds. In fact, results from the supplemental experiment showed that audio-tactile interaction with receding sounds did not vary depending on visuo-tactile stimulation in the synchronous vs. the asynchronous condition. The comparison between the significant results in Experiment 1 and the null results from the supplemental experiment suggests that the effects of the FBI on audio-tactile interaction found in the present study should be interpreted as a genuine change in PPS representation, rather than as a shift in spatial attention. This conclusion is related to the second issue. We used an audio-tactile interaction paradigm to assess the enlargement of PPS representation due to the FBI despite the fact that most data about PPS representation and its plasticity come from experiments where visuo-tactile stimulation was used in monkeys and humans (for reviews Graziano & Cooke, 2006; Makin et al., 2008). Thus, although existing hypotheses about the effects of bodily illusions (such as the rubber hand illusion or the FBI (Ehrsson, 2012, Blanke, 2012)) predict an extension of visual receptive fields of multisensory neurons, no direct predictions have been posited for the auditory receptive fields of multimodal neurons as their spatial properties have been less frequently investigated (Graziano, 1999, Schlack et al., 2005; see Occelli et al., 2011). However, our methodological choice came from the need of separating the type of multisensory interaction used to measure the effect of the FBI on PPS (audio-tactile) from the type of multisensory interaction used to induce the illusion (visuo-tactile). Showing an effect of visuo-tactile stimulation on the spatial boundaries of audio-tactile integration, actually, strengthens the finding of a purely multisensory change in spatial representation due to the FBI. We suggest that this effect depends on a shift of multisensory receptive fields of PPS neurons (Blanke, 2012; Ehrsson et al., 2012; Serino et al., 2013), although we acknowledge that the present data cannot provide neurophysiological evidence to such a proposal.

In conclusion, the present study supports a neurophysiological explanation for the effects of conflicting multisensory stimulation on BSC during the FBI: viewing a tactile simulation on a another body at a distance, while receiving synchronous tactile stimulation on one's own body, changes PPS boundaries. Such change is characterized not simply by an extension of PPS representation towards the location of seen touch, but rather by a shift or translation of PPS from the location of the physical body to the experienced location of the self.

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CHAPTER VIII

UNCONSCIOUS INTEGRATION OF MULTISENSORY BODILY INPUTS IN THE PERIPERSONAL SPACE SHAPES BODILY SELF-CONSCIOUSNESS

The contents of this chapter are adapted from
Noel, J.P., Salomon, R., Lukowska, M., Faivre, N., Metzinger, T., Serino, A., Blanke, O. (2017). Unconscious Integration of Multisensory Bodily Inputs in the Peripersonal Space Shapes Bodily Self-Consciousness. Cognition, 166, 174-183.
doi:10.1016/j.cognition.2017.05.028

Abstract

Recent studies have highlighted the role of multisensory integration as a key mechanism of self-consciousness. In particular, integration of bodily signals within the peripersonal space (PPS) underlies the experience of the self in a body we own (self-identification) and that is experienced as occupying a specific location in space (self-location), two main components of bodily self-consciousness (BSC). Experiments investigating the effects of multisensory integration on BSC have typically employed supra-threshold sensory stimuli, neglecting the role of unconscious sensory signals in BSC, as tested in other consciousness research. Here, we used psychophysical techniques to test whether multisensory integration of bodily stimuli underlying BSC may also occur for multisensory inputs presented below the threshold of conscious perception. Our results indicate that visual stimuli rendered invisible through continuous flash suppression boost processing of tactile stimuli on the body (Exp. 1), and enhance the perception of near-threshold tactile stimuli (Exp. 2), only once they entered PPS. We then employed unconscious multisensory stimulation to manipulate BSC. Participants were presented with tactile stimulation on their body and with visual stimuli on a virtual body, seen at a distance, which were either visible or rendered invisible. We found that participants self-identified with the virtual body following synchronous visuo-tactile stimulation (Exp. 3), and shifted their self-location toward the virtual body (Exp.4), even if stimuli were fully invisible. Our results indicate that multisensory inputs, even outside of awareness, are integrated and affect the phenomenological content of self-consciousness, grounding BSC firmly in the field of psychophysical consciousness studies.

Introduction

Based on clinical and experimental research in humans, it has been proposed that multisensory integration is a key mechanism for self-consciousness. In particular, bodily self-consciousness (BSC) has been shown to depend on the integration of multisensory bodily stimuli (Blanke, 2012; Blanke, Slater, & Serino, 2015; Ehrsson, 2012a; Tsakiris, 2010). Research has focused on two central aspects of BSC: people normally self-identify with a given body, which they perceive as their own (self-identification) and they experience their self at the location of their body (self-location) (Blanke, 2012; Blanke & Metzinger, 2009). The notion that BSC depends on multisensory integration of bodily inputs is evidenced by neurological patients who present deficits in multisensory integration together with an altered perception of their own body (Blanke, Landis, Spinelli, & Seeck, 2004; Blanke, Ortigue, Landis, & Seeck, 2002), and by experimental manipulations of BSC in healthy subjects using multisensory conflicts (Ionta et al., 2011; Lenggenhager, Tadi, Metzinger, & Blanke, 2007; Petkova & Ehrsson, 2008; Petkova, Khoshnevis, & Ehrsson, 2011; Salomon, Lim, Pfeiffer, Gassert, & Blanke 2013). For example, in the full body illusion, viewing an avatar's body being stroked, while concurrently receiving the same tactile stimulation on one's own body, makes participants self-identify with the avatar (Ehrsson, 2007; Petkova & Ehrsson, 2008) and induces changes in self-location such that subjects perceive themselves closer to the avatar's position (Ionta et al., 2011; Lenggenhager et al., 2007).

Under normal conditions, multisensory body-related stimuli occur within a limited distance from the body, which defines the peripersonal space (PPS). Accordingly, neuronal populations have been described both in monkeys and in humans integrating somatosensory stimulation on the body with visual and/or auditory stimuli specifically when presented close to the body (Graziano & Cooke, 2006; Ladavas & Serino, 2008; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997). PPS and BSC are thought to involve common neural structures in premotor, posterior parietal, and temporo-parietal cortex (Blanke et al., 2015; Makin, Holmes, & Ehrsson, 2008; Grivaz et al., 2016) and it has recently been shown that the full body illusion leads to a shift in PPS from the physical body toward the virtual body that participants identify with (Noel, Pfeiffer, Blanke, & Serino, 2015), compatible with an extension of the PPS boundary (Serino, Canzoneri, Marzolla, di Pellegrino, & Magosso, 2015). These data link processing and integration of multisensory stimuli within PPS to self-consciousness, and to BSC in particular (Blanke et al., 2015; Noel et al, 2016).

Conscious experience has also been related to the integration of sensory information in the brain by other authors (Dehaene & Naccache, 2001; Mudrik, Faivre, & Koch, 2014; Tononi, 2008). Indeed, consciousness is characterized by a unity of experience in which information from multiple sensory modalities is integrated and bound together (Bayne, 2002; James, Burkhardt, Bowers, & Skrupskelis, 1981). Recent experimental work has shown that non-visual stimuli that are consciously perceived may be integrated with stimuli rendered invisible through various masking paradigms (i.e. auditory (Alsius & Munhall, 2013; Lunghi, Morrone, & Alais, 2014), tactile (Lunghi & Alais, 2013; Lunghi, Binda, & Morrone, 2010; Salomon, Galli, et al., 2015), olfactory (Zhou, Jiang, He, & Chen, 2010), proprioceptive (Salomon, Lim, Herbelin, Hesselmann, & Blanke, 2013) and vestibular (Salomon, Kaliuzhna, Herbelin, & Blanke, 2015)). It was further shown that even a subliminal auditory and a subliminal visual stimulus can be integrated despite unawareness (Faivre, Mudrik, Schwartz, & Koch, 2014; Noel, Wallace, & Blake, 2015). It is unknown, however, whether integration of unconscious multisensory events affects self-consciousness, and BSC in particular, which is often considered a distinct and specific form of conscious content (Dehaene & Changeux, 2011; Faivre, Salomon, & Blanke, 2015; Gallagher, 2000).

Previous research on the multisensory basis of BSC focused on the integration of sensory inputs that are presented above the visual and tactile thresholds for conscious access. Yet as it has been argued that BSC is based on low-level and pre-reflexive brain mechanisms, it is possible that the sensory events shaping the experience of the self need not be consciously perceived. While there is no experimental evidence suggesting that the multisensory integration processes of BSC do not require conscious awareness of the multisensory stimuli, interactions between unconscious multimodal stimuli have been shown in humans (see above) (Faivre et al., 2014; Salomon, Kaliuzhna, et al., 2015; Salomon, Lim, Herbelin, et al., 2013) and at the neuronal level in anesthetized animals (Graziano, Hu, & Gross, 1997; Meredith & Stein, 1986; Stein & Stanford, 2008). Here, in a series of four experiments, we tested for the first time whether multisensory integration of bodily stimuli underlying BSC also occurs for signals presented below the threshold of conscious perception. We first asked whether tactile stimuli on the body are preferentially integrated with visual stimuli presented within; as compared to outside the PPS, when visual inputs were subliminal and tactile inputs supraliminal (Exp. 1) or when visual were subliminal and tactile inputs were near-threshold (Exp. 2). Next, we investigated whether it is possible to manipulate BSC by using visuo-tactile stimulation administered below the threshold for conscious access. To this aim, we coupled tactile stimulation on the body with invisible synchronous visual stimuli on a virtual body to induce the full body illusion (Lenggenhager et al., 2007) and tested whether this would affect self-identification, as assessed by questionnaires (Exp.3) and self-location, as assessed by the location of PPS boundaries (Exp. 4).

Methods

Participants

In total 98 participants (31 females, mean age = 23.0 ± 2.7) were included in this series of experiments. Thirty-two subjects took part in Exp. 1, 15 in Exp. 2, 25 in Experiment 3, and 26 in Exp. 4 (the first experiment being a between-subject experimental design, while the latter three being within-subjects). All participants were right-handed, had normal or corrected-to-normal visual acuity, reported normal hearing and touch, and had no history of psychiatric or neurological disorder. All volunteers provided written informed consent to participate in the study, which was approved by the Brain Mind Institute Ethics Committee for Human Behavioral Research of the EPFL, and conducted in accordance with the Declaration of Helsinki.

Materials and Procedure

Experiment 1

Visual stimuli consisted of a three-dimensional virtual white wireframe ball either looming toward or receding from the participants' face (Fig 1A). The ball, presented in stereoscopy, travelled approximately 2 meters in virtual space at a velocity of 50 cm/s until making fictive contact with the participant's face, or in the opposite direction in the case of receding stimuli. Visual stimuli were presented on a head-mounted display (HMD, VR1280 Virtual Research Systems, Inc., Santa Clara, CA, USA) with a resolution of 1280x1024 pixels, representing a 60-degree diagonal field of view, at 60 Hz. Half the participants performed the task while the visual stimuli presented were visible (henceforth: Visible group), whereas for the other half of participants (henceforth: Invisible group) the dynamic visual stimulus was suppressed via Continuous Flash Suppression (CFS; Tsuchiya & Koch, 2005). CFS was achieved by presenting circular high-contrast dynamic noise patches suppressors (''Mondrians''), flashed rapidly (10 Hz) to the participants' dominant eye, as determined prior to the study with the Miles test (Miles, 1930). See Supplementary Information online for a full description of the continuous flash suppression procedure and control experiments.

In addition to the visual stimuli, participants' were outfitted with a vibrotactile device (Precision MicroDrives shaftless vibration motors), placed on the forehead. Vibrotactile stimulation was presented supra-threshold for 100 ms. Participants provided speeded responses to vibrotactile stimulation with a wireless gamepad (XBOX 360 controller, Microsoft), which they held in their right hand. In-house software ExpyVR (freely available at http://lnco.epfl.ch/expyvr) was used for the rendering and presentation of visual and vibrotactile stimuli. Reaction times (RTs) were measured relative to the onset of tactile stimulation.

On experimental trials (70% of total trials) both tactile and visual stimulation were administered. The beginning of every trial was indicated by the presentation of a red fixation cross participants were to fixate upon. Then, on experimental trials, after a variable delay of 500 to 1000 ms (uniform distribution), a wireframe ball travelled toward (looming) or away from (receding) the participant's face. At one of seven possible visual stimulus onset asynchronies (vSOA; T1 = 0.5, T2 = 1.0, T3 = 1.5, T4 = 2.0, T5 = 2.5, T6 = 3.0, or T7 = 3.5 seconds), a brief vibrotactile stimulation was delivered. We used the perceived distance from the visual stimulus at the moment of tactile stimulation as the independent variable. Since, for the looming stimuli this distance is inversely proportional to the elapsed looming time, we coded T1 = D7, T2 = D6, and so on. In the case of receding visual stimuli, spatial and temporal dimensions map onto each other linearly and positively such that T1 = D1, T2 = D2, and so on. Previous studies using the same protocol showed that RTs to tactile stimulation decrease once a stimulus enters the participant's PPS (Canzoneri et al., 2012; Teneggi, Canzoneri, di Pellegrino, & Serino, 2013; Serino et al., 2015). Here we investigated whether the distance-dependent modulation of tactile RT is present even when the approaching visual stimuli entering PPS are invisible, suggesting that multisensory integration within the PPS occurs also in the absence of visual awareness. In order to control for a mere temporal effect (i.e., participants might become faster at later delays), we also included a control condition, whereby receding visual stimuli were administered, and for which we predicted no distance-dependent modulation of RT for face stimulation (see e.g., Serino et al., 2015). Additionally, in 20% of trials (baseline trials), no visual stimulation was given. Reaction times to unimodal tactile stimuli were recorded at T1 and T7, and used as baseline to correct for a spurious temporal effect and in order to confirm that speeding in RTs as a consequence of visual stimuli within PPS reflected true multisensory facilitation. Finally, 10% of trials were catch trials, in which a visual stimulus was delivered (either approaching or receding) but no tactile stimulation was presented, and thus participants were to withhold from responding. These catch trials were employed in order to monitor task compliance and avoid an automatic association between visual stimulation and motoric response.

Experiment 2

Materials and procedure followed as for Experiment 1, with two exceptions. First, visible and invisible conditions of visual stimulation were administered within-subjects, in separate blocks, with a counter-balanced order between participants. Secondly, tactile target stimuli were presented with a miniature solenoid, (M & E Solve, Rochester, UK; http://www.me-solve.co.uk, ~ 1 – 2.5V, 5ms) and was surrounded by 4 vibrotactile motors (see above and Supplementary Information) serving as tactile masks, which were active throughout the duration of a trial. The intensity of the tactile target stimulus on the face was titrated with a staircase procedure before each experimental block so to be detected in 60% of trials, without visual stimulation (see Supplementary Information for further details). The intensity of the tactile masks was kept constant.

Experiment 3

The procedure to induce the full body illusion consisted in applying tactile stimulation on the participants' back and visual stimulation on a virtual body (avatar; H: 20,5° W: 11,3°), seen through a HMD. Tactile stimulation was administered by using a haptic robotic system (Salomon, Lim, Pfeiffer, et al., 2013). Visual stimuli consisted of a colored visual dot (size: H: 0.7°, W: 0.7) that was moving up and down along the left side of the avatar's back (see Fig. 1B). In the critical condition inducing the illusion, the movement of the haptic robot was fully synchronized temporally and spatially with that of the dot on the avatar’s back. In the control, asynchronous condition, the visual and tactile stimulation were uncorrelated by using different visual and tactile motion profiles. In order to make the pattern of visuo-tactile stimulation invisible to the participants, visual stimuli was administered in a CFS paradigm, whereby the visual dot was presented to the non-dominant eye, while Mondrians (8.9° x 1°) were presented to the dominant eye In order to measure phenomenological experience associated with the full-body illusion, two experimental questions, adapted from previous designs (Ionta et al., 2011; Lenggenhager, Tadi, Metzinger, & Blanke, 2007; Petkova & Ehrsson, 2008; Petkova, Khoshnevis, & Ehrsson, 2011; Salomon, Lim, Pfeiffer, Gassert, & Blanke 2013) were administered after each 60 s of visuo-tactile stimulation : i) self-identification (Q1:‘How strong was the feeling that the body you saw was you?’) and ii) illusory touch (Q2:‘How strong was the feeling that the touch you felt originated from the body you saw?’). Participants responded using a scale from 1 (Completely disagree) to 10 (Completely agree). Following these two questions, masking efficiency was assessed by asking participants to answered three additional questions: subjective target visibility (Q3: ‘Did you see anything but the Mondrians?’, possible responses; Nothing/ Something/Fully), explicit knowledge of the target’s color (Q4: ‘What color was the dot?’, possible responses; Blue/ Green), and its spatio-temporal relation to the tactile stimulation (Q5: ‘Was movement of the dot synchronized with the touch you felt on your back?’ possible responses; yes/no). No control questions regarding phenomenology associated with the FBI were employed, as on the critical unconscious trials participants were unaware of the visuo-tactile manipulation and thus immune to suggestibility or expectancy biases for which these questions control.

Experiment 4

The procedure to induce the full body illusion was identical to that of experiment 3, with two differences: the omission of the non-masked (visible) condition and longer visuo-tactile stimulation lasting 77 seconds per trial, allowing intermingled testing of PPS. In order to assure that CFS was efficiently preventing visual awareness; participants were required on each trial to press a button in case they saw the visual dot. Intermingled with visuo-tactile stimulation, PPS was measured via an audio-tactile paradigm (Canzoneri et al. 2012; Galli et al., 2015; Noel et al., 2014) The task was similar to that described for Experiment 1 and 2, with the exception that an auditory (broadband noise), and not a visual stimulus approached the participant's chest. Six different audio-tactile distances were probed (see Supplementary Information online). We used audio-tactile stimulation, instead of visuo-tactile stimulation (as in Exp. 1 & 2), in order to keep the experimental manipulation used to induce the full body illusion (visuo-tactile stroking) and that used to measure its effect on peripersonal space (audio-tactile interaction) orthogonal with each other (as in Noel et al., 2015).

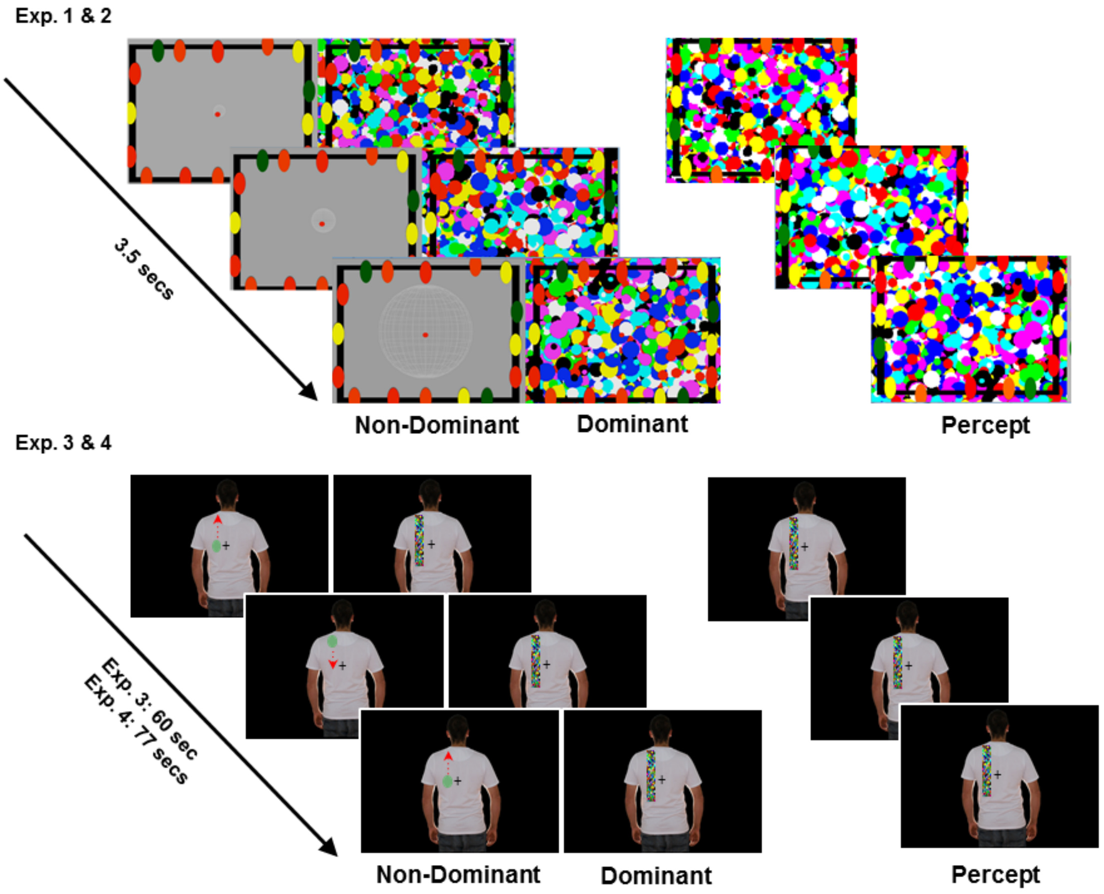

Figure. 8.1. Experimental design. Top. Experimental stimuli in the Invisible condition in Exp. 1 & 2. A wireframe ball approaching the participants' face was presented to the non-dominant eye while highly salient colored masks were rapidly (10hz) flashed to the dominant eye (CFS masking). Due to CFS, participants perceived the masks, while the approaching ball was invisible. Bottom. Experimental stimuli in the Invisible condition in Exp. 3 & 4. An image of a body with a moving dot on the back was presented to the non-dominant eye. The dot could be moving synchronously or asynchronously to the tactile stimulation on the participants' back. Critically, CFS masking of the region of the dot movement in the Invisible trials rendered the dot invisible, thus, both in the synchronous and asynchronous stimulation condition the percept was of a body image with rectangular flashing masks only.

Data Analyses

Trials in which participants reported seeing the visual stimuli, correctly identified the color or did not respond to the awareness questions were removed from the analysis (28% of trials in Exp. 1 and 21% in Exp.2; 4% in Exp. 3 and 12% in Exp. 4). We note that the high number of discarded trials is likely due to the challenge in masking dynamic stimuli as well as the meticulous care taken in identifying trials in which trials were not fully suppressed.

For PPS measurement (Exp. 1-2 & 4), we first calculated on a subject-per-subject basis the mean RT (Exp. 1 & 4) and detection rates (Exp. 2) for the baseline unimodal tactile conditions. Subsequently, the fastest mean baseline condition (i.e., T1) was subtracted from the participant mean in all the other conditions to provide a measure of facilitation induced on tactile processing by visual or auditory stimuli perceived at a different distance from the participant's body (See (Noel et al., 2014; Noel et al., 2015) for a similar approach). Subsequently, on a subject-per-subject basis, RT or detection rates relative to baseline were fitted to both linear and sigmoidal curves (see Canzoneri, Magosso, & Serino, 2012, for details). For each experiment we modelled the data with the best fit (linear for Exp. 1 & 2, and sigmoidal in Exp. 4 – See Supplementary Information) and then compared the values extracted from the fitting procedure across conditions. In experiment 3, we analyzed responses to BSC questions (Q1 & Q2) during the visible and invisible conditions using repeated measures ANOVA with synchronicity (Synchronous/Asynchronous) and visibility (Visible /Invisible) as within-subject factors. Normality of the data was assessed using the Shapiro-Wilk test, and non-parametric tests were used when the normality assumption was violated. When interactions were present, non-parametric Wilcoxon rank order tests were used to explore modulation of BSC within each synchronicity level and corrected for multiple comparisons using the

Holm-Bonferroni approach such that the family-wise error rates were controlled with α=0.05. We supplemented this analysis with a Bayesian analysis (Jasp 8.0) and reported BF10 factors.

