FUNCTIONAL FRACTIONATION OF THE STIMULUS-DRIVEN ATTENTION NETWORK

By

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PREFACE

It has long been recognized that most organisms demonstrate an orienting response to novel, task- irrelevant, salient stimuli in the environment. The presentation of such an oddball event does not only induce physiological, reflexive responses, but also an allocation of cognitive processing resource to the stimulus. Specifically, once the oddball is detected, attention is switched to the oddball, This attentional orienting is followed by an evaluative process to evaluate the potential behavioral significance of the oddball; if it is evaluated to be behaviorally significant, it will be acted upon. Otherwise, attention will be redirected to a goal-oriented task (reorienting of attention). While a network of brain regions, consisting of anterior insula (AI), inferior frontal junction (IFJ), and temporo-parietal junction (TPJ) have been associated with stimulus-driven attention, how distinct processes evoked by the oddball presentation are implemented in the brain remains unknown. This is primarily due to methodological limitations of previous approaches that used too briefly presented stimuli to dissociate the neural substrates underlying each cognitive component of stimulus –driven attention.

In the first chapter of this dissertation, I briefly review the literature on stimulus-drive attention and introduce a novel experimental approach to distinguish neural substrates associated with the distinct cognitive processes evoked by an oddball presentation. The second chapter reports findings that each individual node in the stimulus-driven network plays a different role in stimulus-driven attention, such that the AI, along with the anterior cingulate cortex (ACC), is primarily involved in attentional orienting/reorienting, while the TPJ is involved in stimulus evaluation. The IFJ is

implicated in both processes. Having established the functional dissociation of the network, the third and fourth chapters further elucidate the specific function subserved by individual regions of the network. Specifically, the third chapter is aimed at further understanding the function of the AI in stimulus-driven attention. One school of thought suggests that the AI is primarily engaged by arousing, affective stimuli, whereas another suggests that it primarily acts as a salience detector for attention capture. My findings indicate that the AI is not only involved in attention orienting to a salient stimulus, but that it also plays a role in emotional, affective processing. The fourth chapter aims at further dissociating attention orienting into its two core components; oddball stimulus detection and attention shifting. My findings suggest that the ACC is specialized in switching of attentional sets, whereas the AI is primarily involved in detecting the occurrence of behaviorally significant events, with the IFJ being involved in both processes.

Having specified the roles of each individual node in the stimulus-driven attention network, the dissertation concludes with a neural network model of how a salient, novel and task-irrelevant stimulus captures attention.

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CHAPTER I

INTRODUCTION

In the face of an overwhelming amount of information received by our senses at any instant, attention plays a crucial role in enabling a subset of that information to be prioritized or processed in finer detail at the expense of other information. This selective attention, however, is not a unitary process. On the one hand, attention is often directed by specific goals, memory, or expectations kept in one's mind (goal-directed attention). On the other hand, a significant event or stimulus in the environment, which evokes strong orienting responses (Pavlov, 1927; Sokolov, 1963), also powerfully captures attention in a stimulus-driven manner (Corbetta & Shulman, 2002; Egeth & Yantis, 1997; Theeuwes, 1994; Yantis & Hillstrom, 1994).

Stimulus-driven attention is crucial for survival and adaptive behaviors to the dynamically changing environment, such that even human infants show this adaptive stimulus-driven orienting, just as adults (Fagan, 1990; Kagan, 1994). This stimulus-driven attentional capture, which is often associated with reflexive and physiological responses to the attention-capturing event, actually includes several distinct cognitive processes (Gronau, Sequerra, Cohen, & Ben-Shakhar, 2006; Pavlov, 1927; Sokolov, 1963). Once a salient event is detected and attention is switched to this event (Posner, 1980), an evaluation process takes place to determine its identity, potential behavioral relevance, and the appropriate course of action (Friedman, Cycowicz, & Gaeta, 2001; Kahneman, 1973; Kok, 2001). Depending on the outcome of the evaluative process, the event/stimulus might reside in the focus of attention, or attention might be withdrawn and oriented elsewhere. Specifically, if an attended stimulus is evaluated to be behaviorally relevant, the observer may further interact with or avoid that event. By contrast, if the stimulus is deemed behaviorally inconsequential, attention may be redirected back to goal-oriented behavior (reorienting of attention).