Results

Invisible looming stimuli within the PPS affect tactile perception (Exp 1)

We analyzed RT to the tactile stimulation as a function of the different distances of the virtual ball and its direction, in the visible and invisible conditions. As shown in Fig. 2A, there was a clear distance dependent modulation of RT, as a function of the location of the visual stimulus, both for the Visible and Invisible conditions. This was not the case for Receding visual stimuli, excluding the possibility that the present finding was a mere temporal effect (see supplementary material online, Fig. S2A). Next, we fitted individual data to a linear function (which was the model to best fit the results; see supplementary analysis online), comparing the slope of the function, as a measure of how strongly tactile processing was influenced by the location of the task-irrelevant visible and invisible approaching balls. The presence of a positive slope, steeper for looming visual stimuli, would indicate a stronger multisensory integration effect for visual stimuli entering the PPS. The slope values were submitted to a 2X2 mixed ANOVA with Ball Direction (Looming and Receding), as within-subjects factor, and Condition (Visible and Invisible), as between-subject factor. The main effect of Ball Direction was significant (F(1,28)=69.52, p<.0001, partial η^2 = 0.71; BF_{10}= 8.76; (Jeffreys, 1998; Rouder, Speckman, Sun, Morey, & Iverson, 2009): the slope of the function was positive only for looming (mean slope=0.33±.02) and not for receding (mean slope=0.07±.02) stimuli. There was no main effect of Condition (p=0.64; BF_{10}= 3.01e-11,), nor a Condition X Ball

Direction interaction (p=0.93; BF_{10}= 0.33). Thus, the modulation of tactile processing due to the distance of the task-irrelevant visual stimuli at the time of touch was found for both visible and invisible balls. Importantly, the positive value of the looming slope was significantly different from zero for both conditions (visible: t(14)=11.80,p<0.001; invisible: t(16)=11.60,p<0.001). Hence, a distance-dependent modulation of tactile processing was found when task-irrelevant looming stimuli, that were not consciously perceived, were presented, indicating that multisensory integration within the PPS occurs even in absence of awareness for the visual stimulus.

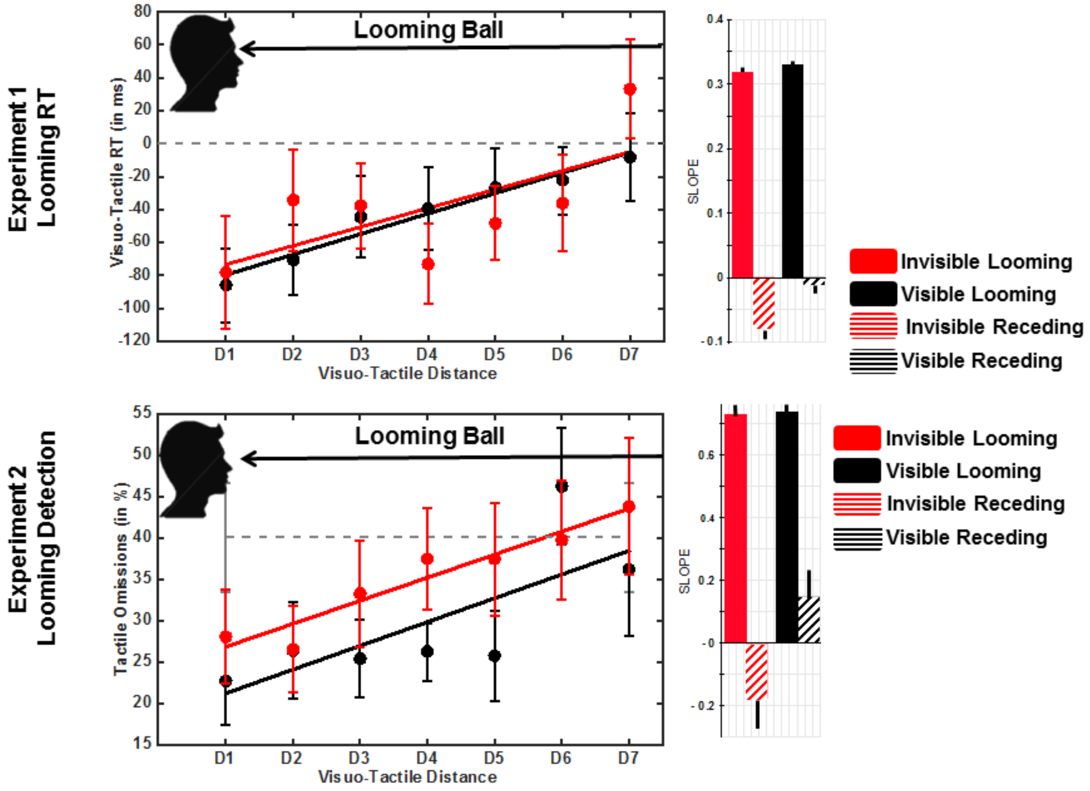

Figure. 8. 2. PPS in absence of awareness. A) Experiment 1. RTs to tactile targets as a function of the distance of the approaching visual stimulus. In order to show a truly multisensory visuo-tactile facilitation effect, RTs are reported as the difference between responses to tactile stimuli when they were coupled with visual stimulation and responses to tactile stimulation alone. Baseline unimodal tactile RTs (administered in 20% of trials) are thus by definition equal to zero (illustrated by the dashed line; (Noel et al., 2015)). Data for both the conditions in which the looming visual stimuli was visible (black) and invisible (red) were fitted to linear functions (see supplementary material online). Error bars indicate +/- 1 S.E.M. For both conditions, tactile processing speeded up as the visual stimulus approached the body. B) Exp. 2. Omission to tactile targets as a function of the distance of the approaching visual stimulus (Convention follows as in A). Tactile stimulation was set to be detected on 60% of trials, (i.e., omitted on 40% of

unimodal tactile trials). Perception increased as the ball approached the body, both in the visible (black) and invisible (red) conditions.

Invisible looming stimuli increase tactile awareness (Exp 2)

In Experiment 2, we investigated whether invisible visual stimuli, occurring within the PPS, modulate not only the processing of supra-threshold tactile stimuli, but also enhance the perception of near-threshold tactile stimulation. To this aim, we used a staircase procedure (see Supplementary Information online), so that tactile targets were perceived in 60% of trials, when presented alone. Then, near-threshold tactile target stimuli were coupled with looming (or receding, as a control condition) visual stimuli that were again either fully visible or rendered invisible through CFS (as in Exp. 1). We predicted that visible and invisible visual stimuli occurring within PPS would also boost the detection of near-threshold tactile stimuli (but only for looming stimuli), thus increasing subjects' accuracy in reporting tactile stimulation. Fig.2B reports the percentage of missed tactile targets as a function of the distance of looming visual stimuli and shows that tactile detection increased as the virtual ball approached the subjects (see Fig.2B). Data were fitted with a linear function (as the best model fitting the data, see supplementary analyses online) and analyzed as in Exp. 1. The main effect of Ball Direction was significant ($F(1,14)=287.03, p< 0.001$, partial $\eta^2 =0.95$; $BF_{10}= 7.09$), with steeper slopes for looming (mean slope=0.73±0.03) as compared to receding visual stimuli (mean slope=0.07±0.001) (see Fig. S2B). As in Exp. 1, there was no main effect of Condition ($p= 0.31$; $BF_{10}= 4.05e-28$), nor a Condition X Ball Direction interaction ($p=0.18$; $BF_{10}= 0.60$), meaning that the same spatially dependent modulation of tactile perception was found both in the visible and in the invisible conditions. To summarize, visual stimuli within the PPS, enhance the perception of near-threshold tactile stimuli on the body, even when they are rendered fully invisible.

Invisible visuo-tactile conflicts modulate self-identification (Exp 3)

Having demonstrated visuo-tactile integration for unconscious sensory inputs within PPS, we next asked whether we could modulate BSC by manipulating the spatio-temporal congruency of visuo-tactile stimuli (Blanke, 2012; Ehrsson, 2007; Lenggenhager et al., 2007), even when the multisensory conflict was not consciously perceived. To this aim, in Exp. 3, we used visuo-tactile stimulation to induce the full body illusion using either fully visible stimuli (as done in previous studies) or identical visual stimuli rendered invisible by means of CFS. Participants received above-threshold tactile stimulation on their back, administered by means of a robotic stroking set up (Ionta et al., 2011; Salomon, Lim, Pfeiffer, et al., 2013), while concurrently seeing an avatar from behind, presented binocularly through a head-mounted display. The avatar was shown on the HMD as receiving tactile stimulation on the back, represented by a colored dot moving at the same speed and to the same extent as the tactile stimulation participants received on their back (see Fig. 1B). In the synchronous condition, normally inducing the full body illusion (Ionta et al., 2011; Lenggenhager et al., 2007; Salomon, Lim, Pfeiffer, et al., 2013), the visual stimulation on the avatar's body and tactile stimulation on the participant's body were corresponding. An asynchronous visuo-tactile stimulation, in which the visual and tactile stimulations were unrelated, was administered as a control condition. The experiment was run in a 2X2 factorial design, in which we manipulated the synchrony of stimulation, as well as the visibility of the moving dot: it was either fully visible, as in the standard full body illusion, or rendered invisible by masking the region of visual stroking with Mondrian patterns flashed to the dominant eye (see Supplementary Information online and (Salomon, Galli, et al., 2015) for details). On each trial, participants were stroked for one minute. Stimulus visibility was strictly controlled (see Supplementary Information for full details). Trials in which participants reported seeing a visual stimulus apart from the masks were removed from analysis (3% of trials).

In the remaining fully suppressed trials participants were at chance for reporting the dot's color and visuo-tactile synchrony (mean accuracy 49% and 50% respectively see supplementary materials for further analysis). The modulation of BSC was measured with two questions (modified from (Lenggenhager et al., 2007)) probing self-identification (Q1:*'How strong was the feeling that the body you saw was you?'*) and illusory touch (Q2:*'How strong was the feeling that the touch you felt originated from the body you saw?'*), using a scale from 1 *(Completely disagree)* to 10 *(Completely agree)*.

Participants' responses indicated that a change in BSC was obtained by means of synchronous stimulation both in the visible and in the invisible conditions. First, a repeated measures ANOVA on Q1 scores with synchrony (Synchronous/Asynchronous) and visibility (Visible/Invisible) as within-subject factors revealed a significant main effect of synchrony (F(1,19)=24.47,p=.00009, partial η^2=0.56), with higher self-identification in the synchronous (M=4.0, S.E.M=0.59) than in the asynchronous (M=3.2, S.E.M=0.59) condition. Moreover, the main effect of visibility was significant (F(1,19)=8.08, p=.01, partial η^2=0.29), with considerably higher self-identification ratings in the visible (M=4.1, S.E.M=0.55) than in the Invisible (M=3.0, S.E.M=0.45) condition. The interaction between synchrony and visibility was also significant (F(1,19)=7.41, p=0.014, partial η^2=0.28), with larger differences in self-identification as a function of synchrony ratings in the visible (Visible-synchronous M=4.8, S.E.M=0.56, Visible-asynchronous M=3.5, S.E.M=0.51) than the invisible (Invisible-synchronous M=3.2, S.E.M=0.44, Invisible-asynchronous M=2.8, S.E.M=0.48) condition. Importantly, non-parametric Wilcoxon paired samples tests (Holm-Bonferroni corrected) revealed significantly higher ratings for self-identification with the avatar after synchronous as compared to asynchronous visuo-tactile stroking both in the Invisible (W(19)=124; p=0.013, Cohen's *d*=0.51) and the Visible (W(19)=196; p=0.0001,Cohen's d=0.96; see Fig. 3) condition. Thus, as mentioned above, both the visible and invisible synchronous visuo-tactile stroking evoked a significantly higher degree of body ownership than their asynchronous counterparts. While the effect size was larger in the visible than invisible condition (conscious, Cohen's d = 1.02 vs. unconscious Cohen's d = 0.54), both conditions showed a medium to large effect size (Cohen, 1977). This result shows that visuo-tactile stimulation led to higher explicit self-identification responses in a synchrony-dependent manner even when participants were not aware of the type of visual stimulation they were receiving. Bayesian tests indicated that for the invisible condition there was moderate (BF_{10}=4) evidence supporting the hypothesis of higher self-identification ratings in the synchronous vs. the asynchronous condition. In the visible condition there was very strong evidence for this hypothesis (BF_{10}=86.8; Jeffreys, 1998; Rouder, Speckman, Sun, Morey, & Iverson, 2009).

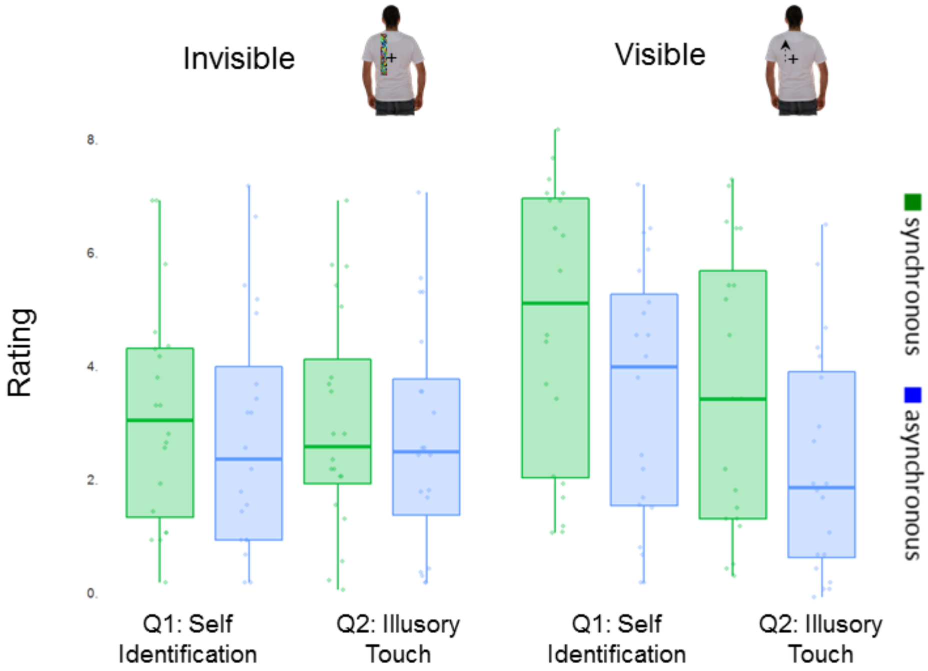

Figure 8.3. Modulation of self-identification by an invisible multisensory conflict. Boxplots of responses to BSC questions relating to self-identification and illusory touch for synchronous and asynchronous visuo-tactile stimulation. Significant modulation was found for the full body illusion condition (synchronous vs. asynchronous visual tactile stimulation) for both invisible (left) and visible (right) conditions. Whiskers represent data range. Dots represent individual participants' scores.

Responses to the second question regarding illusory touch, revealed a significant main effect of synchrony, with higher misattribution of touch (F(1,19)=23.89,p=0.0001,partial η^2 =0.55) in the synchronous (M=3.3, S.E.M=0.45) than in the asynchronous (M=2.5, S.E.M=0.41) condition. The main effect of Visibility was not significant (F(1,19)=0.2, p=0.87, partial η^2 =0.001). The interaction between visibility and synchrony was significant (F(1,19)=12.23, p=0.002, partial η^2=0.39), with larger differences in illusory touch as a function of synchrony in the visible (Visible-synchronous M=3.6, S.E.M=0.56, Visible-asynchronous M=2.3, S.E.M=0.45) than the invisible (Invisible-synchronous M=3, S.E.M=0.56, Invisible-asynchronous M=2.3, S.E.M=0.45) condition. Here, as for self-identification, non-parametric Wilcoxon paired samples tests (Holm-Bonferroni corrected) indicated that participants misattributed tactile stimulation to the virtual body significantly more strongly in the case of synchronous as compared to asynchronous stimulation not only in the visible (W(19)=186; p=0.00009, Cohen's d=1.03), but even in the invisible (W(19)=2.14; p=0.02, Cohen's d=0.47) condition, i.e. when they were not aware of the spatio-temporal pattern of visuo-tactile stimulation (see Fig. 3). Bayesian tests indicated that for the invisible condition there was moderate (BF_{10}=3.28) evidence supporting the hypothesis of higher illusory touch ratings in the synchronous vs. the asynchronous condition. In the visible condition there was decisive evidence for this hypothesis (BF_{10}=150.2). Together, these findings show that modulations of BSC by visuo-tactile conflict occur even when the visual stimuli, and the resulting multisensory conflict, are not consciously experienced. This result is the first empirical evidence that explicit changes in the phenomenal content of BSC arise by manipulating multisensory cues in the absence of awareness.

Invisible visuo-tactile conflicts modulate perceived self-location (Exp 4)

We finally investigated if an unconscious multisensory manipulation of BSC would also modulate self-location (Blanke, 2012; Lenggenhager, Mouthon, & Blanke, 2009; Lenggenhager et al., 2007). Previously, we showed that during the full body illusion (induced with fully perceived visual and tactile stroking), the boundaries of PPS representation, as assessed by means of an audio-tactile interaction task, shifted from being centred at the participants' body, toward the location of the avatar's body with whom the participants identified (Noel et al., 2015). Here, we applied the same paradigm, but tested whether a similar change in PPS, reflecting a change in self-location, can be achieved when visuo-tactile stimulation applied to induce the full body illusion is not visible to the participant. To this aim, epochs of masked visuo-tactile stimulation (as in Exp. 3) were intermingled with audio-tactile trials measuring PPS (see Methods and supplementary information for details). Perceptual awareness for the visual stimuli was controlled as in Exp. 3 and only trials in which the participants were completely unaware were included in the analysis (12% of trials were excluded, see Supplementary Information). The PPS paradigm was similar to that used in Exp. 1, but we used auditory looming stimuli, instead of visual stimuli, in order to keep the form of multisensory stimulation used to induce the full body illusion (visuo-tactile) orthogonal to that used to test its effect on perceived self-location (auditory-tactile). Participants were requested to respond as quickly as possible to a tactile vibration administered on their trunk, while task-irrelevant sounds approached their body. Figure 4A shows RT to tactile targets as a function of the distance of the sound at the time of tactile stimulation. In order to test whether the boundaries of PPS varied between the synchronous and the asynchronous stroking conditions, RTs were fitted with a sigmoidal function (Canzoneri et al., 2012; Serino et al., 2015; Teneggi et al., 2013). The sigmoidal's central point, representing an index of the location of PPS boundary, and slope, representing an index of the gradient of PPS representation were compared (Synchronous vs. Asynchronous). The central point location was significantly different in the Synchronous (M = 4.5, S.E.M. = 0.22) as compared to the Asynchronous (M = 3.8, S.E.M. = 0.45) condition (t(20) =2.452, p = 0.024, partial η^2 = 0.198; BF_{10}= 309.9), indicating that participants' PPS boundary was more distant from the participant's body, and thus closer to the avatar's body, in the Synchronous condition than in the Asynchronous control condition. No main effect of synchrony was found on the slope (p=0.34; BF_{10}= 3.08e-4), which was however different from 0 in both conditions (both p-value<0.03), indicating a distance-dependent modulation of tactile processing. Thus, the manipulation of multisensory cues, of which participants were not aware of (yet inducing changes in the phenomenal content BSC, Exp. 3), caused a shift in self-location toward the virtual body participants identified with, as shown here based on the effect on the PPS boundary (Noel et al., 2015).

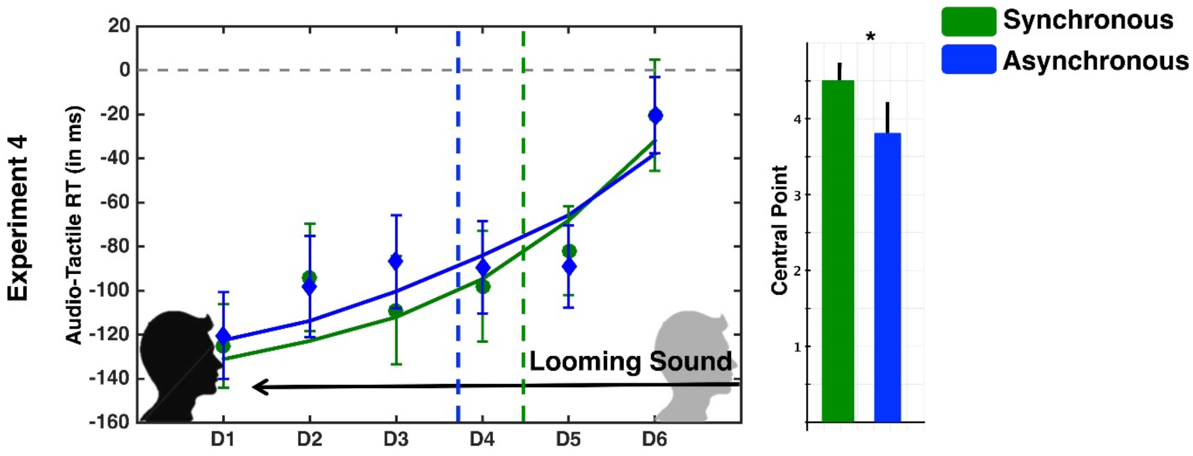

Figure 8.4. Modulation of self-location by an invisible multisensory conflict. RTs to tactile targets as a function of the distance of the approaching auditory stimuli (D7-D1) and the visuo-tactile stroking condition (synchronous in green and asynchronous in blue). RTs are reported as the difference between responses to tactile stimuli when they were coupled with visual stimulation and response to tactile stimulation alone. Baseline unimodal tactile RTs (administered on 20% of trials) are thus by definition equal to zero (illustrated by the dashed line). Data was fitted to a sigmoidal function. Error bars indicate +/- 1 S.E.M. The vertical dashed lines indicate the mean central point of the sigmoidal fitting, computed as a measure of the distance at which sounds start affecting RTs and analysed in order to quantify PPS boundaries. This value was located at a farther distance in the synchronous (green) as compared to the asynchronous (red) visuo-tactile stroking conditions, indicating a more extended PPS in the former case.

Discussion

Unconscious multisensory integration in PPS

The self is essential to our understanding of consciousness (Blanke & Metzinger, 2009; Damasio, 2012; Metzinger, 2004) and recent work has highlighted the role of multisensory integration and PPS in self-consciousness, especially in BSC (for reviews see Blanke, 2012; Blanke et al., 2015; Ehrsson, 2012b; Noel et al., 2016). The present study brings novel comprehensive evidence that multisensory integration in PPS does not require conscious awareness and, importantly, that these unconscious multisensory processes modulate the phenomenological content of BSC.

In the first two experiments we show that multisensory integration of bodily signals within the PPS occurs when visual stimuli are presented below the perceptual threshold. This was demonstrated by showing that visuo-tactile interaction in PPS occurs when visual stimuli are rendered invisible (Exp.1), and in the second experiment even when the tactile stimuli associated with invisible visual stimuli were presented near the tactile threshold (Exp.2). Thus, conscious perception of visual and tactile stimuli is not required for multisensory integration of bodily signals within the PPS. To the best of our knowledge, these findings represent one of the first accounts of increased tactile sensitivity in healthy subjects as a function of the distance of a stimulus in a different modality (e.g. Cléry, Guipponi, Wardak, & Hamed, 2015), and the first to demonstrate this effect unconsciously. In this manner, the current report represents an interesting link with neuropsychological observations (e.g. Farnè, Pavani, Meneghello, & Làdavas, 2000), reporting enhanced cross-modal interaction between contralesional tactile stimulation and ipsilesional visual (or auditory) stimulation in the near space (as opposed to the far space) in patients suffering from cross-modal extinction due to right-brain damage. In the patients, contralesional tactile stimulation is by definition below the threshold of conscious perception (under condition of bilateral stimulation). Thus, the present findings directly bridge classical neuropsychological research, which firstly demonstrated dedicate multisensory processing for stimuli within the PPS in humans, and studies on PPS in healthy subjects.