The overarching goal of my dissertation is to identify neural substrates associated with distinct components of stimulus-driven attention, ultimately revealing how external sensory events are encoded, analyzed, and appropriate reactions are produced.

Behavioral studies of stimulus-driven attention

Given its pivotal importance in adaptive behaviors, much work has been devoted to investigate stimulus-driven attention. An extensively used paradigm is the attentional capture paradigm that contains a salient, singleton stimulus (Bacon & Egeth, 1994; Folk, Remington, & Johnson, 1992; Leber & Egeth, 2006; Theeuwes, 1994). In this paradigm, participants are required to search for a pre-specified target, which is accompanied by distracting, non-target items. In one condition, one of those distractors is created to be drastically distinct from any other items in the display, while there is no such salient distractor in the other condition. The results showed that the presence of a singleton distractor slowed responses to the target, which led to the claim that a salient, singleton stimulus involuntarily captures attention, interfering with the deployment of attention to the target. This finding implies that a salient stimulus, not associated with a goal-directed, planned behavior, captures attention in a stimulus-driven manner (Theeuwes, 1994).

However, a limitation of this paradigm is that the behavioral relevance of attention capturing events is obviously known by experimental settings; any non-target item should be discarded, regardless of what it is and how salient it is. This is hardly the case in real-world situations (Friedman et al., 2001).

Likewise, another form of paradigm used to investigate stimulus-driven attention, the contingent capture paradigm, is not suitable to elucidate the whole picture of stimulus-driven attention either. Similar to the singleton distractor paradigm, it also presents a salient distractor, but importantly, in some cases, the distractor contains target-defining properties (Atchley, Kramer, & Hillstrom, 2000; Folk, Remington, & Johnston, 1992; Folk, Remington, & Wright, 1994; Gibson & Kelsey, 1998). An important finding from studies adopting this paradigm is that a distractor that contains features related to the target has much stronger interference with the deployment of attention to the target than a distractor which does not share any feature with the target. While these studies reveal which factors modulate stimulus-driven attention capture, this paradigm has the same limitation as the singleton capture paradigm in that behavioral relevance of attention capturing event is defined by the task setting. As such, the contingent capture paradigm is inherently limited to elucidate the complete picture of stimulus-driven attention; it is uncertain whether attention was captured in a purely stimulus-driven manner (Simons, 2000).

Contrary to the paradigms above, a surprise oddball paradigm, in which a novel, salient stimulus (oddball) is presented unbeknownst to the participants, closely resembles real-world situations, as the behavioral relevance of the oddball is unknown because it is not included in the task setting (Friedman et al., 2001). Using this paradigm, several studies have found important characteristics of stimulus-driven attention (Asplund, Todd, Snyder, Gilbert, & Marois, 2010; Horstmann & Becker, 2008; Kahneman, 1973; Sokolov, 1963). First, although orienting of attention to the surprising oddball disrupts ongoing goal-directed behavior, this disruptive effect drastically habituates after a few instances of the oddball (Asplund et al., 2010a; Sokolov, 1963). That is, once an oddball becomes familiar, it attracts negligible attention. The finding that a sensory event that initially captured attention no longer does so at later instances suggests that there are processes that determine whether that stimulus should receive attention or not (Friedman et al., 2001; Kahneman, 1973) and, if so, for how long it should be attended to before reorienting attention to the goal-directed behavior. Second, even in the instance that the oddball powerfully grabs attention and disrupts the concurrent goal-directed behavior, individuals can ultimately accomplish task goals, by withdrawing attention from the oddball and reorienting to the goal-directed task (Asplund, Todd, Snyder, Gilbert, et al., 2010; Forster & Lavie, 2011; Horstmann & Becker, 2008). This finding clearly shows that even though people cannot resist attending to task-irrelevant, salient stimuli, goal-directed behaviors quickly regain attention.