Previous behavioural findings showed that the processing of invisible stimuli is affected by concurrent non-visual stimuli above perceptual threshold (Alsius & Munhall, 2013; Lunghi et al., 2010; Lunghi et al., 2014; Maruya, Yang, & Blake, 2007; Salomon, Lim, Herbelin, et al., 2013; Zhou et al., 2010). Data from experiment 1 demonstrate the complementary effect, in which invisible visual stimuli impact processing of supra-threshold tactile stimuli. Experiment 2 further extends this finding, by showing that an invisible visual stimulus even modulates awareness for tactile stimuli near the tactile threshold, thus extending recent work revealing interactions between two unconscious stimuli during sleep (Arzi et al., 2012) and wakefulness (Faivre et al., 2014). The present study is the first report, to the best of our knowledge, of a multisensory interaction between near-threshold tactile and visual stimuli and in revealing that this unconscious visuo-tactile effect depends on the distance from the body (PPS). The present results are compatible with neurophysiological studies showing that, on anesthetized animals, at a single neuron level, multisensory integration occurs in absence of awareness, and that this effect is modulated by the spatial alignment of multisensory inputs (Stein & Stanford, 2008). More specifically concerning the spatial modulation of these multisensory responses as a function of distance from the body, although most studies on bimodal and trimodal neurons mapping PPS in monkeys have been performed on awake animals, there is also evidence of bimodal responses for stimuli within PPS in anesthetized monkeys (Graziano et al., 1997). However, a neural integrative response to multisensory inputs in the absence of awareness does not imply that those inputs can affect conscious perception. The present findings, therefore, extend those neurophysiological data by showing that an unperceived visual stimulus affects the processing of a fully perceived (experiment 1) or even of a near-threshold (experiment 2) tactile event in a distance dependent manner.

These effects might rely on the activation of PPS neurons in the premotor and posterior parietal cortex (Bremmer et al., 2001; Graziano, Cooke, & Taylor, 2000; Huang, Chen, Tran, Holstein, & Sereno, 2012), which are activated not only by above thresholds sensory inputs occurring close to the body (Macaluso & Maravita, 2010; Serino, Canzoneri, & Avenanti, 2011), but possibly also by below-threshold sensory events. Indeed, beyond classical feedforward mechanisms, recent imaging studies have shown representations of body related haptic and proprioceptive signals in visual regions (Astafiev, Stanley, Shulman, & Corbetta, 2004; David et al., 2007; Ionta et al., 2011; Limanowski & Blankenburg, 2016) allowing integration of these signals and their propagation to the posterior parietal cortex and the premotor cortex where bimodal and trimodal neurons mapping the PPS are located (Bremmer et al., 2001; Huang et al., 2012). Furthermore, a recent study employing MEG has revealed that unseen visual information is maintained and propagates from occipital visual regions to parietal and frontal regions (King, Pescetelli, & Dehaene, 2016). Thus, the visual receptive field of PPS neurons may be activated by invisible visual inputs, when these are presented within the PPS, thus interacting with tactile stimulation on the body, speeding up tactile RT or enhancing tactile perception as found in the current experiments.

Unconscious multisensory integration underlies BSC

Recent accounts suggest that modulation of BSC through manipulation of multisensory inputs, as during the full body illusion, depends on the extension of the visual receptive fields of bimodal PPS neurons (Blanke, 2012; Ehrsson, 2012b; Makin et al., 2008; Noel et al., 2015). Based on this and the findings of experiments 1 and 2, we predicted that sub-threshold multisensory stimulation may also impact BSC and subjective responses about the self. This departs from previous studies using visuo-tactile stimulation to manipulate BSC, in which the applied stimuli were well above the perceptual thresholds (e.g. Ehrsson, 2007; Lenggenhager et al., 2007; Petkova & Ehrsson, 2008; Salomon, Lim, Pfeiffer, et al., 2013). While it is evident that we are not consciously aware of most multisensory processing (including those involved in BSC), to date it is not known whether unconscious multisensory stimuli can influence the content of BSC and how such effects with unconscious stimulation compare to effects obtained with conscious stimulation. Here we show that subjective and objective responses about the phenomenal content of BSC are modulated by unconscious multisensory stimuli and that this modulation, although weaker, is qualitatively comparable to modulations obtained with fully conscious stimuli. Experiment 3 indicated that for two patterns of stimulation, which were perceptually identical to the participants - i.e., seeing an avatar (without seeing the stroking) and feeling tactile stimulation - different explicit self-related experiences were induced that depended on an unperceived temporal relationship between visual and tactile stimulation (i.e., synchronous vs. asynchronous). At the subjective level - in experiment 3 - while the response scores for the self-identification and illusory touch questions were not very high in both the visible and invisible conditions, they showed a consistent synchrony dependent modulation, in line with previous studies showing a central role for multisensory integration in BSC (e.g. Ehrsson, 2007; Lenggenhager et al., 2007; Petkova & Ehrsson, 2008; Salomon, Lim, Pfeiffer, et al., 2013). At an implicit level - in experiment 4 - we show that this unconscious multisensory integration not only alters explicit self-identification, but also impacts where participants implicitly perceived themselves to be (implicit self-location), as we observed a shift of the PPS boundary toward the virtual body, in the same direction as induced when multisensory stimuli are administered in fully conscious manner (Noel et al., 2015),

Consciousness is characterized by a unity of experience in which information from multiple sensory modalities is integrated and bound together (Bayne, 2002; James et al., 1981) and, accordingly, current theories of consciousness postulate that integration of information, including unconscious stimuli, is critical for perceptual awareness (Baars, 2002; Mudrik et al., 2014; Tononi, 2008). Recent work has shown that consciously perceived stimuli can be integrated with subliminal stimuli (Alsius & Munhall, 2013; Lunghi et al., 2010; e.g. Lunghi et al., 2014; Salomon, Galli, et al., 2015; Salomon, Kaliuzhna, et al., 2015; Salomon, Lim, Herbelin, et al., 2013; Zhou et al., 2010; for review see Deroy et al., 2016). The present data show that unconscious multisensory integration also extends to a distinct form of conscious content (Dehaene & Changeux, 2011; Faivre et al., 2015; Gallagher, 2000), i.e., self-consciousness targeted experimentally through multisensory stimulation affecting BSC. Thus, we provide the first experimental support to the idea that the multisensory integrative processes underlying BSC are enabled in the absence of stimulus awareness. Importantly, the present findings also show that the phenomenological content of self-consciousness may be manipulated by unconscious multisensory bodily signals. We consider this empirical observation to be particularly significant, as theoretical approaches influential in driving empirical efforts in BSC postulate the existence of a pre-reflective self. This pre-reflective self is the experience of oneself as the subject of experience, prior to any reflexive form of consciousness, whereby the subject takes himself as an object of consciousness (Legrand, 2006). This pre-reflective self is posited to emanate from multisensory and sensorimotor integration and to be the base for higher-order forms of self-representations (Blanke & Metzinger, 2009, Salomon, in press). However, the demonstration of the role of integrated sensory signals to modulate bodily self-consciousness without perceptual awareness was lacking. Thus, BSC is strongly grounded in the field of psychophysical consciousness studies, suggesting that comprehensive notions of self-consciousness may follow similar principles. It is, nonetheless, important to highlight that future work may further characterize the phenomenological experience associated with the full-body illusion under conscious and unconscious conditions. Using additional illusory paradigms, such as the body swapping illusion (e.g. Petkova and Ehrsson, 2008) or manipulations of ownership based on visuomotor correspondences (Banakou, Groten, & Slater, 2013; Banakou & Slater, 2014) as well as further_neuroimaging (e.g., fMRI) and physiological (e.g., skin conductance) measurements and further phenomenological probing (e.g., expanded questionnaires) could increase our understanding of the mechanisms underlying unconscious modulations of BSC.

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CHAPTER IX

MULTISENSORY INTEGRATION IN THE PERI-PERSONAL SPACE OF PATIENTS WITH DISORDERS OF CONSCIOUSNESS AND COMMAND-MOTOR DISSOCIATION

The contents of this chapter are adapted from a manuscript in preparation; Noel, J.P., Johr, J., Perdikis, S., Silva, M., Schneider, C.., Pincherle, A., Millan, J., Wallace, M., Diserens, K., Serino, A. (in prep). Multisensory Integration in the Peri-Personal Space of Patients with Disorders of Consciousness and Command-Motor Dissociation.

Abstract

Behavioral assessments of consciousness based on overt command following cannot differentiate between patients with impaired awareness from those who demonstrate a sharp dissociation between intent/awareness and motor capacity; cognitive motor dissociation (CMD). In turn, researchers have leveraged neuroimaging techniques to measure consciousness. Here we expand on this work by developing an electroencephalography (EEG)-based measure of peri-personal space (PPS) and applying this metric to patients with disorders of consciousness (DOC) & CMD. Delineating PPS in these patients is of interest as PPS is widely considered a multisensory-motor space allowing human-environment interactions. In Experiment 1, we determine a "normative" physiological index of PPS by recording EEG from healthy volunteers (N=19) during tactile (T), auditory (A), or audio-tactile (AT) stimulation. Importantly, auditory stimuli could be delivered near (5cm) or far (75cm) from participants. Global field power contrasts between paired (AT) and summed (A+T) responses demonstrated multisensory supra-additivity solely when AT stimuli were presented near, i.e., within the PPS, and highlighted somatosensory-motor sensors as electrodes of interest. Additionally topographical analyses revealed that distinct neural networks were recruited when stimuli were presented in the peri- (vs. extra-) personal space. Given these results, in Experiment 2, EEG was recorded from somatosensory-motor electrodes in DOC/CMD patients (N = 17, 30 sessions), and the measure of PPS developed in Experiment 1 was related to both clinical assessments and quantitative electrophysiological measures of consciousness (i.e., neural complexity). Results demonstrated a significant correlation between the PPS measure and consciousness-level as indexed via quantitative, but not clinical measures. Furthermore, preserved multisensory processing within the PPS was found in CMD patients, differently from non-CMD DOC patients. Taken together, these results suggest the utility of this novel assessment of DOC by measuring the integrity of multisensory-motor PPS processing. This approach may allow differentiating between groups of patients considered to be within the DOC spectrum, but who may nonetheless retain a minimal form of self-awareness, particularly patients with CMD.

Introduction

Detailing the neural and computational mechanisms enabling wakefulness and conscious experience is a central and unanswered question within systems neuroscience despite its paramount clinical implications for patients with disorders of consciousness (DOCs; Bernat, 2006). Specifying the exact nature and gravity of impoverished environmental and self-awareness within these patients remains a medical challenge, with critical consequences on the patient's outcome. Currently, DOC patients are typically classified either as comatose, or if emerging from this state, as within vegetative state (VS; also referred to as unresponsive wakefulness syndrome, UWS; Laureys et al., 2010) or as within a minimally conscious state (MCS; Giacino et al., 2014). Both VS/UWS and MCS patients exhibit preserved and residual arousal, however MCS patients show signs of intentional behavior, whereas VS patients remain largely unresponsive (Laureys et al., 2010; Giacino et al., 2002). This classification of consciousness-level is routinely performed at the bedside and is based on behavioral tests, such as the Coma Recovery Scale (CRS-R; Giacino et al., 2004). Unfortunately, despite great efforts in improving these observational assessments, they suffer from a number of limitations (Giacino et al., 2009) contributing to a high number of misdiagnoses (Andrews et al., 1996; van Erp et al., 2015). In particular, due to the fact that they depend on validated scales essentially evaluating motoric and verbal responses (even if minimal), behavioral assessments cannot differentiate between patients with impaired awareness and those with a reduced motor outflow (Laureys et al., 2004; Giacino et al., 2009; Pignat et al., 2016).

In turn, researchers and clinicians have used neuroimaging techniques (Birbaumer et al., 1999; Owen et al., 2006; Laureys et al., 2012) aiming at describing intentionality in the absence of an overt response as quantified by the GCS. This line of research has suggested the possibility of detecting awareness in VS/MCS patients (Owen et al., 2006; Owen, 2014), and in a few cases even to restore communication (Monti et al., 2010). More importantly, these findings have led researchers and clinicians to acknowledge that while command following and the production of motor responses are clear indices of awareness, conscious states and motor outflow/language capacity may be dissociated. Thus, a novel category of DOC, i.e., cognitive motor dissociation has been proposed (CMD; Schiff, 2015; Pignat et al., 2016; Edlow et al., 2017; Curley et al., 2018). Accordingly, a novel clinical scale, i.e., the Motor Behavior Tool (MBT; Pignat et al., 2016), has been developed to specifically differentiate between DOC patients with (CMD patients) and without (non-CMD) command motor dissociation.

Here, we aim at furthering our understanding of the link between awareness and motor output by indexing the peri-personal space (PPS; Rizzolatti et al., 1997; di Pellegrino et al., 1997) in DOC (see Naro et al., 2018 for a similar approach) and CMD patients. The PPS is the space immediately adjacent and surrounding the body (Serino et al., 2015; Noel et al., 2015, 2017), which is largely taken to index body-environment interactions (Clery et al., 2015; Serino et al., 2017; Noel et al., 2018). In fact, PPS is encoded by multisensory neurons within a fronto-parietal network (Duhamel et al., 1998; Graziano et al., 1999, 2000) which respond to tactile stimuli on the body and to visual and/or auditory stimuli when these are presented within a limited distance from the body, i.e., within the neurons' multisensory receptive fields. The extent of the neurons' receptive fields, and thus the limit of the PPS, largely depend on the possibility of interacting with objects in the external world. For instance, PPS reduces if action possibility is limited due to prolonged immobilization (Bassolino et al., 2015) or loss of a body part (amputation; Canzoneri et al., 2013). Conversely, PPS extends in depth when using a tool to act upon far objects (Iriki et al., 1996; Maravita & Iriki, 2004) or when the speed of incoming and potentially threating stimuli increases (Fogassi et al., 1996; Noel et al., 2018). Further, solely the intent of acting upon objects (Brozzoli et al., 2009; 2010) or moving in space (Noel et al., 2015; Galli et al., 2015; Pfeiffer et al., 2018) has been reported to remap the PPS, hence suggesting that the PPS may index motor intent, even in the absence of motor output. Thus, PPS might be considered an interface for individual-environment interactions (Serino et al., 2017), and therefore may be altered in patients with DOC. In addition, its functioning may differentiate patients evidencing intention, without being able to implement it, from those who are completely isolated from the external world.

In order to measure PPS in DOC/CMD patients, this study is conducted in two parts. In a first experiment we determine the electroencephalography (EEG)-derived neural correlates of audio-tactile PPS surrounding the arm in healthy participants. We consider PPS to be evidenced when multisensory integration (i.e., sum of unisensory responses ≠ multisensory response) is modulated as a function of observer-stimuli distance. This step is novel and important as audio-tactile PPS has only been electrophysiologically probed via intracranial recordings in epileptic patients and around the trunk (Bernasconi et al., 2018). Further, in Experiment 1 the healthy participants maintain their eyes closed and make no overt response, in order to mimic the clinical conditions by necessity present in DOC/CMD patients. In Experiment 2, we tested the PPS metric developed in Experiment 1 in patients along the DOC spectrum. A total of 17 patients were tested, and among those, few patients were tested multiple times during their recovery, thus resulting in a total of 30 EEG recordings from DOC/CMD patients. We searched for electrophysiological markers of preserved vs. impaired multisensory PPS processing in patients and we analyzed those indexes with respect to the patients' clinical profiles, as assessed both by the classic CRS-R or by the new MBT, aiming at identifying CMB patients.

Methods

Participants

Experiment 1 – healthy participants

Nineteen healthy participants (9 females, age = 24.4 ± 3.9 years old) took part in this study. All participants were right-handed, self-reported no auditory or somatosensory impairment and had normal or corrected-to-normal vision. Participants provided informed consent to take part in the study, which was approved by the local ethic committee of the canton of Vaud, Switzerland. Participants were remunerated with 20 Swiss Francs for their time.

Experiment 2 – DOC patients

Seventeen patients lying within the DOC spectrum (3 females, age = 47.9 ± 18.5 years old, range = 23 – 73 years old), as defined via the CRS, took part in this study. A total of 30 EEG sessions were completed with these patients (1-5 sessions per patient), for a total of 96 blocks of trials (250 trials/block, 3.2 blocks/session on average; range = 1-7 blocks/session). The patients were in-patients at the Unit of Acute Neuro-Rehabilitation at the University Hospital of Lausanne (CHUV). Patients were diagnosed by clinical neurologists and neuropsychologists via repeated administration of the Coma Recovery Scale-Revised (CRS-R; Giacino et al., 2004) and the Motor-Behavior Tool (Pignat et al., 2016; see Table 1 for clinical detail and diagnosis according to CRS-R and MBT). On occasions, when a clinical score did not exist for the day of experimental recordings, a linear interpolation between the most proximal scores was performed; the longest time between clinical scoring and the nearest EEG session was 4 days. Overall there was no difference in CRS-R between patients classified as CMD and non-CMD (t=0.70, p=0.48), highlighting the complementarity (i.e., distinct clinical dimensions) of the CRS-R and MBT scales. The exclusion criteria for the DOC/CMD patients included: i) current neuromuscular function blockers or sedation, and/or ii) a premorbid history of developmental, psychiatric or neurological illness resulting in documented functional disabilities at the time of damage. Of the included patients, 3 were deemed to be in MCS, 1 was in Locked-In Syndrome, 7 were VS/UWS, and 6 were comatose. Given clinical evaluations and administration of the MBT (Pignat et al., 2016), 21 sessions were considered to be conducted with patients putatively in CMD state (and not “true” DOC), while the remaining 9 sessions were conducted with patients without CMD (i.e., true DOC patients). Etiologies differed; 9 patients visited the Neuro-Rehabilitation Unit due to an ischemic stroke or hemorrhage, while the rest had a traumatic brain injury (see Table 1). All of the included patients received a standardized intensive program of rehabilitation, including physical, occupational, neuropsychological and speech therapies totaling at least 5 hours per day. Caregivers of every patients provided informed consent to take part in the study, which was approved by the local ethic committee of the canton of Vaud, Switzerland.

Material and Apparatus

Experiment 1 – healthy participants

Auditory stimulation was administered at different distances while tactile stimuli were applied on the participants’ arm. The auditory stimuli consisted of 50ms of white noise administered via loudspeakers (Z120 Portable Speakers, Logitech, Lausanne, Switzerland) placed 5 cm (65.2 dB Sound Pressure Level (SPL)) and 75 cm (64.1 dB SPL) from the participant’s extended arm in the depth dimension (see Figure 1). Tactile stimuli were equally 50ms (pulses at 35Hz) in duration and administered via functional electrical stimulation (FES; MED-EL Medical Electronics, MOTIONSTIM 8, Innsbruck, Austria) and two electrodes (positive and negative, Flextrode Plus) placed on the extensor *digitorum communis* (i.e., dorsal part of the arm approaching the elbow) at 70% of each participant's motor threshold, which was determined immediately prior to initializing the experimental procedure. Somatosensory stimulation ranged between 5 mA and 11 mA. In addition to the two electrodes placed on the participant's right arm for delivery of tactile stimulation, an additional contact was placed on their right shoulder (depicted in Figure 1 between electrodes solely for illustration purposes). This last electrode was connected to earth ground in order to nullify putative electrical artifacts pertaining to the FES stimulation. In the case of multisensory trials, auditory and tactile stimuli were administered synchronously.

Experiment 2 – DOC patients

Materials and apparatus was identical in patients and in healthy participants for exception that placement of the loudspeakers was by necessity approximate due to configuration constraints in the neuro-rehabilitation unit. The distance between speakers was always 70 cm (as for Experiment 1), but the distance of the nearest speaker to the arm varied (largest distance ~15cm, which is largely considered to still be within peri-hand space; Serino et al., 2015). Further, for 2 patients FES was given on the left arm (as opposed to right arm in the rest of patients and healthy participants), due to either configuration constraints or traumatic brain injury impeding EEG on the left brain. For these patients EEG recordings were left-right symmetrically flipped.

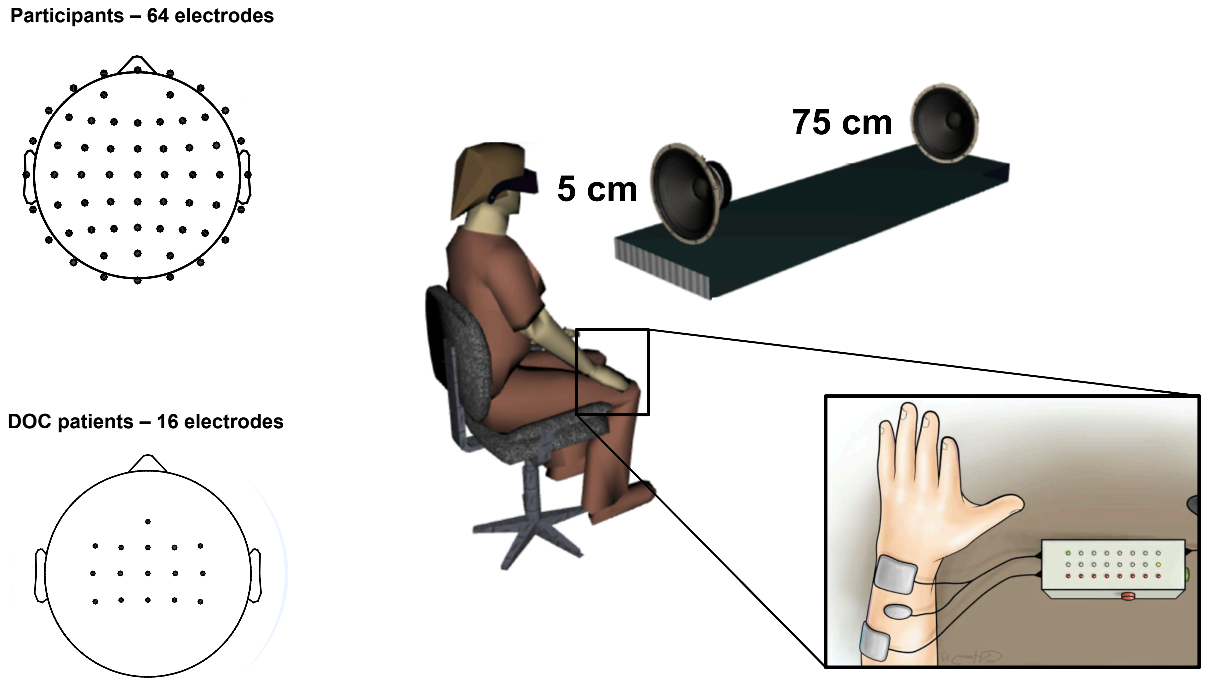
Procedure

Experiment 1 – healthy participants

Participants sat at a table in a light and sound-controlled environment. Electrodes were placed on their arm, and their FES motor threshold was determined. Accordingly, the intensity of tactile stimulation was set (70% of motor threshold), and participants were asked to close their eyes and simply relax. Three blocks of audio-tactile stimulation were conducted. Each block consisted of 250 trials; 50 unisensory tactile, 50 unisensory audio near, 50 unisensory audio far, 50 audio-tactile near, and 50 audio-tactile far. The order of these trials was fully randomized within a block and inter-trial interval consisted of 1.5-2 seconds (uniform distribution). Each block of trials had a duration of 10 minutes. Between blocks participants were given a short break and allowed to open their eyes.

Experiment 2 – DOC patients

The procedure was identical with patients to that in healthy participants with the exception that testing took part at the Unit of Acute Neuro-Rehabilitation at the University Hospital of Lausanne (CHUV) and patients laid in a supine position (approximately 130°) while testing occurred. Further, due to clinical demands a variable number of blocks were recorded in patients, averaging 3.2 blocks per session and ranging from 1 to 7 blocks per session.