As briefly reviewed above, behavioral studies have revealed that the presentation of an oddball stimulus incurs several distinct processes. First, once a novel, salient stimulus (oddball) is detected, attention is switched to the detected oddball (Posner, 1980). Second, after this stimulus-driven orienting, the oddball stimulus is under an attention-demanding evaluative process (Kahneman, 1973). This process determines the behavioral significance of the unknown stimulus, which includes its identification and categorization perhaps by comparing it with internal representations and expectations, such as target templates (Ciesielski, Madden, Bligh, & Schopflocher, 1985; Courchesne, Hillyard, & Galambos, 1975; Decety & Lamm, 2007; Delplanque, Silvert, Hot, & Sequeira, 2005; Donchin & Coles, 1988; Doricchi, Macci, Silvetti, & Macaluso, 2010; Geng & Mangun, 2011; Polich, 2007). Finally, if an oddball stimulus is evaluated to be behaviorally irrelevant following its identification and categorization, attention will be reoriented back to the goal-oriented behavior. Otherwise, action (e.g avoidance) will be taken to deal with the attended stimulus.

Neural correlates of stimulus-driven attention

It is now well established that several distinct regions form a stimulus-driven attention network that is recruited by the occurrence of oddballs (Asplund, Todd, Snyder, & Marois, 2010; Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002; Downar, Crawley, Mikulis, & Davis, 2000, 2002; Marois, Leung, & Gore, 2000). This stimulus-driven attention network (Figure 1) includes lateral inferior prefrontal cortex (inferior frontal junction), ventral prefrontal area (anterior insula) and temporo-parietal junction (Corbetta et al., 2008). The specialization of these regions in stimulus-driven attention is further illustrated by findings that this network is largely distinct from another set of regions typically activated during goal-directed behaviors, including the frontal eye field and superior parietal regions (Asplund, Todd, Snyder, & Marois, 2010; Corbetta & Shulman, 2002; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Yantis et al., 2002).

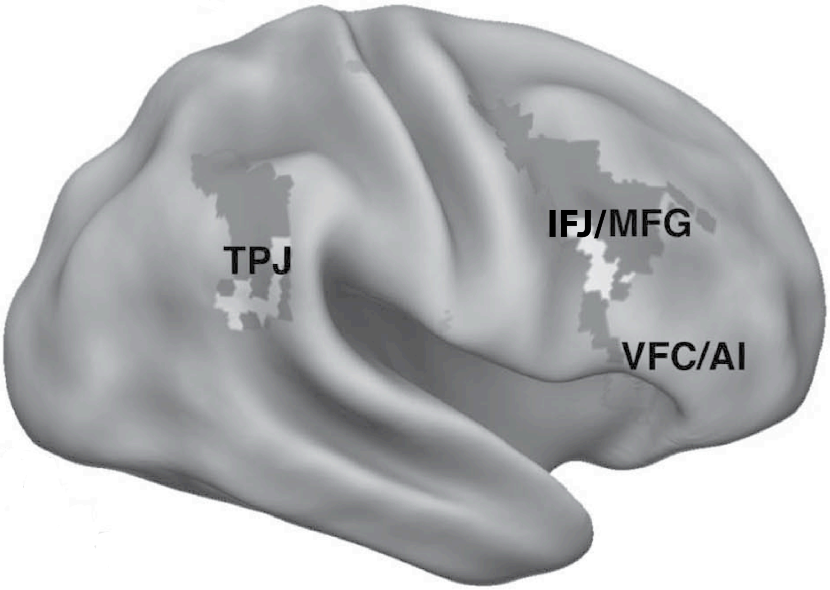

Figure 1. Brain regions in the stimulus-driven attention network. TPJ – temporoparietal junction, IFJ – inferior frontal junction, MFG – middle frontal gyrus, VFC – ventral frontal cortex, AI – anterior insula. Adapted from Corbetta et al. (2008).