Participants – 64 electrodes

DOC patients – 16 electrodes

Figure 9. 1. Methods. Healthy participants (Experiment 1) and patients with disorders of consciousness (DOC patients; Experiment 2) were exposed to tactile (FES stimulation), auditory (white noise), and audio-tactile stimulation while EEG was recorded. A full montage with 64 electrodes was used in healthy participants (top left), while 16 electrodes (bottom left) centered on somatosensory and parietal regions were recorded due to clinical limitations and results from Experiment 1. Auditory stimulation could be administered either close (~5 cm) to the participant's arm (location of tactile stimulation), or far from the arm (~75cm). In turn, there were a total of 5 conditions; tactile alone, auditory near alone, auditory far alone, audio-tactile near, audio-tactile far.

EEG Acquisition and Preprocessing

Experiment 1 – healthy participants

Continuous EEG was collected via a 64-channel EEG system (g.tec medical engineering, GmbH, Graz, Austria) with a sampling rate of 512 Hz (g.HIamp, g.tec medical engineering, GmbH, Graz, Austria) and referenced to the average of electrical activity at the left and right earlobes. Data were acquired with in-house EEG acquisition software (eegdev; http://cnbi.epfl.ch/software/eegdev.html) developed by the CNBI lab at EPFL and further pre-processed using MATLAB and EEGLAB (Delorme & Makeig, 2004). In pre-processing, data were notch filtered at 50 Hz and bandpass filtered from 0.1 Hz to 40 Hz using a 4th order bi-directional zero-phase infinite impulse response (IIR) filter. Epochs from 100 ms before to 500 ms after stimuli onset were extracted for each condition separately. Artifact contaminated trials and bad channels were identified and removed through a combination of automated rejection of trials in which any channel exceeded ±200 µV and rigorous visual inspection. A mean of 139.1 (S.E.M = 2.5) trials per conditions were retained (92.7%), while 0.7% (S.E.M = 0.43%) of channels were removed per participant. Bad channels were reconstructed using spherical spline interpolation (Perrin et al., 1987). Lastly, epochs were baseline corrected to the 100 ms pre stimulus onset. No re-referencing (e.g., to the average) was done, as patients did not count with a full montage, and hence average re-referencing was not possible in Experiment 2.

Experiment 2 – DOC patients

Acquisition and pre-processing of EEG data was identical in patients as it was in healthy participants, with the exception that acquisition was effectuated via a 16-channel EEG system (g.USBamp and g.Nautilus, g.tech medical engineering, GmbH, Graz, Austria) and referenced solely to the right earlobe. Sensors were positioned to cover motor and somatosensory areas (Fz, FC1, FC3, FCZ, FC2, FC4, C3, C1, CZ, C2, C4, CP3, CP1, CPZ, CP2, and CP4). A mean of 42.1 (S.E.M = 1.2) trials per condition/block were retained (86.2%). No channels were removed in patients.

Analyses (Experiment 1 - healthy)

Global Field Power

The global electric field strength was quantified using global field power (GFP; Lehman & Skrandies, 1980). This measure is equivalent to the standard deviation of the trial-averaged voltage values across the entire electrode montage at a given time point, and represents a reference- and topographic-independent measure of evoked potential magnitude (Murray et al., 2008; Koenig and Melie-Garcia, 2010). This measure is used here to index the presence (or absence) of evoked potentials during tactile, auditory near, auditory far, audio-tactile near, and audio-tactile far trials. Further, it is used as a data-reduction technique by summarizing 64 distinct time-series (i.e., electrodes) into a singular one. In a first pass, we calculated average GFPs for each subject, as well as for the population of participants as a whole (i.e., grand average) and for every condition. Time-resolved t-tests against zero were performed at each time-point from 100 ms pre-stimuli presentation to 500 post-stimuli onset in order to determine periods of significant evoked potentials. To account for the temporal auto-correlation existent in EEG data we apply a 9.7 ms (5 samples at 512 Hz) contiguous data-point temporal criterion for significance (Guthrie and Buchwald, 1991; see Noel et al., 2018, and Simon et al., 2017, for a similar approach).

After demonstrating the presence of evoked potentials relative to baseline, to ascertain true multisensory interactions, we contrasted the GFP evoked by the audiovisual condition (near and far), to the sum of the unisensory responses (e.g., Cappe et al., 2012; Noel et al., 2018). The subject average response (at the voltage level and for all 64 electrodes separately) to near and far auditory presentation were summed to the subject's response to tactile stimulation alone, and GFP was computed again. A time-resolved ANOVA was compute at each time-point in order to determine main effects of distance (near vs. far) and sensory stimulation type (paired = AT vs. sum = A+T). Further, after baseline correction we assessed the interaction between distance and sensory stimulation. This latter effect is of central interest, as it would reveal a PPS effect; namely, a multisensory effect that is space dependent (see Bernasconi et al., 2018 for a similar rationale).

Event-Related Potentials

ERPs were obtained by time domain-averaging trials binned for each condition and for each electrode separately at the single-subject level and then averaging across subjects. Given out interest in indexing PPS – a multisensory spatial phenomenon – in an initial pass we focused on the AT near and far conditions. Further, given the GFP results (see below) we initially focused the analysis on two restricted time-periods; time periods t1 (191ms to 238ms post-stimuli onset) and t2 (332-384ms post-stimuli onset). This analysis revealed a number of electrodes demonstrating a spatial modulation of multisensory responses, and hence likely driving the GFP results. Nonetheless, solely 2 of these electrodes – C4 and CP4 – were present in both time-periods and recorded in

DOC patients. Thus, to derive a normative model of what ought to be expected as a PPS correlate in the named electrodes, we averaged these electrodes together and examine the time-course of auditory, tactile, and audio-tactile evoked responses. Here the analysis followed the rational explained above for the GFP results. We examined the presence of evoked potentials, then constructed summed responses and contrasted the effect of spatial location (peri-personal vs. extra-personal space) as a function of whether a true multisensory stimuli had been presented or not. Further, for completeness we report the difference in evoked activity to auditory alone and audio-tactile stimulation as a function of distance. As for the GFP analyses, in order to account for the inherent multiple comparisons and auto-correlation problem in EEG, we set a temporal criterion of at least 5 consecutive time points (Guthrie & Buchwald, 1991).

Topographic Analyses

GFP and ERP analysis index differences in neural strength, amplitude, and/or latency, but do not take into account the relative spatial distribution of voltages across the scalp as an interesting dependent variable. Hence, here for completeness and taking advantage of counting with a full-montage of electrodes in healthy participants, we performed topographical analyses. Changes in EEG topography forcibly follow from changes in the configuration of the underlying active electric dipoles (Lehmann, 1987; although the contrary is not necessarily true), and thus, the performed topographical analyses index when experimental conditions activated distinct sets of brain networks. To test the topography of evoked potentials as a function of sensory stimulation (paired vs. sum) and distance (near vs. far), we used a Global Dissimilarity measure (DISS; Lehmann and Skrandies, 1980). DISS is equivalent to the root-square-mean difference between the potentials measured at each electrode for different conditions, normalized by the instantaneous GFP (L2-norm, in this case). Statistically, the DISS value at each time point was compared to an empirical distribution derived from permuting the condition label of the data from each participant. This analysis is based on a non-parametric randomization procedure (5000 randomizations per time point) and is implemented in the RAGU software (Koenig et al., 2011). Significance threshold was set here to alpha < 0.05, and a time-resolved 2 (sensory stimulation; paired vs. sum) x 2 (distance; near vs. far) topographic ANOVA (TANOVA) on DISS values was performed to identify statistical differences between neural generator configurations for the distinct sensory stimulations as a function of distance. Further, as these analyses revealed a significant sensory stimulation type by distance interaction (in addition to main effects, see below), we moreover segmented these topographies into distinct microstates via topographic cluster analysis based on a hierarchical clustering algorithm (Murray et al., 2008). This clustering identifies stable electric topographies (i.e., "microstates" or "maps"). The optimal number of maps (i.e. the minimal number of microstates accounting for a large portion of the datasets variance) was determined using a modified Krzanowski-Lai criterion (see Murray et al., 2008). Microstates identified in the grand average response (ATnear, ATfar, Anear+T, Afar + T) were then back fitted in a procedure wherein each time point for every single-subject condition-specific average evoked response is labeled according to the template map with which it best correlates (Murray et al., 2008). These back-fitted maps can then be statistically contrasted for the duration and interval over which they are present as a function of sensory stimulation and distance condition.

EEG complexity

Recent studies have suggested that EEG signal complexity or diversity is a reliable index of consciousness level, indicating that brain activity is enhanced relative to normal when individuals have ingested psychedelic drugs (Schartner et al., 2017a), and reduced in non-REM sleep (Andrillon et al., 2016; Schartner et al., 2017b), under anesthesia (Zhang et al., 2001; Sarasso et al., 2015; Schartner et al., 2015), or in disorders of consciousness (Casali et al., 2013). Hence, here we apply the Lempel-Ziv complexity (LZc; Lempel & Ziv, 1976) algorithm as an objective and EEG-based metric of consciousness impairment. This is critical within the current aim of indexing PPS in DOC patients, as the effort in performing this indexing is in ameliorating upon behavioral-only diagnosis that may confound awareness with the ability to perform motor actions. Hence, in addition to the "subjective" diagnosis (i.e., the clinical assessment) we utilize LZc here as an "objective" measure of consciousness.

LZc is the most popular out of the Kolmogorov class (routinely used to generate TIFF images and ZIP files), and measures the approximate amount of non-redundant information contained within a string by estimating the minimal size of the 'vocabulary' necessary to describe the entirety of the information contained within the string in a lossless manner. That is, it is a lossless compression algorithm. Before applying the LZc algorithm we discarded data from all electrodes except the 16 sensors present in both participants (Experiment 1) and patients (Experiment 2), and converted our signal into a binary sequence. For every condition, participant, and trial separately we first full-wave rectified the signal and computed the mean evoked response for the particular subject and trial type. Then, for every trial, we assigned a value of '1' to a time point if the trial response was above the mean response for that particular time point, participant, and trial type. If the trial response was contrarily under the mean response, a value of '0' was assigned. This binarized data matrix (observations x trials) was then concatenated observation-by-observation into a single vector, and finally the LZc complexity algorithm determined the size of the dictionary needed to account for the pattern of binary strings observed. As LZc is maximal when data is random, in order to normalize the measure, data on a trial level was randomly shuffled in time, and then the same procedure as with the un-shuffled data was applied. The final estimate of normalized LZc complexity is given as the complexity ratio between the un-shuffled and shuffled data (see Schartner et al., 2017a and Noel et al., 2018 for a similar approach).

Analyses (Experiment 2 – DOC patients)

Analyses in Experiment 2 largely followed the rationale from Experiment 1 and were entirely hypotheses driven given results from healthy participants. Namely, while we present the time-course of evoked potentials to auditory, tactile, and audio-tactile stimuli presentation for completeness (although this analysis averages across different ages, causes of disorder, and DOC diagnosis), the central analysis examined the relationship between diagnosis of consciousness (both "subjective" and "objective") and the PPS metric derived in Experiment 1. That is, we examined the differential multisensory effect (pair vs. sum) as a function of distance (near vs. far) solely in C4 and CP4 (averaged) and solely during time-periods t1 and t2, due to the normative effect observed in healthy participants.

Of note, the PPS metric and diagnosis of consciousness are performed for each session separately (a total of 23 sessions) and not averaged across sessions and within patients (a total of 14 patients), as DOC diagnosis and CRS-R scores may change across sessions.

Results

Experiment 1 – Healthy Participants

Global Field Power

As illustrated in Figure 2, analysis of GFP demonstrated significant evoked potentials for tactile (red; 101-110ms post-stimuli onset and 150ms post-stimuli onset onward), auditory near (blue continuous; 105-164ms post-stimuli onset and 177ms post-stimuli onset onward), auditory far (blue dashed; 275ms post-stimuli onset onward), audiotactile near (light purple continuous; 117ms post-stimuli onset onward), and audiotactile far (light purple dashed; 187ms post-stimuli onset onward, t-tests to zero, all $p<0.05$) stimuli. Thus, as reliable evoked potentials were successfully indexed, we next computed the GFP associated with true multisensory presentations (pair conditions, light purple; ATnear and ATfar), as well as with conditions with equivalent energies yet not concurrently presented (sum conditions, dark purple; Anear + T, and Afar + T; see Cappe et al., 2012 and Noel et al., 2018, for a similar approach). In order to index whether the co-presentation of stimuli resulted in multisensory integration as a function of distance (near vs. far) we subtracted the paired response (e.g., ATnear) from summed responses (e.g., Anear + T) and contrasted distances via a paired t-test. This analysis showed two time-periods where paired and summed responses differed as a function of distance; 191-238ms post-stimuli onset (t1, highlighted in gray in bottom panel of Figure 2) and 332-384ms post-stimuli onset (t2, highlighted in gray in the bottom panel of Figure 2). Interestingly, contrasts of each distance to its pre-stimuli baseline (t-test of sum minus pair GFP to zero) demonstrated two significant epochs for the near distance (189-230ms post-stimuli onset, and 255-449ms post-stimuli onset), and a sole epoch for the far distance (257ms post-stimuli onset onward). The earlier epoch within which only the near distance is different from zero is a case of supra-additivity (AT>A+T), while the latter epoch within which both near and far conditions show a multisensory modulation are instances of sub-additivity (AT<A+T). Taken together, hence, GFP results demonstrate two time-periods (t1 and t2) wherein multisensory responses are different from the linear addition of sensory energies, which is further modulated by distance; a PPS effect. In turn, analysis of ERPs is initially restricted within this time window.

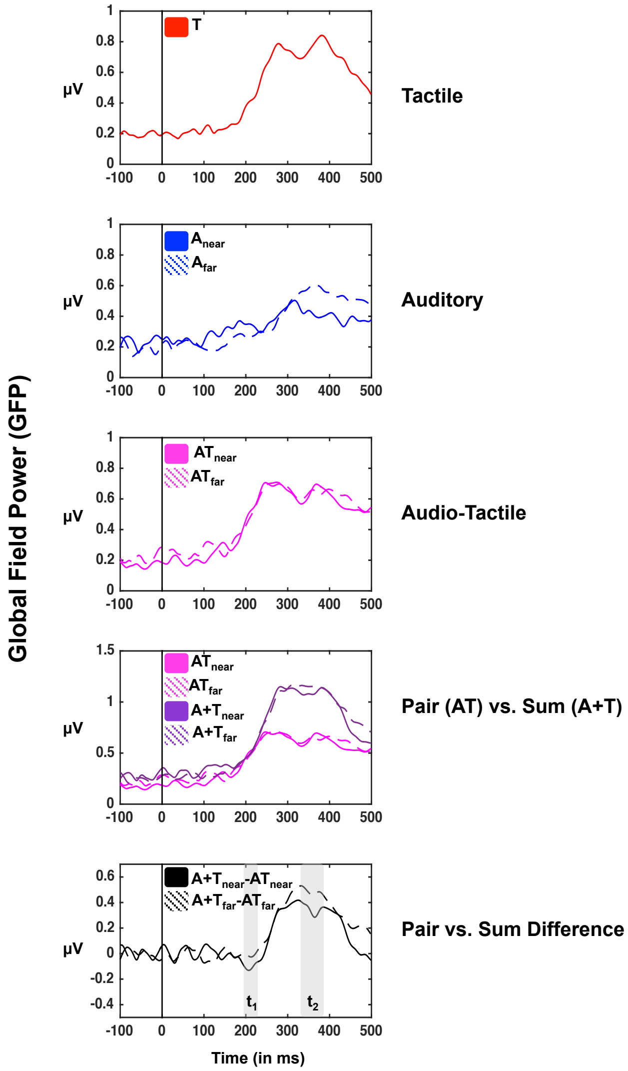


Figure 9.2. Global Field Power (GFP) in healthy participants as a function of sensory stimulation. GFP (spatial standard deviation over all electrodes) was calculated for every participant and sensory stimulation condition and then averaged across participants. Sensory stimulation evoked a significant deviation in GFP with respect to baseline for all conditions; tactile (red), auditory (blue; continous = near; dashed = far), and audio-tactile (light purple; continous = near; dashed = far). Further, mean voltages for auditory and tactile conditions (at the same distance) were summed

and the GFP of this artificial conditon was computed in order to contrast the paired GFP (audio-tactile condition; AT) with a summed condition (A+T; dark purple). The difference between paired and summed conditions is shown in the bottom-most panel (black continous = difference GFP in the near condition; black summed = difference GFP in the far condition). Differences GFP demonstrated two time-periods of interest. Between 191 and 238ms post-stimuli onset the difference GFP between paired and summed stimuli for the near condition was significantly different from zero (no difference) and from the difference evoked in the far condition. Secondly, between 332 and 384ms post-stimuli onset, the difference GFPs for both near and far stimulations were signficiantly difference from zero.

Event-Related Potentials

The GFP analysis reduced the potential state-space of analysis from 64 electrodes to a sole time-series and identified time-periods of interest. Hence, in the ERP analysis we focused on time periods between 191-238ms and 332-384ms post-stimuli onset in order to identify electrodes of interest. As illustrated in Figure 3, and as expected, the scalp distribution of voltages during AT presentation within these time-periods was centro-parietal (top two panels). The contrast between AT presentations when auditory information was presented near (top row) vs. far (middle row) revealed about 15-20 electrodes demonstrating a significant effect within the time-periods of interest (Figure 3, bottom row). Two of these electrodes, C4 and CP4, were common across time-periods (t1 and t2) and across participant's and patient's montages (see Figure 1 for montages, and Figures 4 and 6 for illustration of electrodes C4-CP4).

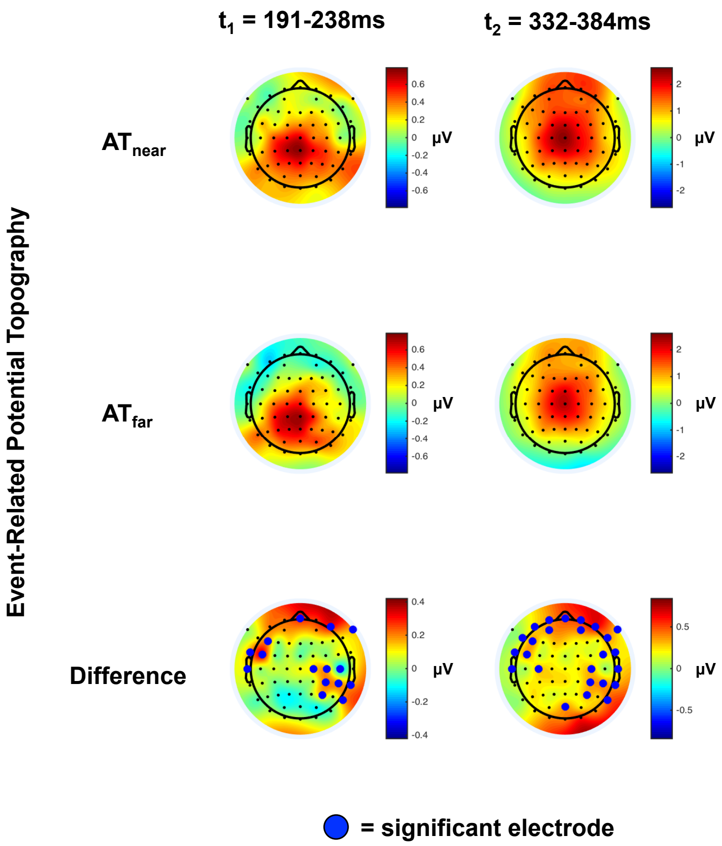


Figure 9.3. Topographic representation of voltages during time-periods of significant GFP difference between near and far conditions. AT ERPs (near = top; far = bottom) during 191-238ms (t1) and 332-384ms (t2) post-stimuli onset demonstrate a centro-parietal distribution at the scalp level. Bottom panel shows the sensor-wise difference between ATnear and ATfar, and electrodes highlighted by a green dot are significantly different between ATnear and ATfar conditions. Two electrodes (C4 and CP4) show significant differences between distances in both time-periods (t1 and t2), and are also present in DOC patients (see Figure 1, bottom left), and hence ERP analysis is focused on these electrodes.

In turn, we averaged across electrodes C4 and CP4 and examined the evoked responses at these electrodes. This analysis serves as a normative model for what ought to be expected as the correlate of PPS in these electrodes (which contribute to the global effect as indexed via the GFP analysis). A one-sample t-test to zero revealed significant changes from baseline due to tactile (between 82-169ms post-stimuli onset and 222ms post-stimuli onset and onward), auditory near (between 172-192ms post-stimuli onset and 222ms post-stimuli onset and onward), auditory far (between 99-152ms post-stimuli onset and 193ms post-stimuli onset and onward), audio-tactile near (between 76-89ms post-stimuli onset and 160ms post-stimuli onset and onward) and audio-tactile far (between 99-150ms post-stimuli onset and 179ms post-stimuli onset and onward) presentations (Figure 4, top row). Further, when contrasting paired vs. summed responses (Figure 4, bottom row), a paired-samples t-test demonstrated a significant multisensory effect between 138-240ms post-stimuli onset and 263-453ms post-stimuli onset in the near condition, and between 257ms post-stimuli onset and onward for the far condition. The early effect in the near condition was supra-additive (mean between 138ms-240 ms = 0.55μV, S.E.M = 0.18 μV, t-test to zero, t = 2.97, p = 0.009), while the later effect in the near condition and the effect in the far condition were both sub-additive (near condition, mean between 263ms-453 ms = 0.79 μV, S.E.M = 0.19 μV, t-test to zero, t = 4.14, p = 8.64e-4; far condition, mean between 257ms-500 ms = 1.01 μV, S.E.M = 0.24 μV, t-test to zero, t = 4.14, p = 8.61.e-4, Figure 4E). Interestingly, the supra-additivity was seemingly driven by a shift in the latency of response (see Figure 4D); the major positive deflection starting around 145ms (S.E.M = 8.6ms) post-stimuli onset in the paired condition and around 184ms (S.E.M = 11.85) post-stimuli onset in the summed condition (determined as the peak of the second numerical derivative of the time-course; paired t-tests between latencies, t = 2.66, p = 0.01). The direct contrast between the multisensory effect (i.e., summed response – paired response) as a function of distance via a paired t-test showed two time-periods where these differed, between 156ms and 261ms post-stimuli onset (driven by the supra-additivity present in the near condition solely) and between 330ms and 382ms post-stimuli onset (driven by the sub-additive effect present in both near and far conditions).

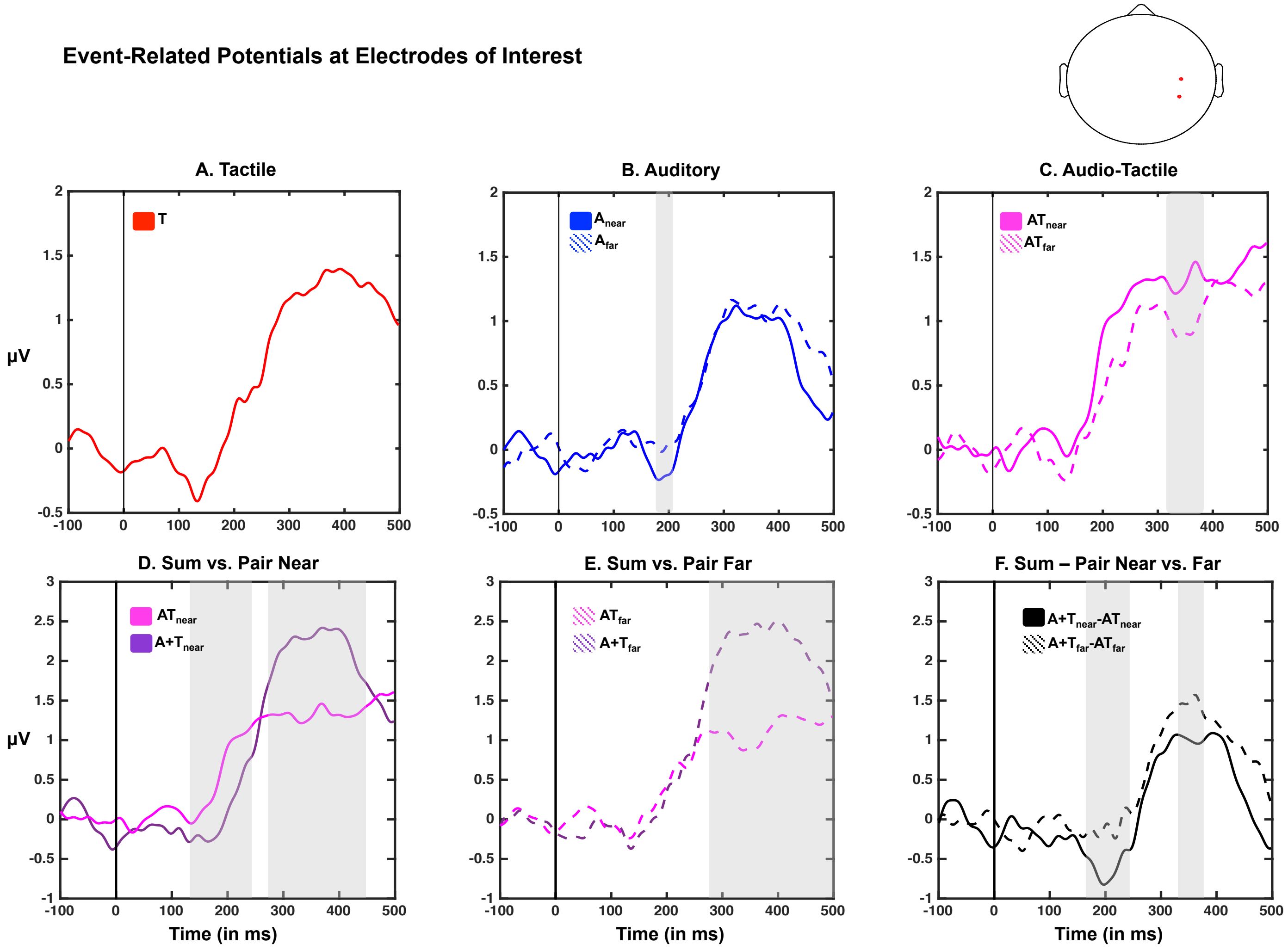


Figure 9.4. Event-Related Potentials in C4/CP4. Top panel illustrates the event-related potential to tactile (red), auditory (bue; continous = near; dashed = far), and audio-tactile (light purple; continous = near; dashed = far) at C4/CP4 in healthy participants. Areas shaded in gray demonstrate a significant difference between near and far conditions. Bottom left and center panels illustrate the difference between paired (light purple) and summed (dark purple) ERPs, while the right-most panel demonstrates the multisensory differential as a function of distance; interestingly, a multisensory effect seems present

solely in the near condition around 200 ms post-stimuli onset. This difference appears to be due to a latency effect (bottom left panel; positive deflection occuring earlier in the paired than summed activity).

Topographical Dissimilarity

Taking advantage of the fact that a full-montage was recorded in healthy participants, and in an effort to provide an entire picture regarding audio-tactile peri-arm neural encoding we assessed the topography of voltages across paired and summed evoked potentials – even though this analysis is not possible in patients due to their limited sensory coverage. A 2 (pair vs. sum) x 2 (near vs. far) non-parametric TANOVA (Murray et al., 2008), demonstrated a significant main effect of sensory stimulation (52-97 ms post-stimuli onset, and 120ms post-stimuli onset onward), as well as a main effect of distance (99-128ms post-stimuli onset and 474ms post-stimuli onset and onward). Further, the interaction between these variables was significant (between 30-69ms post-stimuli onset and between 85-155ms post-stimuli onset), arguing that not solely multisensory vs. the sum of unisensory responses evokes differential neural patterns, but further, that multisensory stimuli engage different neural networks as a function of their relative distance/distance to the body. Back projecting average neural pattern templates onto subjects and conditions specified that map 1 (Figure 5, top right, red) was present for a longer duration in the ATnear condition (M = 126ms) than in any other condition (ATfar, M = 51ms; A+Tnear, M = 30ms; A+Tfar = 54ms), which resulted in a significant main effect of sensory stimuli condition (pair vs. sum, $p = 0.01$), as well as a significant interaction between sensory stimulation and distance ($p = 2.0e-4$), but not in a main effect of distance ($p = 0.76$). Contrarily, map 2 (Figure 5, second row right column, gray) was present for a shorter duration in the ATnear condition (M = 7ms) than in the ATfar (M = 50ms), A+Tnear (M = 71ms), A+Tfar (M = 61ms) conditions. Similarly to the case of map 1, this pattern of results for map 2 resulted in a significant main effect of sensory stimulation ($p = 0.02$), as well as in a significant interaction ($p = 0.007$), but not in a main effect of distance ($p = 0.59$). Lastly, the presence of map 3 in paired conditions

(Figure 5, third row right column, blue) and map 4 in summed conditions (Figure 5, fourth row right column, green) differentiated between these experimental manipulations (main effect of sensory stimulation, $p = 4e-4$ and $p = 1e-3$, respectively) but did not show a significant interaction (all $p>0.38$), and thus did not bifurcate between peri- and extra-personal space.

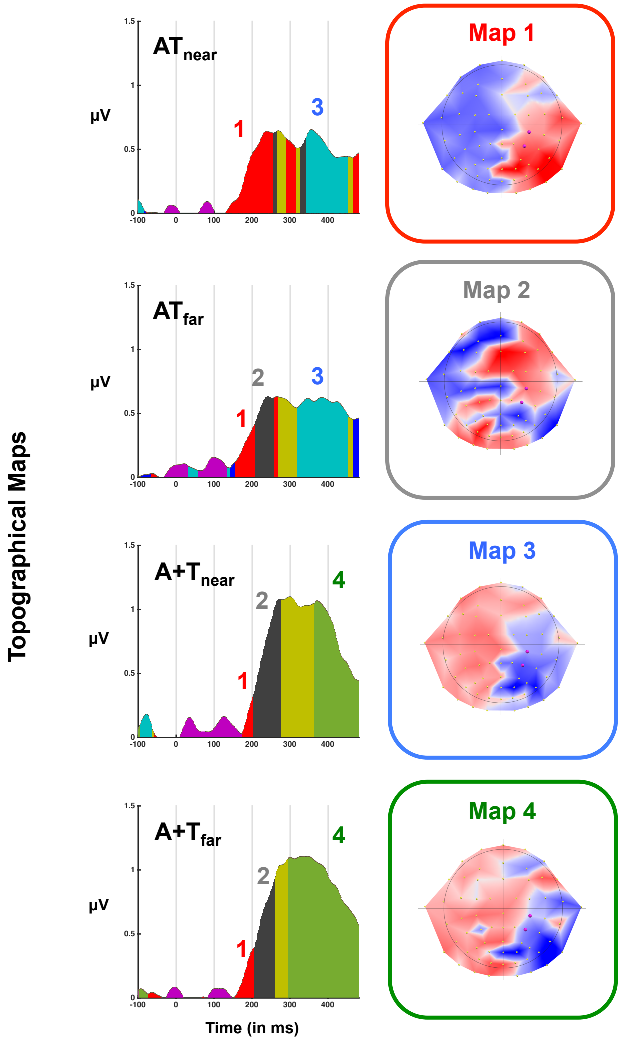


Figure 9. 5. Topographical Maps. Topographic cluster analysis identified a restricted number of maps that could account for the topographical distributions present during audio-tactile processing of stimuli both in the near and far space. Interestingly, map 1 (red, right panel) was present for all conditions (from top to botton; audio-tactile near; audio-tactile far; audio+tactile near; audio+tactile far) but was short-leaved for all

conditons except for audio-tactile near; the peri-personal space condition. In the rest of conditions, map 1 was replaced by map 2 (gray, right panel). A second clear distinction existed between conditions: map 3 (blue, right panel) was present at large delays in multisensory conditions (audio-tactile near and audio-tactile far), while instead map 4 (green, right panel) was present in summed conditions.

Neural Complexity

On average the normalized neural complexity associated with evoked responses in healthy participants was 0.28 (S.E.M. = 3.3e-04) and demonstrated a remarkably limited variance (range = 0.278 -0.298). A one-way ANOVA suggested there was no difference in evoked LZc across sensory stimulation conditions (p = 0.08).

Experiment 2 – DOC Patients

Event-Related Potentials

As illustrated in Figure 6 (top row), on average a response to audio-tactile stimuli was discernable in DOC/CMD patients during t1 when auditory stimuli were presented near (averaged across the epoch; M = 0.97 μV, t-test to zero, t = 2.21, p = 0.035) but not far (M = 0.14 μV, t-test to zero, t = 0.29, p = 0.77). An evoked audio-tactile response was evidenced both when auditory stimuli were presented near (M = 1.13 μV, t-test to zero, t = 3.49, p = 0.001) and far (M = 1.24 μV, t-test to zero, t = 2.50, p = 0.017) during t2. The PPS effect described in Experiment 1 ([(Anear + T) - ATnear] - [(Afar + T) - ATfar], interaction between pair vs. sum as a function of distance) was significant in DOC/CMD patients during t1 (p = 0.048; analogous to Figure 6, second row, left panel, red being different from zero) but not t2 (p = 0.92; Figure 6, second row, right panel, black). Interestingly, direct comparison of the PPS effect in DOC/CMD patients and healthy participants (Experiment 1) was not significant during t1 (t = 0.06, p = 0.94), nor t2 (t = 0.54, p = 0.58). Thus, while evoked responses were variable, overall DOC/CMD patients seemingly demonstrated differential processing for multisensory stimuli presented near vs. far from their body that was similar to the PPS effect present in TD participants. A majority of the patients sample - patients that would all be categorized as DOC unless specifically tested for motor-command dissociation, as executed here via the MBT (Pignat et al., 2016) - was in fact composed of patients putatively with CMD, and therefore in a last step we examined whether PPS processing was further evidenced in CMD than non-CMD patients. Comparison of the PPS effect between these two latter groups demonstrated a significant effect during t1 (t = 2.13, p = 0.041) but not t2 (t = 1.55, p = 0.13). The differential PPS effect at t1 was driven by the fact that a PPS effect was present in CMD patients (t = 2.23, p = 0.03), but absent in cases when the MBT indicated no CMD (t = 1.06, p = 0.32; Figure 6, bottom row).

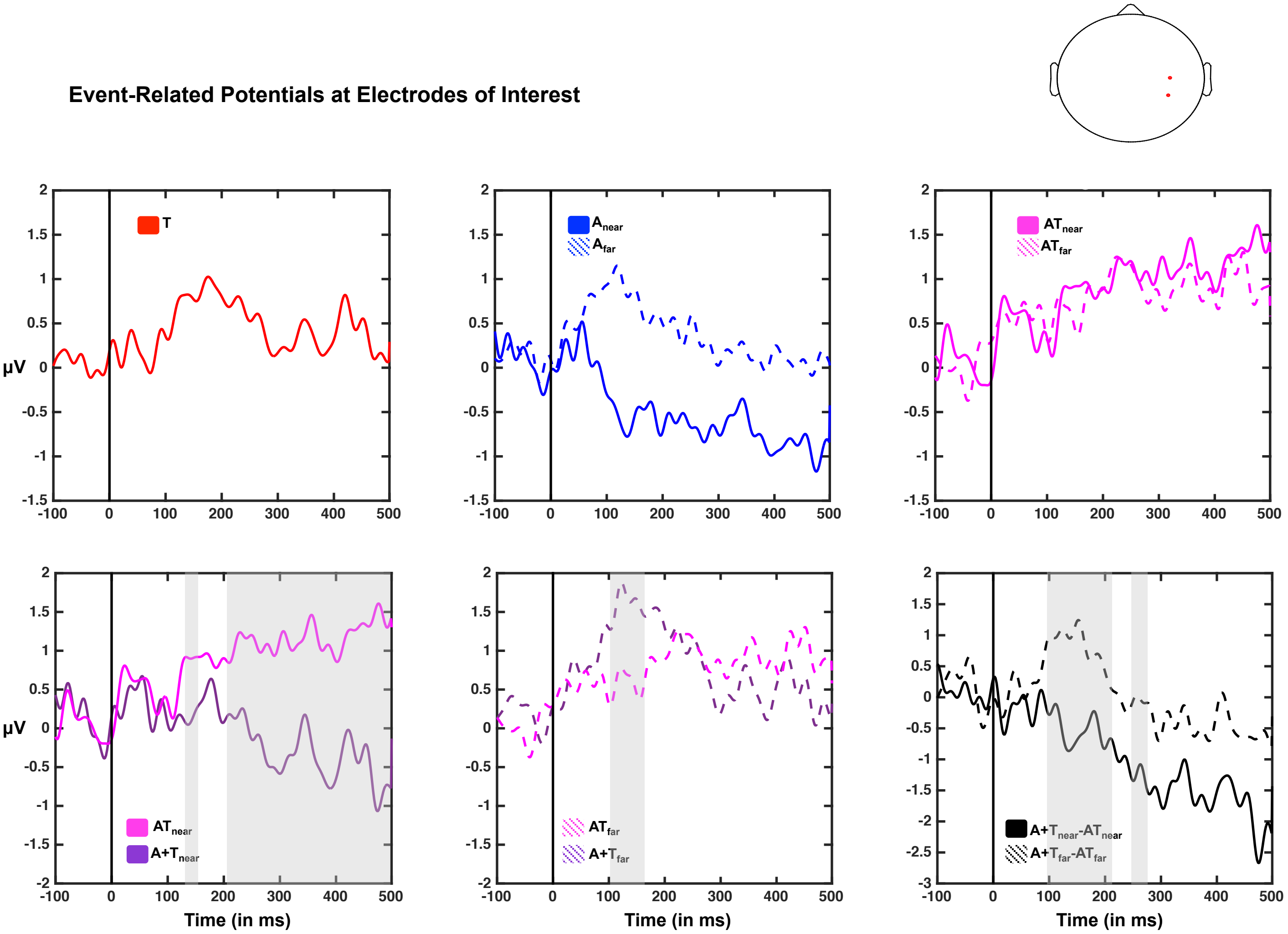


Figure 9.6. Event-Related Potentials in C4/CP4 in DOC patients. This figure is organized as Figure 4. Clear ERPs are difficult to discern in patients – putatively as a number of etiologies are confounded in the averging process. Most strincking difference vis-à-vis the healthy participants is the total absence or inclusively putative reversal in the ERP to the auditory near condition. Nevertheless, bottom right-most shows a difference between near and far multisensory effects (pair vs. sum) that is in the same direction as in healthy participants, and hence this distinction may be quantified and contrasted to levels of consciousness (measured either via Lempel-Ziv complexity of clinical questionnaire).

Neural Complexity

On average the normalized neural complexity associated with evoked responses in DOC/CMD patients was 0.27 (S.E.M. = 0.009). This value did not significantly change as a function of the nature of sensory stimulation, as suggested by the lack of a significant one-way ANOVA ($p = 0.98$). On the other hand, and as expected given prior work (e.g., Casali et al., 2013), a 2 (groups; patients vs. healthy participants) x 5 (sensory stimulation) mixed-model ANOVA did demonstrate a main effect of group ($p = 0.043$). The other variables were non-significant (all $p > 0.21$). Lastly, as illustrated in Figure 7A (every dot is an EEG session color coded, hot colors = highest LZc averaged across all sensory stimulation conditions, cold colors = lowest LZc averaged across all sensory stimulation conditions) it must be highlighted that while the majority of DOC patients had LZc values below the healthy participants, some patients had values that were comparable with or inclusively above the mean neural complexity of healthy participants, suggesting a wide range of consciousness-level impairment. This large variability is to be expected given the heterogeneity in DOC patients within the current study (in fact a majority putatively being CMD as opposed to true DOC, see *Participants* section), and is explored in the next section, where consciousness impairment (as diagnosed via clinicians or neural complexity) is correlated with PPS processing. On average, LZ complexity did not differ between CMD and non-CMD patients ($t = 0.61$, $p = 0.54$).

Relation between PPS and objective and subjective measures of consciousness.

The central question of the current study is to determine whether individuals at different stages within the DOC spectrum (and inclusively putatively misdiagnosed as

DOC instead of CMD) may differentially exhibit neural correlates of PPS. Thus, patients within a wide spectrum of DOCs were recruited and a correlational analysis is employed here. Interestingly, the correlation between the PPS effect (e.g., $[\text{sum-pair}]_{\text{near}}$ - $[\text{sum-pair}]_{\text{far}}$, and hence further negative values indicating further PPS encoding) at time-period t1 (191-238ms post-stimuli onset, time-period demonstrating multisensory supra-additivity, as indicated via GFP analysis and specifically when audio and tactile stimuli are presented in proximity) and normalized LZ complexity was significant and negative ($r = -0.42$, $p = 0.01$, Figure 7B). That is, seemingly, the greater neural complexity data a patient exhibited, the more this patient differentiated between uni- and multi-sensory presentations as a function of distance. This relationship did not hold for the later time-period of interest as determined via Experiment 1, but did suggest a trend (t2, $r = -0.22$, $p = 0.24$, Figure 7C). Interestingly, when performing these correlations again while dividing between CMD and non-CMD patients, results suggest that LZ complexity and the PPS effect correlate at t1 ($r = -0.44$, $p = 0.04$) and not t2 ($r = -0.15$, $p = 0.50$) for non-CMD patients (as above). However, for CMD patients we don’t observe a significant relation at t1 ($r = -0.45$, $p = 0.21$, likely due to the relatively small sample; R-value is of similar magnitude as for DOC/CMD patients reported above) but we do at t2 ($r = -0.76$, $p = 0.01$). That is, putatively the lack of correlation at t2 on the overall patient group (DOC+CMD) is due to conflicting relationship for CMD and non-CMD patients.

Remarkably, there was a strong trend for a correlation between the CRS-R scores (clinical measure of consciousness) and neural complexity (electrophysiological quantitative measure of consciousness; $r = 0.30$, $p = 0.10$, Figure 7D). However, there was no relationship between CRS-R scores and the PPS measure (t1, $r = -0.09$, $p = 0.61$; t2 = - 0.14, $p = 0.45$, Figures 7E and 7F, respectively). The correlations between the CRS-R and LZ complexity, as well as between the former and the magnitude of the

PPS effect did not change when CMD and non-CMD patients were analyzed separately (all $p>0.07$).

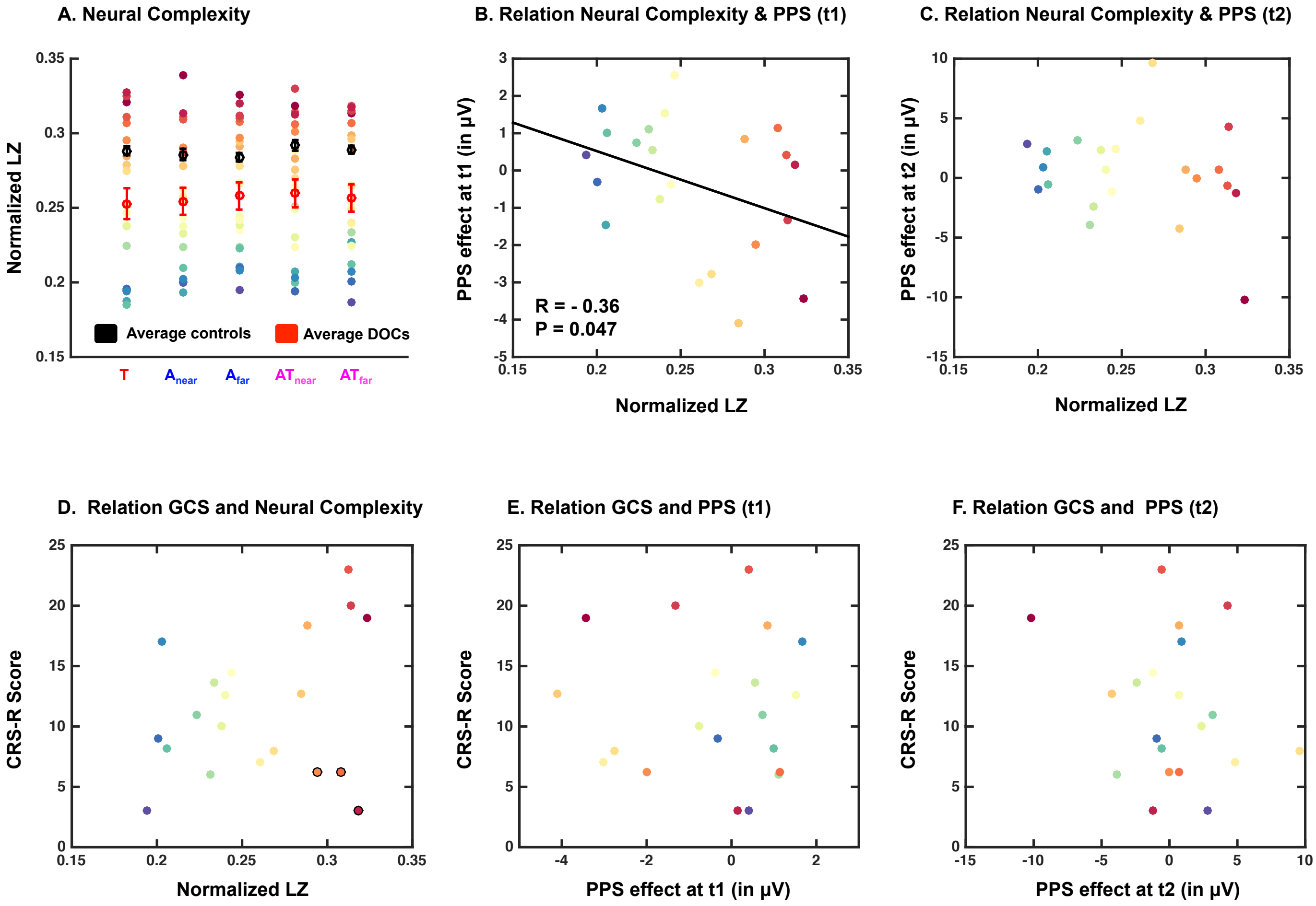


Figure 9. 7. Contrast of PPS effect measured in DOC patients with Lempel-Ziv (LZ) complexity and clinical assessments. A; Top left-most panel shows the average normalized LZ computed in healthy control participants (Experiment 1; black) and in DOC patients (Experiment 2; red) as a function of sensory stimulation (Tactile = red; audio near = first blue; audio far = second blue; audio-tactile near = first purple; audio-tactile far = second purple). Further, individuals subject data (color coded from most to least complex averaged across sensory stimulation conditions) is shown for patients,

which surprinsingly show that while on average patients show less LZ complexity, there are a few participants with higher than average LZ complexity. **B;** Significant correlation (r = -0.36, p =0.047) between the PPS effect (average voltage at C4/CP4 for [(A+Tnear) – ATnear]- (A+Tfar) – ATfar]; negative values indicating a PPS effect) and normalized LZ at time-period t1. **C;** Same as **B,** for time-period t2; this time period not showing a significant correlation. **D;** Correlation between the (full) clincal assessment of consciousness – Glasgow Coma Scale (GCS) – and normalized LZ complexity, a neurophysiological measure of consciousness. These measures are not significantly correlated, demonstrating a discrepancy between bedside assessments reliant on behavioral output and neurophysiological measurements. Interestingly, however, a strong positive correlation exists (r = 0.68, p = 0.003) if three patients (dots outlined in black; putative misdiagnosis) that were clinically not considered to be responsive, but neurophysiologically are deemed to demonstrate a high level of neural complexity, are removed. **E** and **F**; There was no correlation between the PPS measure and behavioral assesments of consciousness.

Discussion

Neuroimaging techniques have demonstrated that current state-of-the-art clinical assessments of consciousness may misdiagnosis patients, in large measure due to cognitive-motor dissociations (Owen et al., 2006; Monti et al., 2010). In turn, in the last decade panoply of neural predictors of preserved consciousness have been proposed (Faugeras et al., 2012; King et al., 2013; Tzovara et al., 2015; see Giacino et al., 2014, and Laureys & Schiff, 2012, for reviews). In contrast to these previous reports, here we propose to use a multisensory (vs. unisensory) stimulation paradigm tapping into a primordial and very specific sensorimotor network, i.e., PPS, in order to assess consciousness-level (see Graziano & Cooke, 2006, for a review of the role of PPS in defense behavior). The PPS is a multisensory-motor space mediating self-environment interaction (Serino et al., 2017). Thus, evidence for a representation of this space in DOC/CMD patients would be evidence for engagement of sensorimotor systems (which further can be molded by intentionality) and putatively for a primitive form of self-awareness (see below; Blanke, 2012; Blanke et al., 2015). Overall, results demonstrate that PPS processing is generally impaired, yet widely varying, in patients within the DOC spectrum (as assessed via the CRS-R). Importantly, the multisensory representation of this space is seemingly graded with level of consciousness, as indexed via EEG complexity, and remains present in patients with CMDs (vs. non-CMDs).

In a first step we established the “normative model” of PPS representation by assessing the EEG correlates of audio-tactile integration for near vs. far stimuli in healthy subjects. Firstly, Global Field Power (GFP) was computed, as it is a well established and reference-free (Murray et al., 2008) measure of neural strength that additionally serves as a data-reduction tool. This measure indicated that reliable evoked responses were obtained during tactile, auditory, and audio-tactile presentation. Further, GFPs for summed conditions (i.e., auditory + tactile) were constructed and compared to the multisensory condition in order to determine time-periods where evidence for a multisensory non-linearity existed (see Noel et al., 2018; Bernasconi et al., 2018; for a similar approach). This analysis revealed the presence of a supra-additivity effect 191 to 238 ms post-stimuli onset, solely when auditory and tactile stimulation were presented in close spatial proximity; namely, a PPS effect. A further dissociation between near and far spaces occurred between 332 and 384 ms post-stimuli onset. However, in this second case both conditions demonstrated a sub-additivity with regard the linear unisensory summation model. Electrodes driving the GFP multisensory space-specific difference were located in centro-parietal areas. Although it is not possible to make strong claims about the localization of the effects, the location of these electrodes are fully compatible with brain regions where PPS processing has been localized by neuroimaging studies on humans (see Grivaz et al., 2017 for a meta-analysis). Lastly with regard to full-montage analyses, not only did the strength of neural generators differ, but also their spatial configuration (after normalizing strength). Interestingly, while the near audio-tactile condition was fully dissociable from other comparable conditions (i.e., audio-tactile far, audio + tactile near, audio + tactile far) by its topography at a relatively early latency (~150 ms), at latter latencies (~350 ms) it was the paired (audio-tactile, regardless of distance) vs. summed (audio + tactile, regardless of distance) distinction that emerged. In sum, strength and spatial configuration of evoked EEG activity at early latencies differentiated the peri-personal and extra-personal space. These findings mimic prior evidence for EEG-based supra-additive effects (e.g., Sperdin et al., 2010; although arguably these are the minority vis-à-vis sub-additive effects) and are well in line with the spatial principle of multisensory integration (Murray & Wallace, 2012). Most importantly, these results demonstrate a PPS effect with a similar latency to the sole other electrophysiological study recording neural response to audio-tactile stimulation within vs. outside the PPS (with intracranial recording; Bernasconi et al., 2018)

Due to clinical constraints, the recordings from DOC/CMD patients were not conducted will full-montages, but with a reduced setup counting with 16 fronto-parietal electrodes. Thus, in order to allow for direct comparison between the healthy participants and DOC/CMD patients, in a further step we restricted an analogous analysis to the above-described GFP analysis to electrodes C4 and CP4 in healthy participants. These electrodes were chosen due to the fact that they demonstrated significant electrode-wise modulations as a function of distance and sensory stimulation across both time-periods (191-238ms and 332-384ms) and the fact that these electrodes were present in the clinical montage used in DOC/CMD patients. This ERP analysis revealed a nearly identical pattern to the GFP analysis, while further revealing a clear latency shift for the paired vs. summed condition exclusively in the near condition. This latency shift resulted in supra-additivity for the near multisensory condition in the mentioned electrodes around 200 ms post-stimuli onset.

Having restricted our analysis in time (191-238ms and 332-384ms post-stimuli onset) and space (C4/CP4) based on the experiment with healthy participants, we explored evoked-potentials in DOC patients (as classified via CRS-R) during the presentation of tactile, auditory, and audio-tactile stimulation in peri- and extra-personal space. Group averaged responses were modest and arguably far from typical, which is to be expected in relatively elder participants and when averaging across patients with different diagnoses and even different etiologies within a diagnostic category. Importantly, nonetheless, the DOC/CMD group-averaged analysis did indicate a multisensory effect (sum condition different from pair) that was space-dependent. Interestingly, this PPS effect in patients was present in the first time-period analyzed (where it was no different from the effect present in healthy controls), but was absent at the later latency. Further bifurcation of the patient group into CMD and non-CMD patients revealed that the PPS effect present in DOC patients was specifically driven by CMD patients (vs. non-CMD). Indeed, direct comparison between CMD and non-CMD patients revealed that a space dependent modulation of audio-tactile processing was present in the former but not the latter group.

Given that PPS processing was seemingly present in DOC patients to varying degrees, we attempted to relate the multisensory processing of objects in near and far space (i.e., PPS) to both clinical assessment and quantitative electrophysiological (i.e., neural complexity) measures of consciousness. Interestingly, the PPS measure correlated with the neural complexity measure, which has been shown to successfully differentiate comatose, VS/UWS, MCS, and healthy participants (Casali et al., 2013; Schartner et al., 2015) as well as between asleep and awake participants (Andrillon et al., 2016). Similarly this latter measure showed a strong trend in relating to the CRS-R, the clinical evaluation of consciousness-level. However, the PPS measure did not correlate with clinical assessments. We consider this a strength of the current study and not a limitation, as misdiagnoses (or at least the limited prognostic value of clinical assessments) in allegedly DOC patients are well documented (Andrews et al., 1996; van Erp et al., 2015). That is, it was precisely our objective here to characterize PPS across a wide spectrum of DOC diagnoses and supplement clinical evaluations with a neuroimaging-based evaluation for the potential for human-environment interactions and self-awareness. If clinical evaluations and EEG-derived indexing of PPS would demonstrate a perfect correlation, there would be no added value from the latter to the former.

A last aspect that merits discussion regards the utility in evaluating PPS in DOC patients if this delineation co-varies with neural complexity - a measure considered a “quantitative” index of consciousness. The first utility in delineating PPS in these patients is that the PPS effect, but not LZ complexity or the CRS-R can dissociate between CMD and non-CMD patients. Secondly, while neural complexity has been shown to successfully differentiate across distinct levels of consciousness (Casali et al., 2013), this metric has more of an engineering than a scientific flavor. That is, while the neural complexity measure can be argued to be derived from the Information Integration Theory (IIT; Tononi, 2012; Tononi & Koch, 2015; Tononi et al., 2016) of consciousness, the direct link between the IIT, it's "consciousness-meter" phi (Mayner et al., 2017; Oizumi et al., 2014), perturbation complexity index (PCI; Casali et al., 2013), and Lempel-Ziv complexity (Schartner et al., 2015) is far from obvious (see Ibañez-Molina et al., 2018). On the other hand, the delineation of PPS counts with a well-established scientific history; the PPS is known to be encoded by multisensory neurons with depth restricted receptive fields (Duhamel et al., 1998; Graziano et al., 1999, 2000) and to remap as a function of human-environment interactions (Serino et al., 2017; Noel et al., 2015, 2018). Further, the PPS is taken to reflect self-location (Noel et al., 2015; Salomon et al., 2017) and has been directly linked to body ownership (Blanke et al., 2015; Noel et al., 2018), two key components of bodily self-consciousness, i.e., the feeling of experiencing the external world from a specific location coinciding with a body that is felt as one' own (Blanke and Metzinger, 2007; Blanke, 2012). Indeed, it has been proposed that the multisensory integration of body-related information within the PPS is at the basis of a primitive self-awareness (Blanke, 2012; Blanke et al., 2015; Noel et al., 2018). Thus, by demonstrating a PPS representation that is graded with the level of consciousness (as shown here), it may be suggested that at least a portion of these patients retain a minimal form of self-awareness; that linked to one's own body. This focus on a minimal and bodily-ground selfhood differentiates the current attempt to map PPS in DOC patients from classic approaches to the topic consciousness, such as the IIT and the derived neural complexity measure, which focus on awareness of external events without specific reference to the self.

In conclusion, we develop a neuroimaging-based PPS metric in healthy individuals and demonstrate that applied to DOC patients this meter scales with consciousness-level as determined via an EEG-based quantitative measure of consciousness but not clinical assessments of consciousness. Further, CMD patients (but not non-CMD) evidenced PPS processing. Hence, the findings indicate that certain DOC patients are capable of multisensory integration, which is itself modulated by the spatial proximity of the unisensory components (Noel et al., 2015). Arguably, this finding supports the fact that certain DOC patients (i.e., CMD patients) are capable of recruiting a neural system that is adjacent to the motor system and putatively inclusively capable of a minimal form of self-awareness (Blanke, 2012; Blanke et al., 2015). Clinically, these results highlight the importance of providing neurorehabilitation opportunities to acute patients deemed as within the DOC spectrum according to the CRS-R, as these patients may solely need training in motor and language functions to regain full capacities, as opposed to regaining consciousness.

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CHAPTER X

GENERAL DISCUSSION

Summary of Results and Their Relation

Succinctly, the aim of the current dissertation was to leverage multisensory neurons, circuits, brains, and bodies in studying perceptual awareness. The motivation behind this goal was twofold; the fact that our phenomenological experience is multisensory, and the fact that an array of contemporary theories of consciousness posit integration as a central tenet in their model.

In a first step we simply probe Crick & Koch's (1990) assumption that all forms of consciousness follow similar organizational principles. Indeed, if insights derived from the study of visual awareness can generalize across modalities, and from unisensory to multisensory contexts, not only would this obviate the need for separate "consciousness sciences" (e.g., visual awareness, auditory awareness, audiovisual awareness), but more importantly it would also lend support for our current understandings of consciousness as a general model encompassing all sensory systems. Thus, in a first experimental chapter (Chapter III) we examined whether the neural correlates for report of detection were equivalent in visual, auditory, and audiovisual modalities. We presented participants with stimuli at detection threshold in the different modalities and index the neural correlates of detection/report for these different sensory signals. As hypothesized by Dehaene's GNW theory (Dehaene & Changeux, 2011; Dehaene et al., 2018), results suggest that the presence of sustained and relatively late evoked potentials is associated with perceptual awareness. This observation was true regardless of sensory modality. On the other hand, more detailed EEG metrics indexing trial-to-trial variability in response and signal complexity as a function of perceptual state (McIntosh et al., 2008; Schurger et al., 2010, 2015; Casali et al., 2013) only generalized across unisensory modalities (vision and auditory), but not across the unisensory – multisensory divide (i.e. A = V ≠ AV). Further, when unisensory signals were added to create an artificial "summed" condition, this response differed in global field power from the true multisensory condition (i.e., "paired" condition) when participants reported the stimuli, but not when they were unaware of it. Thus, two main conclusions may be drawn from this experiment. First, in line with Baars' postulate (Baars, 1988, 2002), unconscious multisensory integration was not observed, at least insofar as indexed by global field power and when contrasting paired vs. summed responses. Secondly, the neural correlates of detection/report generalized across the unisensory modalities, but not to the multisensory context. Indeed, only the presence of late evoked responses was similar across multisensory conditions (not signal reproducibility or complexity), and this metric has been suggested to be most closely associated with overt responses as opposed to awareness (see Tsuchiya et al., 2015 and discussion below). Taken together, the results question Crick & Koch's (1990) assumption that insights from visual awareness may be extrapolated to other sensory and multisensory systems.

Given these results, in Chapter IV we took the opposite approach, and set out to test whether the study of multisensory processing could inform existing theories of consciousness. Additionally, we aimed to further investigate whether multisensory integration is possible under unconscious conditions. An open question within the science of consciousness – and one that seemingly could be informed by the study of multisensory integration – is whether perceptual awareness is “all-or-none” or graded (see e.g., Cleeremans & Jimenez, 2002). The GNW theory (Dehaene & Changeux, 2011), for example, clearly stipulates that at the neural level there is a step-like state transition between unconsciousness and consciousness, while integrated information theory (IIT; Tononi et al., 2016), proposes that all systems may potentially possess a modicum of consciousness, given that they are imbued with the capacity for integrating information. In other words, GNW sides with the idea of consciousness being “all-or-one” (including behaviorally, Cleeremans & Jimenez, 2002), while IIT conceives of consciousness as being graded. Traditionally, a difficulty in addressing this question empirically has been in allowing for partial awareness conditions. However, this becomes tractable within a multisensory context, where audiovisual presentations can be perceived as audiovisual (full consciousness), not perceived (no consciousness), or either solely as auditory or visual (partial consciousness). Thus, in the experiments detailed in Chapter IV we have participants perform a speeded response to tactile stimuli, which are preceded by either valid or invalid cues in auditory, visual, or audiovisual modalities (i.e., cue congruency task). The cues are presented at detection threshold, and in addition to the speeded reaction to touch, participants report their subjective experience of the cue. Each participant takes part in 10 one hour-long sessions, in order to collect a sufficiently large sample of partially aware trials. Overall, behavioral analyses of cue-congruency effects demonstrate a graded relation between perceptual awareness and multisensory performance, seemingly supporting the IIT. In a series of follow-up experiments we modify the relative temporal and spatial position of the auditory and visual cues in order to test the principles of multisensory integration (i.e., multisensory performance, if based on integration, should be better at close spatio-temporal proximities between the cues). Here, no discernable pattern is observed, indicating that while multisensory performance co-varies with perceptual awareness, there was no clear evidence for unconscious multisensory *integration* at the behavioral level. Interestingly, when this congruency task is mimicked via neural networks that are *in principle* and according to the GNW theory capable of either audiovisual, auditory, visual, or no consciousness – given non-linear input-output functions at each sensory node and the pattern of feedback connectivity – results also suggest a graded relation between multisensory performance and perceptual awareness. That is, seemingly a neural network in line with “all-or-none” consciousness can elicit a graded relation between perceptual awareness and performance, thus partially reconciling the IIT and GNW.

Taken together, whereas Chapter III suggests that insights pertaining to perceptual awareness derived from visual neurosciences may not be directly applied to the multisensory case, Chapter IV demonstrates how utilizing multisensory paradigms can inform existent consciousness theories – in particular allowing for partially aware conditions. Furthermore, results did not demonstrate unconscious multisensory integration at either the behavioral (Chapter IV) or neural ensemble levels (i.e., EEG; Chapter III). Nonetheless, it is well established that multisensory integration can occur unconsciously at the level of single unit responses. In fact, the early studies defining the process of multisensory integration and delineating its principles were all executed under an anesthetized preparation (see Wallace et al., 1996, 1997, 2006 for examples). Thus, in the last experimental chapter of the first part of the dissertation (see below) we aimed to further test the two frontrunner theories of consciousness (Dehaene’s GNW and Tononi’s IIT), while directly indexing multisensory integration at the single-unit level.

Briefly, the GNW theory (Dehaene & Changeux, 2011) states that conscious percepts are associated with long and sustained periods of activity and is indexed by the process of neural ignition; a non-linear relationship between neural firing and the transition from unconsciousness to consciousness. Namely, when a stimulus is consciously perceived, it recruits a widely distributed neural network (particularly fronto-parietal lobes). The IIT (Tononi & Koch, 2015; Tononi et al., 2016) on the other hand is more concerned with the architecture of a neural network than with the dynamics happening within it. In this theory, consciousness-level (e.g., awake, anesthetized, asleep) is related to the degree of integrated information the network supports. Both these theories have received substantial empirical support (see Casali et al., 2013; Gaillard et al., 2009; Joglekar et al., 2018, for examples), although in particular for the IIT, this support is by and large indirect and almost absent in neurophysiology (the GNW theory does come with neurophysiology support; van Vugt et al., 2018). The total absence empirical single-unit electrophysiology evidence for IIT is due to the large computational overhead of this model, making any direct test of the IIT in biological systems impossible. To circumvent this limitation, in Chapter V we derive a number of neurophysiological predictions directly inspired in the GNW theory (Dehaene & Changeux, 2011) and the IIT (Tononi et al., 2016). The GNW theory predictions are that consciousness should be associated with sustained periods of neural activity (much as in Chapter III) and conscious percepts should evoke neural ignition (i.e., the co-activation of sensory and higher-order areas) more readily than unconscious percepts. The IIT predictions – which we formalized in a model suggesting that a neural network converging on an integrative neuron should bear a larger degree of integrated information than a network structured around a neuron that simply converges information – are that as consciousness is lost it is the neurons that integrate information (as opposed to converge information) that should be most readily impacted. Conversely, in this theory, when an animal is conscious, it is the neurons that integrate that should most readily demonstrate features of consciousness. To test these predictions we analyzed a dataset comprised of simultaneous single unit recordings in primary somatosensory cortex and ventral pre-motor as monkeys are presented with auditory, tactile, and audio-tactile stimuli and as they are progressively rendered unconscious via the administration of propofol (see Ishizawa et al., 2016). Results generally supported the GNW theory by suggesting that neural responses to auditory, tactile, and audio-tactile stimulation are further sustained when animals are conscious vs. unconscious (the IIT makes no straight-forward prediction vis-à-vis the time-course of single-unit activity as a function of consciousness). Further, the findings also indicate a higher probability of observing neural ignition (in this case operationalized as the co-activation of S1 and vPM on a single trial) under conscious than unconscious conditions. On the other hand, results do not support the IIT. In fact, we observed that when animals were rendered unconscious, it was the convergent neurons (i.e., those that responded indiscriminately to auditory and tactile stimuli) and not the integrative ones (i.e., those that were further driven by multisensory than unisensory presentations) that were most readily impacted. Namely, convergent neurons stop converging information more frequently than integrative neurons stop integrating when animals are rendered unconscious. Further, neurons demonstrating multisensory enhancement exhibited this property of retaining their category under behaviorally-defined unconsciousness to a greater extent than neurons demonstrating multisensory depression. Thus, the more a neuron demonstrated multisensory gain, the less impacted it was by the loss of consciousness. Similarly, we tested whether integrative or convergent neurons most readily demonstrated properties of consciousness when animals were aware, and of unconsciousness when the animal was unconscious. Analyses of the population of neurons as a whole showed that when a monkey is rendered unconscious, the complexity and the average degree of noise correlation increases (see Ecker et al., 2014, for a similar observation). These properties – increased complexity and noise correlation – were more readily observed in convergent than integrative neurons when animals were rendered unconscious, suggesting that the former better tracked the level of consciousness of the animal.

Overall, thus, in this third experimental chapter we suggest that the GNW theory (Dehaene & Changeux, 2011) but not the IIT (Tononi et al., 2016) is supported in neurophysiological recordings. More importantly for the current purposes, we illustrate how the process of multisensory integration, and the fact that by presenting multisensory stimuli we can categorize neurons as being either convergent or integrative, we can inform theories of consciousness. However, it is true that the IIT does not make direct predictions about the process of multisensory integration and its relation to perceptual awareness (the GNW theory does; Baars, 2002). Further, it is possible that the predictions we derived from the mathematics surrounding the IIT were a more difficult bar to clear than those predictions derived form the GNW. Similarly, we acknowledge that the predictions we generated from the IIT were put forward given computational results that were based on an unrealistically simple neural network (e.g., condensing the brain to 3 nodes).

More broadly, it can be argued that both theories examined share a strong philosophical approach to the science of consciousness. Namely, they are theories taking an "outside-in" approach to the science of consciousness (see Chapter I), in that they conceive that sensory stimuli are first filtered through the sensory periphery and then re-assembled up the (non-linear and reentrant) central nervous systems' hierarchy. In the second part of the dissertation, therefore, we examine the "minimal phenomenal selfhood" (Blanke & Metzinger, 2009) approach to consciousness, with a particular emphasis on peri-personal space (PPS; Rizzolatti et al., 1997; di Pellegrino et al., 1997) encoding. This approach is very different from the GNW theory (Dehaene & Changeux, 2011) and IIT (Tononi et al., 2016) in that it takes an "inside-out" lens; it argues that a central question in consciousness studies is self-consciousness, as without a self there is no entity to be the subject of experience (Legrand, 2006; Legrand et al., 2007). That is, the subjective experience of objects or events happening in the external environment may be as much imposed onto the world given bodily signals (Blanke, 2012), the sense of agency (Synofzik et al., 2008; Friston, 2012), affordances (Gibson, 1978; Proffitt, 2006; Witt & Proffitt, 2007), and priors generally (Seth, 2013; Friston, 2018), as it is driven by exteroceptive sensory signals perturbing the sensory periphery. Furthermore, this approach has converged on strongly considering the process of multisensory integration as key in scaffolding a minimal sense of body ownership and self-location (see Blanke et al., 2015). Thus, by probing multisensory hypotheses relating to the minimal selfhood approach to consciousness, we may not only inform the mentioned model, but also illustrate how examining the process of multisensory integration can inform consciousness approaches generally (across the “outside-in”/”inside-out” spectrum).

Heavily based on the observation that during the rubber-hand illusion (RHI; Botvinick & Cohen, 1998) PPS neurons recalibrate as to encode the position of the illusory hand and not the real hand (Graziano et al., 2000), Blanke (2012) hypothesized that bodily self-consciousness is rooted in the process of multisensory integration within the PPS and that during the full-body illusion (FBI; Lenggenhager et al., 2007) the PPS may encode the position of the self, as opposed to that of the body. That is, the sense of self-location can be dissociated from the physical location of the body during illusions such as the FBI (Lenggenhager et al., 2007; Blanke & Metzinger, 2009), and the hypothesis is that PPS surrounds the self-location, not the body (Blanke, 2012; Blanke et al., 2015). It is well established that PPS neurons are bimodal, in that they respond to tactile stimulation on the body, as well as to visual or auditory stimuli near but not far from the body. However, there is no direct evidence for the fact that these neurons are truly *integrative* - the closest evidence is from Avillac et al., 2007, whom demonstrate multisensory integration in VIP, an area known to house PPS neurons, but there is no evidence that these researchers were recording from PPS neurons. Thus, before examining the interplay between PPS and bodily self-consciousness (self-location, more specifically) in Chapter VI, we first attempted to establish whether neural signals associated with PPS are truly examples of multisensory *integration* as opposed to convergence or interaction. We recorded ECOG from epileptic patients while presenting auditory stimuli both near and far from patients, as well administrating tactile stimulation on the body. These signals were analyzed within the classic multisensory framework (Stein & Meredith, 1993) searching for supra- or sub-additive responses as examples of multisensory integration. Interestingly, results suggested that in fact most PPS sensors – those that were modulated by the proximity of multisensory sensory signals – integrated information from different senses.

Having suggested that PPS responses were (at least partially) integrative, in Chapter VII we directly tested Blanke's (2012) conjecture; that PPS encodes the position of the self and not the body. Participants viewed themselves from the back in virtual reality as if placed two meters in front of themselves, and viewed tactile stimulation on the virtual avatar that was either in synchrony or not with a true touch on their own back. During the synchronous condition, but not the control asynchronous one, participants reported feeling ownership over the virtual body and a sense of drifting toward it. In addition to self-reported phenomenology, we measured trunk-centered PPS in participants by asking them to perform speeded responses to tactile stimulation applied on their chest. Concurrently, to the tactile stimulation, a "task-irrelevant" sound either approached or receded from the participants. Results suggested that near sounds facilitated tactile reaction times, while far sounds did not. Further, this multisensory facilitation had a sigmoidal profile – reaction times did not decrease linearly with distance, but categorically. Thus, the pattern of reaction times suggested a true boundary between the peri-personal and extra-personal space (see Galli et al., 2015, Pfeiffer et al., 2018, for other experiments employing this techniques to measure PPS). Most strikingly, under synchronous visuo-tactile stroking the central point of the sigmoidal function characterizing space-dependent audio-tactile detection facilitation translated forward in space, both when measuring the front and back space. That is, under the FBI condition trunk-centered PPS translated in space as to encode the virtual avatar, the self-space, and not the true location of the body.

In Chapter VIII, in a series of experiments we replicated and extended the findings from Chapter VII. Importantly, the philosophical argument scaffolding the study of the minimal self is that a "pre-reflective" self must exist in order for there to be a subject of experience (Legrand, 2006). This proto-self, it is taken, is scaffolded on the process of multisensory integration (Blanke, 2012). However, there was no evidence supporting the fact that unconscious (i.e., "pre-reflective") multisensory interactions could shape bodily self-consciousness. Thus, in Chapter VIII we first demonstrated via reaction times and detection rates that a PPS could be delineated even when the approaching exteroceptive stimuli is not perceived (see Farne & Ladavas, 2000; Ladavas & Serino, 2008, for early neuropsychological evaluation of PPS employing detection rates as opposed to reaction times as their main dependent variable). Next we employed a master-slave robotic device to induce the FBI while masking via CFS the location of touch on the virtual avatar. In other words, participants were not aware of the visuo-tactile synchrony condition. Nonetheless, under these conditions participant's bodily self-consciousness was still altered in that they more often reported ownership over the virtual avatar in the synchronous than asynchronous condition (even when the subjective experience of tactile stroking was identical). Lastly, replicating and extending Chapter VII, when we induced the FBI and mapped PPS unconsciously, this latter representation translated forward in space as to encode the location of the virtual avatar and not the physical location of their own body. In summary, results indicate that unconscious multisensory interactions can alter (overt) bodily self-consciousness, hence supporting the argument that unconscious multisensory processes may scaffold a minimal form of selfhood (self-location in this case).

In the last experimental chapter of the dissertation (Chapter IX) we aimed at translating the observation that PPS may be a component scaffolding a proto-self into the clinical domain. Further, this last experimental chapter aimed at utilizing the electrophysiological index of PPS developed in Chapter VI in a translational setting. In addition to supporting a minimal sense of selfhood, researchers have demonstrated that PPS remaps during action, and even prior to executing an action (Brozzoli et al., 2009, 2010). As such, we could perhaps leverage the mapping of PPS to index a minimal form of self-awareness, as well as an intent to move, in patients diagnosed with disorders of consciousness (DOC). These aspects, self-awareness and the demonstration of intentionality are two central components of consciousness, and in turn demonstrating a PPS encoding in DOC patients could potentially be informative from a diagnosis perspective. Indeed, the prevalence of misdiagnoses in disorders of consciousness is high (van Erp et al., 2015; usually underestimating consciousness-level) in great part due to cognitive-motor dissociations (Schiff, 2015) where participants could in principle understand commands but can not show intentionality as assessed in clinical evaluation; via motor output. In building toward demonstrating intentionality in patients with disorders of consciousness and as assessed via multisensory interactions, in this chapter we first establish the EEG correlates of PPS in healthy subjects (as opposed to ECOG correlates in epileptic patients in Chapter VI), and then question whether this marker of PPS is present in patients with disorders of consciousness, as well as in patients with command-motor dissociation (CMD; Pignat et al., 2016). In line with findings from Chapter VI, results in healthy participants demonstrated a time-period (~

200 post-stimuli onset) where the response evoked from paired audio-tactile stimuli was different from that evoked by the artificially summed (audio + tactile) condition, and this effect was specific to when audio-tactile stimuli were presented near and not far from one another. This differential response was driven in part by centro-parietal electrodes, and thus these electrodes were examined in patients with disorders of consciousness. As expected in a heterogeneous group of patients, many of whom were subject to traumatic brain injuries, the group average evoked potentials were very modest and atypical (Tzovara et al., 2013). However, at a group level results seemed to indicate a PPS encoding in patients with CMD, but not in DOC patients without CMD (i.e., "true" DOC patients). Further, on an individual subject basis there was a correlation between participants audio-tactile PPS effect (difference between paired and summed conditions as a function of distance) and their degree of EEG complexity; this latter measure arguably being an "objective" EEG-derived measure of consciousness level (see e.g., Schartner et al., 2015, 2017, and Chapters III and V). Interestingly, neither the PPS measure nor the signal complexity measure correlated with clinical assessments of consciousness, implying a disconnect between electrophysiologically derived metrics of consciousness and clinical assessments in these patients. In sum, these results suggest a wide range of states of self-awareness in patients with disorders of consciousness and are a promising stepping-stone toward measuring intentionality-related PPS remapping in these patients.

Interpretation and Limitations of Main Results

As a whole the results comprised within this dissertation suggest that insights derived from the study of visual awareness may not be straightforwardly translated to the study of multisensory awareness, and thus questions whether prominent theories of consciousness address visual awareness specifically or perceptual awareness generally. Further, while multisensory integration was evidenced at the single-unit level, there was no unequivocal evidence for unconscious multisensory *integration* as indexed via EEG or behavior. However, unconscious multisensory *interactions* in behavior did occur (also see Papai & Soto-Faraco, 2017; Barutchu et al., 2018 for example), and these shaped bodily self-consciousness.

A detailed discussion regarding each of the results summarized above can be found within their appropriate chapters. In turn, instead of reiterating these passages, in the following I briefly discuss major themes and limitations, ideas and perspectives that are brought forward by the conjunction of multiple chapters, as opposed to chapters in isolation.

Reportability and Consciousness

A major theme from the first experimental chapters is that seemingly findings from visual neuroscience may not be directly translated to a science of multisensory perceptual awareness; the neural correlates of visual and auditory perception do not generalize to the audiovisual condition (Chapter III), and contrarily, when subjective experience is matched (i.e., multisensory presentations leading to unisensory perception), performance may still differ (Chapter IV). The sole exception we observed to this general finding was in the presence of late and sustained EEG components when stimuli were perceived, regardless of modality, and the absence of this P300 (Rutiku et al., 2015) or P3b (Chennu & Bekinschtein, 2012; Koivisto & Revonsuo, 2007) signal when stimuli were not perceived. Fittingly, Chapter V equally demonstrates stronger neural activity (in this case, spikes) when either auditory, tactile, or audio-tactile stimuli are administered to a conscious in contrast to unconscious monkey. Further, an interesting study employing MEG has recently ratified this observation (Sanchez et al., 2017) by presenting participants with stimuli near detection threshold in the auditory, visual, and tactile modalities. In their univariate approach Sanchez and colleagues (2017) indicate that perceived stimuli, regardless of modality, are associated with late and sustained activity, as observed in Chapter III and V, and as suggested by Dehaene and colleagues (Dehaene & Changeux, 2011). Then, the authors go on to perform a multivariate analysis and attempt to decode reports of detection, both within modalities (i.e., train on vision and decode in vision) and across modalities (i.e., train in vision and decode in audition). Findings show that cross-modality decoding of detection reports is possible, and a searchlight analysis suggests that decoding is solely possible along the diagonal – i.e., at similar latencies. Sanchez and colleagues (2017), therefore, conclude that there is a common supramodal signature of conscious perception.

These results, and the similarities and dissimilarities between Sanchez et al., 2017 (MEG study) and Chapter III (EEG study) merit a few comments. First, it must be highlighted that Sanchez et al., 2017 is a cross-modal study, while Chapter III is a multisensory study. That is, the studies are congruent in highlighting similar consciousness markers across unisensory modalities, but only Chapter III questions whether unisensory insights can be extrapolated to multisensory conditions. According to the findings from this chapter, only the presence of a P300 or P3b in conscious but not unconscious conditions is seen in both unisensory to multisensory contexts. Thus, while the Sanchez et al., 2017 observation that the P300 can be generalized across unisensory conditions is seemingly correct, it is less clear whether conscious percepts are largely associated with supramodal signatures beyond the P300; the reproducibility and complexity of conscious signals did not generalize to audiovisual conditions in the results reported in Chapter III. Secondly, given that auditory, visual, and tactile perceived stimuli are all different from their non-perceived counterparts in that they evoked larger and more sustained neural responses, and the fact that cross-modal decoding was solely possible along the diagonal, it is likely that the decoding approach is simply picking up on the response magnitude differences that are apparent in the univariate approach. These observations lead us to the question; within the context of consciousness studies what exactly is the late and sustained activity (P300, P3b) indexing?

A first possibility is that the P300/P3b is indeed indicating a supramodal process. Stimuli that are experienced consciously evoke strong responses in primary sensory areas, subsequently leading to the recruitment of fronto-parietal regions, which ultimately generates recurrent neural dynamics leading to a supramodal representation of the contents of consciousness (Dehaene & Changeux, 2011). A second possibility is that the P300/P3b relates to the demand of reporting the presence of a stimuli; a confound present both in Sanchez et al., 2017 and in Chapter III. Indeed, recent studies employing "no report paradigms" and measuring pupil dilation or optokinetic nystagmus instead (as a proxy for overt report), have suggested that frontal lobe BOLD activity (Frässle et al., 2014), modulations in alpha and beta bands (Pitts et al., 2014), and the presence of a P300 (Pitts et al., 2014) only differentiate between perceived and non-perceived stimuli when participants have to overtly report the stimuli (see Tsuchiya et al., 2015 for a review, and Overgaard & Fazekas, 2016, for a reply to the review). Thus, it may very likely be that the P300/P3b is not a common supramodal signature of conscious perception, but a signature of report. This possibility will have to be further investigated in the future (see next section) and questions whether any of the neural measures of consciousness employed in Chapter III generalized from unisensory to multisensory contexts.

Integration vs. Interaction

A second theme present throughout the dissertation relates to the distinction between multisensory *integration* and multisensory *interactions*. The former relates to sensory information amalgamating in order to give rise to novel information not present in its constituent inputs (e.g., A+V≠AV), while the latter simply refers to the process where distinct pieces of information can impact one another regardless of sensory modality. The distinction is important within the study of perceptual awareness, as some theories of consciousness postulate that perceptual awareness is needed for integration and not interaction (e.g., Baars, 2002; "Consciousness is needed to *integrate* multiple sensory inputs"), or claim that consciousness level is proportional to the amount of information that is *integrated* within the brain (e.g., Tononi et al., 2016; "[…] information that is specified by a system that is irreducible to that specified by its parts"). Others, such as the minimal phenomenal selfhood approach to consciousness routinely claim that multisensory integration within the peri-personal space may scaffold bodily self-consciousness, yet "true" integration is seldomly tested (the vast majority of studies indexing multisensory *interactions* instead). Thus, within the framework of the minimal phenomenal selfhood, it is unclear whether true multisensory integration is needed to scaffold bodily self-consciousness, or whether multisensory interactions are sufficient.

A long tradition holds that if multisensory evoked spiking responses are greater (multisensory enhancement) or smaller (multisensory depression) than the sum or maximal of unisensory responses, then multisensory integration has occurred (Stein & Meredith, 1993; Wallace & Stein, 1997; Wallace et al., 1996, 2006; Stein & Stanford, 2008). In other words, some meaningful transformation seemingly must have occurred at the level of the multisensory neuron. In Chapter V we made use of this single-unit definition to expressly tackle the question of whether integrative neurons were most impacted during the loss of consciousness, as it could be conjectured in light of the IIT (Tononi et al., 2016). This definition has also been utilized to index multisensory integration at larger scales (e.g., M/EEG: Hagan et al., 2009; fMRI: Stevenson & James, 2009; but see Beauchamp, 2005; Stanford & Stein, 2007; Spence, 2013, for critics of applying this metric to measures of neural ensembles). Hence, in Chapters III, VI, and IX we made use of the same definition while employing EEG (Chapter III and IX) and ECOG (Chapter VI). Under these definitions, as expected, in Chapters VI and IX the results suggest multisensory integration in peri-personal space. Similarly, findings indicated a reduction in the number of integrative neurons, and the extent to which these neurons integrated their different inputs, when animals were rendered unconscious (Chapter V). And lastly, in line with Baars' (2002) speculation that multisensory integration is not possible outside awareness, in Chapter III we found no difference between "paired" and "summed" global field responses when participants did not perceive the stimuli being presented.

Importantly, in contrast to the above-mentioned chapters, in Chapter IV, VII, and VIII – the behavioral chapters – it was not multisensory *integration* but *interaction* that was indexed. This distinction between multisensory integration and interaction is particularly important to note for Chapter VIII where results indicate that unconscious multisensory interactions can shape overt bodily self-consciousness. These findings are not in opposition to the rest of the dissertation (e.g., Chapter III) since while there was no convincing evidence for unconscious multisensory *integration* throughout the dissertation, unconscious multisensory *interactions* are commonly present in the literature (e.g., Faivre et al., 2014; Pápai & Soto-Faraco, 2017; Barutchu et al., 2018) and evidenced in multiple projects of the current dissertation (Chapters IV and VIII). Of course, the fact that the behavioral projects encompassed within the dissertation did not index "true" multisensory integration is a limitation that must be acknowledged and explained. The difficulty stems from the fact that behaviorally integration is most clearly evidenced when subjects either report a percept that could only be conveyed by the synthesis of sensory signals (e.g., McGurk effect; McGurk & MacDonald, 1976) or when behavioral performance beats the race-model (i.e., statistical facilitation; Raab, 1962; Miller, 1982, 1986). In other words, the former relies on self-report a subjective experience (which is difficult to do if there is no experience), while the latter relies on comparing cumulative probability distributions of detection reaction times (also difficult to do when stimuli are not perceived). In Chapter IV we did not contrast multisensory reaction times to a statistical facilitation benchmark, as reaction times were to (unisensory) tactile targets, and not the multisensory cues. Similarly, in Chapters VII and VIII multisensory interactions were indexed as the behavioral measure of PPS requires testing at an array of distances which precluded from collecting a sufficiently large number of reaction times per condition in order to build cumulative probability distributions (but see Teramoto et al., 2017 for a study computing race-model violations in order to index peri-personal space). In short, therefore, throughout the dissertation we observe clear evidence for unconscious multisensory *interactions* but not *integration.*

A second (more general) caveat relates to the definition of multisensory *integration*. As stated above, the long held tradition within physiology is to categorize neurons as integrative if there is some sort of non-linear input-output function when administrating stimuli from different modalities (Stein & Meredith, 1993; Wallace & Stein, 1997; Wallace et al., 1996, 2006; Stein & Stanford, 2008). However, it is a matter of debate whether the definitions and principles of multisensory integration derived from the superior colliculus apply to the neocortical mantle (Bizley et al., 2007; Meijer et al., 2017), to large neural ensemble measures (Beauchamp, 2005), and to human behavior (Spence, 2013). In fact, it may be argued that the current gold standard for multisensory integration in cortical processing and behavior is the indexing of optimal cue combination (e.g., Ernst & Banks, 2002; Alais & Burr, 2004). And interestingly, from a neural standpoint due to noise-properties of neurons, this optimal cue combination seemingly may require linear additivity and not supra- or sub-additivity (Ma et al., 2006), much as multiplication becomes addition on a log-scale (although see Orban et al., 2016, for a different approach as to how uncertainty may be represented in the brain). Thus, in the future it may be interesting to probe unconscious multisensory integration while adopting a cue combination definition for integration, as opposed to a supra- and/or sub-additivity one.

While the multisensory field has strong definitions for what it considered to be “integration”, it is also true that a number of definitions exist. Vexingly, the definitions for “integration” are not very precise in most theories of consciousness. In turn, it is difficult to ascertain which definition of “integration”, from a multisensory perspective, should be used in testing particular theories of consciousness. In the future it will be important for these latter theories to more specifically detail what they refer to as “integration”.

Complexity

The quantification of neural “complexity” is becoming an increasingly popular tool to gauge awareness, particularly within clinical settings (see Sara & Pistoia, 2010; Casali et al., 2013; Sarasso et al., 2015; Schartner et al., 2015, 2017; Cavanna et al., 2017), and is a measure used within several of the Chapters of the current dissertation Chapters (III, V, IX). Indeed, researchers have demonstrated that by either first perturbing the brain via transcranial magnetic stimulation (TMS) and then quantifying EEG-evoked complexity via the Lempel-Ziv algorithm (LZ; Lempel & Ziv, 1976) or simply by quantifying LZ complexity on resting state EEG data, one can differentiate between comatose, vegetative state, and minimally conscious patients (Casali et al., 2013;

Schartner et al., 2015). Similarly, this measure can be used to categorize stages of sleep (Andrillon et al., 2016) and has been shown to be elevated in volunteers under the influence of Psilocybin (Schartner et al., 2015). The vast majority of neurobiological signals wherein LZ has been quantified are M/EEG datasets, but interestingly a few studies have also demonstrated that LZ complexity is also higher in the single cell firing patterns of awake vs. asleep or anesthetized rats (Abasolo et al., 2015; Hudetz et al., 2015). To the best of my knowledge, however, Chapter V is the first study quantify LZ complexity as a function of consciousness-level in non-human primate single units, and Chapter III is the first to describe LZ complexity in EEG signals as a function of perceptual awareness (e.g., seen vs. unseen; *conscious content*), as opposed to level of awareness (e.g., asleep vs. awake; *wakefulness*. Although see Boly et al., 2015 for an fMRI study correlating LZ complexity in BOLD responses with complexity of stimuli). As such, there are two main aspects of the complexity data contained within the dissertation that merit discussion; 1) LZ complexity as a function of consciousness level and along levels of description, and 2) LZ complexity as a function of consciousness content vs. level.

Regarding the first point, LZ complexity was measured in EEG signals in patients with disorders of consciousness (DOC; Chapter IX), as well as from the firing rates of neurons in non-human primates whom where progressively anesthetized (Chapter V). Results from the EEG dataset are in line with previous observations, suggesting that patients within the DOC spectrum have on average reduced EEG complexity vis-à-vis healthy adults. Further, the normalized evoked complexity here was about 0.3 (range from 0.2 to 0.4), which is well in line with previous studies (e.g., Casali et al., 2013 reports ~0.31 as a cutoff between consciousness and unconsciousness). Interestingly, within our EEG dataset we also observe a trend for a correlation between clinical assessments of consciousness and evoked normalized LZ complexity, which to the best of our knowledge has not been previously reported. In Chapter V we quantify LZ complexity in spiking patterns as non-human primates are anesthetized. In this chapter, contrary to previous reports in rats (e.g., Abasolo et al., 2015) we observe an elevated neural complexity in anesthetized (asleep in Abasolo et al., 2015) vs. awake states. A possibility is that these conflicting results are due to the different animal models employed, or the difference between anesthesia and natural sleep. However, a more likely explanation revolves around the different techniques employed for coarse-graining the signals recorded. In more detail, LZ complexity is 1) computed in binary sequences, and 2) seemingly scales with entropy (Amigo et al., 2004). For example, if a binary sequence is composed of either all zeros or all ones, reshuffling this sequence will make no difference, and thus the original sequence and the shuffled version will have equal LZ complexities (normalized LZ = 1). Thus, the overall number of ‘0’ vs. ‘1’ will restrict the upper bound of the LZ complexity measure. To overcome this limitation data is typically binarized. The EEG studies cited above set a threshold (commonly the median voltage of a fully rectified signal) and convert data to ‘1’ if a particular time-point is above this threshold, and a ‘0’ if below it. Of course, this method is arbitrary, but it does assure common entropy across conditions and datasets; it is solely the arrangement of ‘0’ and ‘1’ that changes. Spiking data is already binarized, and thus Abasolo et al., 2004 (and others; Amigo et al., 2004) have routinely not employed a coarse-graining and/or binarization technique. In Chapter V, however, we did, as anesthesia is known to reduce firing rates and thus change entropy. This choice (binarizing spikes or not) represent a clear distinction between Chapter V and the previous studies indexing LZ complexity in spiking activity and could explain the different pattern of results in Abasalo et al., 2015 and Amigo et al., 2004 on one hand, and Chapter V on the other. Importantly, the juxtaposition of Chapters V and IX suggest that there is no direct mapping between LZ complexity at different levels of analysis (EEG vs. spikes), but this conclusion is likely to depend on an array of analytical choices, and thus remains a question open for investigation.

In terms of quantifying LZ complexity as a function of the content of consciousness, in Chapter III we contrast EEG signal complexity as a function of perceptual awareness and sensory modality, while in Chapter IX we contrast EEG complexity between unisensory and multisensory stimuli presented within peri- and extra-personal space. Overall, results show no difference according to the spatial location of sensory stimuli, but did reveal a significant difference between perceptual states. Lastly, while Chapter III did show differential complexity as a function of sensory modality, Chapter IX did not. A potential explanation for this discrepancy between chapters is that while in Chapter III complexity was calculated on the entire montage (as in Andrillon et al., 2016; Schartner et al., 2015; 2017), in Chapter IX we only had access to two electrodes (C4 and CP4) due to clinical limitations. Regardless, while it remains an open question whether neural complexity may dissociate between stimuli from distinct sensory modalities (see Boly et al., 2015, and conflicting results between Chapter III and IX), the measure does appear to be sensitive to stimulus detection (shown both in Chapter III and V). Remarkably, while a higher level of consciousness (e.g., awake as opposed to asleep) is related to higher LZ complexity, or higher perturbation complexity index (PCI; Casali et al., 2013), perception of stimuli is associated with a reduced degree of complexity. The likely explanation for this discrepancy relates to the nature of the perturbation applied. Take the example of PCI (Casali et al., 2013), where TMS is applied to the scalp, and LZ complexity is used to quantify the evoked perturbation. The rationale behind this measure is that according to the IIT (Tononi et al., 2016) consciousness should be associated with intricately intertwined neural networks capable of information integration. Thus, when the brain is artificially perturbed, according to IIT a system capable of housing a high level of consciousness should demonstrate a complex spatio-temporal ripple of neural activity. On the other hand, when the “perturbation” applied to the brain isn’t TMS, but simply the presentation of a stimulus, a very different type of network comes online. Arguably, through evolution and development our neural systems mold to execute the processes they are demanded to do in order to survive in their particular environment. Thus, when a stimulus is processed (vs. TMS is applied), ecological neural networks are engaged; i.e., we are not indexing how many different and intertwined neural networks can an artificial perturbation recruit, but contrarily how well does a singular and functionally established network function. Of course, this explanation for the differential pattern of LZ complexity as a function of consciousness level and consciousness content is merely a speculation at this point, and thus will require further experiments to ratify or falsify[1].

Peri-Personal Space and Phenomenal Content

The second part of the dissertation (“consciousness from the inside-out”) focused on establishing that peri-personal space encoding is (at least partially) rooted in the process of multisensory integration (Chapter VI), and that this space marks self-location and not necessarily the space occupied by the body (Chapters VII and VIII). Now, the philosophical argument behind the minimal selfhood approach to consciousness is that there ought to be a subject to experience exteroceptive signals, and hence a pre-reflective bodily self-consciousness built via multisensory integration in the peri-personal space supports perceptual awareness (Legrand, 2006; Blanke, 2012). In the current dissertation we have made progress toward establishing that multisensory integration (see Chapter VI) in the peri-personal space scaffolds a particular aspect of bodily self-

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[1] Personal communication with Dr. Jason Samaha suggests that other groups have equally observed a decrease in LZ complexity when stimuli are perceived vs. not in unpublished work.

consciousness; namely, self-location (Chapters VII and VIII; Noel et al., 2015; Salomon et al., 2017). However, less progress was made vis-à-vis body ownership and first-person perspective (the other main constituents of bodily self-consciousness according to Blanke & Metzinger, 2009). Further, the question whether peri-personal space encoding affects perceptual awareness was left untouched. Interestingly, however, a rapidly growing body of literature within cognitive psychology has documented a "hand proximity effect" on visual processing (Brockmole et al., 2012, 2013).

The "hand proximity effect" generally demonstrates that placing one's hands near visual (or auditory; Tseng et al., 2014) stimuli facilitates the perceptual and cognitive processing of these stimuli (see Brockmole et al., 2012, 2013 for reviews). Early studies suggested that participants respond more quickly (Reed, et al., 2006; 2010) and accurately (Dufour & Touzalin, 2008) to targets presented near their hands, while latter studies have suggested that the near-hand area is biased toward "figure" representations in perceptual figure–ground segregation (Cosman & Vecera, 2010) and that participants show improved visual short-term memory (Tseng & Bridgeman, 2011) for objects placed near their hands. Thus, the "hand proximity effect" seemingly applies throughout the visual hierarchy, impacting aspects of visual processing from detection and discrimination to working memory and fusion (see Brockmole et al., 2012, 2013 for reviews, and Reed et al., 2013, 2017 for ERP studies demonstrating hand proximity impacting VEPs at distinct latencies; e.g., the N1 and P3).

Importantly, the effects of hand proximity remain – yet are reduced - when participants cannot see their hands (Abrams et al., 2008; Reed et al., 2006), implying that proprioceptive signals alone are capable of engendering the "hand proximity effect" and that visual processing is facilitated by the multisensory representation of the hand. Nonetheless, whether this multisensory effect is summative or multiplicative is unknown. Further, studies have reported that as the distance between the hand and the visual stimuli is increased (i.e., side of hand near computer monitor vs. side of visual target) there is a corresponding decrease in the magnitude of the hand proximity effect (Reed et al., 2006, 2010; Tseng & Bridgeman, 2011), and that this effect is specific to the hand (i.e., input from the body); a visual anchor of equivalent shape and size to a hand did not change participant's performance on visual tasks when placed near or far from the stimuli (Reed et al., 2006). Lastly, merely holding a tool that is placed near visual targets facilitates the detection of these stimuli (Reed et al., 2010). Taken together, these results are very similar to results within the peri-personal space literature indicating 1) a somewhat gradual drop-off in tactile processing as visual (Serino et al., 2017) or auditory (Noel et al., 2015; Galli et al., 2015) stimuli are placed further away from the body, 2) that peri-personal space is dependent on multisensory signals (Serino et al., 2017; Bernasconi et al., 2018), and 3) that this representation enlarges as to include tools participants are handling (Iriki et al., 1996; Maravita & Iriki, 2004). Now, whether the "hand proximity effect" and peri-personal space representation are dependent or largely independent processes is unknown (untested); future studies should index visual processing of stimuli placed near a fake hand, as this one is stroked either in synchrony or out of synchrony with the real hand, as in the RHI (Botvinick & Cohen, 1998), and in order to translate the PPS surrounding the real hand toward the fake hand with (or not; asynchronous condition; as in Chapters VI and VII). The hypothesis would be that "hand proximity effects" are present near the fake hand in synchronous stroking conditions, but not in asynchronous conditions. Further, to the best of my knowledge while the "hand proximity effect" has been reported for a wide array of visual tasks (e.g., change detection, congruency priming, figure-ground segregation) there is no report indicating enhanced detection of at-threshold visual stimuli, and thus it is unknown whether the "hand proximity effect" applies to visual awareness (but see Suh et al., 2018 for a recent demonstration that actions may amplify the sensory signal from subliminally presented objects). Regardless, the fact that a wide array of studies emanating from a completely different body of literature from that of peri-personal space representation indicates that visual processing is impacted by the proximity of hands to visual targets is encouraging in suggesting that peri-personal space (inside-out approach to consciousness) may impact visual awareness (additionally see Van der Root et al., 2017 and Salomon et al., 2013, for a demonstration that body ownership does impact visual awareness).

Future Directions

Within the current dissertation I have argued that the neural correlates of awareness are distinct for the multisensory case vs. the sum of unisensory cases. Further, I have illustrated how by leveraging the process of multisensory integration we can probe behavioral performance under full, no, and partially aware conditions, as well as functionally label neurons as either integrative or convergent, and utilize this label to test between popular theories of consciousness. Lastly, in a series of experiments I have confirmed that peri-personal space encoding relies on multisensory *integration* (vs. interactions) and that multisensory integration within the peri-personal space can shape bodily self-consciousness. A number of follow up experiments promise to further our understanding vis-à-vis these particular processes. Perhaps more importantly, the current dissertation argues that by and large the study of consciousness, focusing on visual awareness, has been limited in scope in contrast with our introspective experience of the world as inherently multisensory. Further, a vast array of theories of consciousness exist, some taking an outside-in approach to the question of interest, while others take an inside-out perspective. Here, I have argued that likely perceptual awareness should be understood as a dynamical process dependent on both the nature of external signals and how these impact sensory periphery and are translated up the neural hierarchy, as well as dependent on the already existent neural “internal backdrop” (Musall et al., 2018). Of course, it is unlikely that today any theoretician would argue otherwise, however the impact of the “inside-out” approach is seemingly still being underestimated (see Musall et al., 2018, who employed a general linear model decoding approach while video recording testing subjects and concluded that internal task-independent variables accounted for well over 80% of the explained variance). I have attempted to bridge between the extremes of the theoretical spectrum relating to consciousness by highlighting their commonality in considering neural integration as critical to consciousness. However, more direct examinations of the interaction between the “outside-in” and “inside-out” approach to consciousness are needed. In the following I first detail specific follow-up experiments that could built on particular chapters/experiments within the dissertation[2]. Then, I discuss longer-term approaches that could examine perceptual awareness both from the outside-in and the inside-out, hence bridging the gap between the extremes of the theoretical spectrum.

Short-Term

Chapter III suggests that among the different EEG indices of perceptual awareness only the presence of late and sustained activity translates from vision to audition to audiovisual modalities. However, as briefly discussed above, this measure has recently been suggested to relate most closely to background conditions necessary for awareness, and not to phenomenological awareness itself (Tsuchiya et al., 2015). More specifically, it may be that the presence of late and sustained activity relates to the report of awareness, or access consciousness in Block’s terminology (Block, 1995), and

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[2] Anecdotally, a large portion of the experiments put forward in this section are currently underway.

not phenomenological consciousness. In order to disentangle this possibility in a follow up experiment it will be advisable to employ a no-report paradigm, where the content of subjective experience is indexed via pupillometry or galvanic skin responses (Frässle et al., 2014; Pitts et al., 2014; Turi et al., 2018), and not overt report. A similar critique (and follow-up experiment) is applicable to Chapter V. Here, an overt response was required from non-human primates in order to index level of consciousness. Arguably, the demand of reporting itself is unlikely to alter single-unit properties in S1 and vPM (with exception of the spiking activity corollary to tactile stimulation during response; see control experiment in Ishizawa et al., 2016) but the fact that these animals had to be extensively trained to report the presence of sensory stimuli could profoundly modify circuit motifs.

More generally, regarding Chapter V, it must be acknowledged that the experimental manipulation of administering propofol to non-human primates had both its advantages and limitations. On the positive side, this manipulation unequivocally assured the monkeys were unconscious and allows for a direct clinical translation into anesthetics usage. Of course, the specificity of ascribing the reported effects to the action of propofol on the nervous system can be a considerable asset, although this specificity remains to be tested. On the negative side, it must be acknowledged that administering an anesthetic in order to study consciousness conflates two very distinct aspects of the phenomenon; level and content. In Chapter V we report a greater frequency of "neural ignition" under the unanesthetized than the anesthetized condition, and suggest that this finding is in line with Dehaene's GNW (Dehaene & Changeux, 2011). This observation is true in that the content of consciousness is not possible if there is not a minimal level of wakefulness, however we cannot pinpoint if this observation also holds when solely the content and not the level of consciousness is absent. Further, we cannot ascertain whether the effects reported in Chapter V relate specially to propofol administration, or whether they apply more generally to conscious states. In order to address these limitations two follow up experiments are needed. First, replicating the effects from Chapter V with a different anesthetic would be informative regarding specificity. This effort is currently underway by utilizing Ketamine (an NMDA antagonist; vs. propofol, a GABA agonist). If the effects replicate, this would suggest that they are applicable to consciousness-level generally, while if they do not, it would suggest that differential neural ignition and the fact that convergent (vs. integrative) neurons more faithfully track the level of consciousness of the animal are specific properties of propofol administration and GABAergic signaling. Second, an entirely distinct type of experiment is possible, where monkeys are not anesthetized but simply presented with at-threshold or masked stimuli, while neural activity is simultaneously recorded from multiple brain regions. Ideally, this experiment would be undertaken both prior to report training – indexing content of consciousness via pupillometry or galvanic skin responses – as well as after training and during overt report. In this manner we could ascertain whether the effects reported in Chapter V hold when solely the content of consciousness differs across trials and when no report is requested.

Regarding the second part of the dissertation concerning peri-personal space (PPS), a number of follow-up experiments would build toward establishing whether this representation scaffolds bodily self-consciousness specifically and perceptual awareness generally (discussed above), as well as establishing whether this measure could be of utility in translational efforts. A number of these latter efforts are currently underway (see next paragraph), but in order to truly accelerate the utility of PPS mapping in DOC diagnosis we must first take a step back into basic science. PPS has been shown to remap just prior to starting a movement (Brozzoli et al., 2009, 2010), however it remains unclear why, how, and when specifically. A possibility is that PPS remapping coincides in time with the intent of moving. An exciting prospect would be to map PPS via a cross-modal congruency task (CCE; Spence et al., 2004; Spence & Driver, 2004) in conjunction with the Libet task (Libet et al., 1983). In this latter task participants are asked to produce a movement (usually finger tapping) whenever they decide to, and while watching a dot quickly circle around a clock. Then, they are asked to report the location of the dot around the clock when they decided to move, and when they actually moved. Correspondingly, the CCE has in the past been employed to estimate the timing of PPS remapping (see Brozzoli et al., 2009, 2010 for detail). Thus, if the CCE was executed under a self-paced regime, as EEG is being recorded, and as participants self-report the timing of their will to move, we could ascertain the relative timing of PPS remapping, subjective intentionality ("W-time" in Libet's lexicon), and the readiness potential (a negative voltage EEG deflection peaking at the time of movement, ramping up about 1000-500ms prior to movement; see Libet et al., 1983 for detail). This undertaking would be interesting from a translational perspective, as a gold standard in establishing consciousness is the presence of intentionality (see Owen, 2018). Hence, if PPS can be utilized to index the intention to move, the presence of this signal in DOC patients would be a clear indication of preserved consciousness.

Apart from mapping PPS in patients with DOC (Chapter IX) we can also do so during sleep (another condition where consciousness-level is decreased relative to standard wakefulness) and when subjects are under the influence of psychedelics (Psilocybin, specifically). This last project is particularly interesting in that it aims at delineating PPS in an altered state of consciousness that is not pathological (see Schartner et al., 2017, for a similar approach) and self-reports of subjects under Psilocybin routinely include the feeling of "ego-dissolution" (Millière, 2017). Hence, by mapping PPS under this drug-altered state we could putatively *physically* map this subjective "ego-dissolution". We expect a phenomenological "ego-dissolution" to map onto a flattening of the slope demarking the bifurcation between near and far multisensory space.

A last avenue of potential interest within the PPS field is that of neural dynamics, and cortical-subcortical interactions more specifically. Originally PPS was mapped via single-unit recordings in specific cortical regions of non-human primates (Graziano et al., 1997, 1999, Graziano & Cooke, 2006). Interestingly, the putamen (Graziano & Gross, 1993) has also been documented to possess multisensory neurons with depth-restricted receptive fields that are anchored on specific body parts. This early work was then translated first to neuropsychological observations (Farne & Ladavas, 2000; Ladavas & Serino, 2008) and then neuroimaging (Brozzoli et al., 2011, 2012; Gentile et al., 2013; see Grivaz et al., 2017 for a recent meta-analysis). Unfortunately, the vast majority of neuroimaging has been in fMRI, and thus, while this work has confirmed a similar PPS system in humans as that described in non-human primates, we still have relatively little insight regarding the neural dynamics at play in PPS. Large-scale neural recording in human (M/EEG), as well as high-density and multi-area neurophysiological recordings in animal models are necessary to close this gap. Interestingly, a panoply of recent human work has suggested a strong social component to PPS mapping (e.g., remaps as a function of quality of social interactions, Teneggi et al., 2013; Pellecin et al., 2017; or maps the location of not only the self but also of others, Brozzoli et al., 2013), clearly suggesting that the PPS system interacts with a wide array of other neural networks. In a disparate line of research, recent work has demonstrated that place cells in bats (Omer et al., 2018) and rats (Danjo et al., 2018) encode not only the location of the self, but also that of other animals in one's environment. Hence, documenting the interplay between classic cortical PPS networks and the Hippocampus housing place cells (Dombeck et al., 2010), as well as Entorhinal cortex housing grid cells (Hafting et al., 2005, McNaughton et al., 2006), could inform how subcortex and cortex dynamically interact to establish the egocentric representation of oneself and others in the environment.

Long-Term Vision

The “short term” projects outlined above promise to address certain of the limitations present within the pages of the current dissertation, to broaden our understanding of the role of peri-personal space in self-consciousness, and to further illustrate how examining multisensory processes may inform the study of consciousness. However, the longer-term vision ought to revolve around closing the gap between the outside-in and inside-out approaches to consciousness. Accomplishing this goal may be centered around two key concepts; active sensing and perceptual metamers.

Sensory processing is often regarded as a passive process in which biological receptors such as mechanoreceptors or photoreceptors transduce physical energy into a neural code. And indeed, this view of perception largely guides experimental protocols where, for instance, participants are routinely asked to passively fixate on a crosshair. However, in our daily lives sensory signals do not simply impinge on our sensory periphery, but are actively gated via the rhythmicity of sensory input given motor output and/or attentional sampling (Schroeder et al., 2010). Refocusing the study of perception under this naturalistic and active context closes the gap between the outside-in and inside-out approaches to perceptual awareness, as under this active/closed-loop framework both sides of the equation dynamically impact one another.

Cases of active sensing are numerous and relatively straightforward in unisensory modalities. The examples par excellence are likely that of echolocation (Thomas et al., 2004) and electrolocation (von der Emde & Schwartz, 2003) where unless a sensory signal is emitted, reflected, and received again, nothing is perceived.

Thus, the organisms directly control the sensory sampling of their world given the frequency at which sensory signals are emitted. In humans similar cases of unisensory active sensing exist, sometimes taking an overt form (e.g., sniffing in olfaction), and at times being more covert in nature (e.g., vision; although saccading during visual exploration is very much an active and overt process, Otero-Millan et al., 2008). In olfaction, odor stimulation requires airflow to draw volatile molecules into contact with odor receptors on the membranes of olfactory sensory neurons buried deep within the nose, and thus sniffing dramatically regulates olfactory perception. Sniffing has been documented to be in-phase with neural beta and gamma bands (Young & Wilson, 1999), affect absorption rate of the olfactory epithelial mucus (Scott-Johnson et al., 2000), and to serve as an active filter regulating background order conditions for second order olfactory bulb neurons (Verhagen et al., 2007). In vision, apart from the role of saccades and the impact of these on neural patterns (see Nowak & Bullier, 1997 for a review), an array of recent work has highlighted the role of alpha phase (Busch et al., 2009; van Rullen & MacDonald, 2012; Chakravarthi & van Rullen, 2012) and peak frequency (Samaha et al., 2015b; Cecere et al., 2015) in visual cortex to modulate visual perception (van Rullen & Koch, 2003; van Rullen, 2016), expectations (Samaha et al., 2015a; Samaha et al., 2016), and attention (Busch & van Rullen, 2010). Further, recent evidence suggests that the phase of alpha band oscillations may be under voluntary control (Samaha et al., 2015a; Wutz et al., 2018), and hence visual processing may not be understood without accounting for what Churchland and colleagues denominate the “internal backdrop” (Musall et al., 2018; see also Stringer et al., 2018), and how this latter one is altered by sensory history and action (Ashourian & Loewenstein, 2011; Harvey et al., 2012; Fischer & Whitney, 2014; Akrami et al., 2018).

Now, active sensing becomes particularly interesting within a multisensory context. As alluded to in the Introduction, the modern study of multisensory integration is deeply vested in Bayesian computations with numerous studies suggesting that visuo-tactile (e.g., Ernst & Banks, 2002), audio-visual (e.g., Alais & Burr, 2004), and visuo-proprioceptive (van Beers et al., 1999) synthesis, among others, is statistically optimal. Further, theoretical studies have suggested that this optimal multisensory integration emerges naturally from the convergence of unisensory signals (Ma et al., 2006), and neuroimaging studies have delineated the transition from no-integration, to forced-fusion (i.e., maximum likelihood estimation), to causal inference integration across brain regions (Rohe & Noppeney, 2015, 2016). Thus, indexing whether cues combine optimally or not has become a hallmark of multisensory integration in the modern study of multisensory processing (see Rahnev & Denison, 2018, for a similar argument). Now, somewhat counter-intuitively, recent studies have suggested multisensory integration can be supra-optimal (Raposo et al., 2012; Nikbakht et al., 2018), which raises the question as to how is this possible? Shalom and Zaidel (2018) suggest that supra-optimality may result from underestimating unisensory performance. That is, if measured auditory likelihoods, for instance, are taken not to be solely derived from a auditory estimates but from the combination of an auditory likelihood and a flat visual likelihood (auditory conditions actually being the presence of auditory signals and the absence of a visual signal; audiovisual signals being the standard state of affairs), then researchers are commonly underestimating the reliability associated with unisensory likelihoods. This would lead to erroneous claims of multisensory supra-optimality. Another (non-mutually exclusive) possibility is that of active sensing (see Nikbakht et al., 2018 for this argument). Namely, presenting multisensory cues could allow for cross-modal signals to back-propagate and inform unisensory likelihoods. For instance, when audiovisual stimuli are presented, it is possible that the visual signals interact with early auditory representation and sharpen it (see Gruters et al., 2018 for an example of eye movements affecting eardrum function; Falchier et al., 2002; Rockland & Ojima, 2003;

see Ghazanfar & Schroeder, 2006; for a review of multisensory interaction happening at very early stages of sensory processing). That is, it may veritably be that multisensory stimulation reduces the variability associated with unisensory likelihoods through the process of active sensing. Thus, when presenting both auditory and visual signals, not only is there more information than in unisensory cases, but the variance associated with the unisensory likelihoods is reduced as well. A similar logic can also be applied in behavior. Indeed, apart from the neural or "representational" unisensory benefits that could occur during multisensory presentations, it is also possible that multisensory cues result in more efficient motoric sampling of unisensory object features. This also resulting in a reduction of variance associated with the multisensory context. More broadly, particularly within the multisensory context (because of cross-modal signals interacting and sharpening one another, as well as modifications in sensing behavior) seemingly active sensing – the "inside-out" component of the closed loop between the self and the environment – can tangibly impact the faithfulness of neural representations, likely impacting subjective experience as well.

The second notion which may result key in furthering our understanding of perceptual awareness is that of multisensory metamers. Perceptual metamers are identical perceptual estimates formed from physically distinct signals (see Deroy et al., 2016 for a review). Multisensory examples can be found within the study of the ventriloquist effect (Recanzone, 1998; Bertelson et al., 2000). For example, in the case where an auditory and visual signal are presented with a small spatial disparity (e.g., visual signal at +3° from fixation and auditory signal at -3° from fixation) and with equal reliability, participants will likely report the perception of an audiovisual event or object at fixation; that is, they will be subject to a partial ventriloquist effect (more commonly visual likelihoods are more reliable than auditory ones, and thus visual capture occurs). Similarly, if auditory and visual signals were presented at 0°, participants would equally report an audiovisual event or object at fixation. In other words, these two conditions of conflicting and non-conflicting audio-visual stimuli would be multisensory perceptual metamers.

Seemingly a critical open question within the study of multisensory perceptual awareness is whether participants may retain certain sensitivity to discrepancies between multisensory perceptual metamers. That is, philosophically, even if we experience the world as multisensory, it is far from obvious that awareness is truly multisensory, as opposed to a rapid succession of unisensory percepts in "phenomenal unity" (Deroy et al., 2014; Deroy et al., 2014; Bayne, 2014; Spence & Bayne, 2014; Briscoe, 2016, 2017). Arguably a strong point of evidence in favor of the former possibility (i.e., true multisensory awareness) would be to demonstrate that when multisensory percepts are formed, access to the unisensory features is lost; that is, there is no unisensory percept sustaining the multisensory percept and participants cannot differentiate (on any dimension) between multisensory perceptual metamers.

Surprisingly a very limited number of studies have queried the nature of unisensory representations during a multisensory percept. In a notable exception, Hillis and colleagues (2002) had participants judge which stimuli in a succession of three was the odd one out – no further instruction was given. The stimuli were surface slants specified via visual cues (disparity and texture) or objects of different sizes specified via multisensory cues (visual and haptic). The cues (e.g., disparity and texture) were either congruent or incongruent and the rationale of the study was that if cue fusion were mandatory, then the discrimination thresholds of the two features (either disparity and texture or visual and haptic cues) would co-vary as specified by the maximum likelihood estimation (Landy et al., 1995). Results suggested that cue fusion was mandatory within the visual modality, but not across modalities (Hillis et al., 2002). That is, seemingly in the multisensory condition participants retained a certain degree of access to unisensory likelihoods. This result would suggest that when multisensory percepts are formed, the phenomenology associated with this percept might nonetheless be sustained by unisensory estimates. That is, seemingly our introspection of the world as multisensory may be erroneous, and instead multisensory percepts may be nothing more than the simultaneous occurrence of unisensory percepts. In other words, on subjective experience directly taps into unisensory representation, and not at the (fused) multisensory stage. If this is truly the case, it would make sense that neural correlates of awareness translate from visual to auditory modalities, but not to the multisensory case (Chapter III). Further, it would suggest that the study of perceptual awareness should 1) focus on unisensory cases, but additionally 2) also scrutinize how and why independent representations are maintained even though the neural architecture for multisensory representations is in place. Nevertheless, given the paucity of studies indexing multisensory metamers and access to unisensory estimates under multisensory perception, this is very much a wide-open area for future investigation.

Conclusion

The study of perceptual awareness is one of the ultimate frontiers in contemporary neuroscience; how do 3 pounds of biological flesh give rise to subjectivity? A host of neurobiological theories of consciousness exist, the vast majority of these originating from visual neurosciences and lying on a spectrum, from those posing the burden of explanation on the outside-in process of assembling sensory signals up the neural and cognitive hierarchy ultimately leading to perception, to those arguing that perception is imposed from the inside-out onto the world given prior experience, bodily representations, and affordances. Interestingly, the majority of these theories – in fact those lying at the extreme of the outside-in/inside-out spectrum –

speculate that information integration is central in engendering perception. In turn, here I attempted to re-align the study of perceptual awareness with our subjective experience of the world as inherently multisensory, and to leverage the process of multisensory integration – where integration is a *de facto* process – in the study of consciousness. Results suggest that insights derived from visual neuroscience may not be straightforwardly applied to the multisensory case (e.g., different neural correlates for perceptual awareness across these contexts), and instead suggest that contrarily to hypotheses from prominent theories of consciousness, perceptual awareness is graded and most faithfully tracked in the firing pattern of convergent rather than integrative neurons. On the other hand, findings do support the claim that peri-personal space is (at least partially) scaffolded on the process of multisensory integration, and that this space pre-reflectively encodes the location of the self as opposed to that of the body. Finally, results suggest that the mapping of peri-personal space may be utilized in diagnosing disorders of consciousness. Taken together, the present results suggest that the process of multisensory integration may inform already existent, and potentially give rise to new theories of perceptual awareness, and highlight that perceptual awareness is likely a dynamic process – both within the brain being supported by reentrant circuit motif, and in the external milieu, with the world impacting neural processing and this latter one biasing environmental representations. Future work will have to aim to bring the outside-in and inside-out approaches to consciousness closer together, and may benefit from scrutinizing the interplay between perceptual awareness and active sensing, as well as between unisensory and multisensory likelihoods of perceptual metamers.

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