While the stimulus-driven attention network has been implicated in oddball processing, the functional contribution of individual region in this network is poorly understood. Specifically, it remains unknown how distinct processes evoked by the presentation of an oddball (stimulus-driven orienting, evaluating, and reorienting attention to the goal-oriented task) are implemented in the brain. The findings that the regions in the stimulus-driven attention network are co-activated when attention is captured by an oddball stimulus suggest that these areas are commonly involved in orienting of attention to the oddball stimulus (Corbetta & Shulman, 2002). However, it is also possible that some of the activities elicited by the oddball reflect evaluating the stimulus (Downar et al., 2002), followed by reorienting attention to the goal-directed behavior, rather than just orienting. Furthermore, it also remains unknown whether each region plays a common role or whether they each perform different computations. As reviewed below, previous work suggests that each node in the stimulus-driven attention network might fulfill a different function in human cognition.

Functions of individual nodes in the stimulus-driven attention network

One key region of the stimulus-driven attention network, the temporo-parietal junction (TPJ), has been implicated in orienting attention to salient or behaviorally relevant events (Corbetta & Shulman, 2002; Serences et al., 2005). However, growing evidence suggests that the TPJ may not be solely dedicated to attentional orienting. It was shown that a similar region contributes to social cognition, such as reasoning about other people's mental state (Frith & Frith, 2006; Hampton, Bossaerts, & O'Doherty, 2008; Mitchell, 2008; Saxe & Kanwisher, 2003). That is, the region activated by the occurrence of behaviorally relevant stimulus may also be involved in the cognitive process of inferring the mental states of other people (Mitchell, 2008), though some studies suggest that attentional orienting and social cognition might be mediated by separate subdivisions within the TPJ (Mars et al., 2012; Scholz, Triantafyllou, Whitfield-Gabrieli, Brown, & Saxe, 2009; Young, Dodell-Feder, & Saxe, 2010). This finding that the broad region of the TPJ is also involved in social cognition casts a doubt about the hypothesis that the main role of the TPJ is to orient attention toward the stimulus. It is possible that a common process incurred by both attentional orienting and social cognition is subserved by the TPJ, thereby resulting in co-localization of two functions in this region (Cabeza, Ciaramelli, & Moscovitch, 2012; Corbetta et al., 2008; Decety & Lamm, 2007). Such a process might correspond to the evaluation of external sensory events to determine their behavioral relevance, and comparing and updating internal predictions relative to those events (Decety & Lamm, 2007; Doricchi et al., 2010; Geng & Mangun, 2011; Polich, 2007). In line with this, many ERP studies suggest that the P3 component associated with evaluating novel stimuli originates from the inferior part of the parietal cortex (Bledowski et al., 2004; Ciesielski et al., 1985; Courchesne et al., 1975; Friedman et al., 2001; Linden, 2005), where the TPJ is located.

Similar to the TPJ, the anterior insula (AI) also shows robust activity to salient events in many studies (Corbetta et al., 2008; Crottaz-Herbette & Menon, 2006; Downar et al., 2000, 2002; Linden et al., 1999). Even though the AI was reported to be co-activated with the TPJ by the presentation of a salient stimulus (Corbetta et al., 2008), the function of the AI seems to be different from the TPJ; while the TPJ is usually suppressed with increasing demands of goal-directed tasks (Shulman, Astafiev, McAvoy, d'Avossa, & Corbetta, 2007; Todd, Fougnie, & Marois, 2005), the AI seems to be involved in performance of such tasks. Specifically, it shows enhanced activity in dual-task conditions, compared to single task conditions (Tombu et al., 2011). It is also implicated in exerting cognitive control in a wide range of tasks (Dosenbach, Visscher, Palmer, & Miezin, 2006; Duncan, 2010; Woolgar, Hampshire, Thompson, & Duncan, 2011; Woolgar, Thompson, Bor, & Duncan, 2011). Furthermore, the AI was recently suggested to play a critical role in perceptual decision making (Ploran et al., 2007) and switching between distinct brain networks across different types of tasks (Sridharan, Levitin, & Menon, 2008). Besides its pervasive involvement in attention and perception, there are a plethora of presumed functions ascribed to the AI; in particular, it has been implicated in body awareness, mood, addiction behavior, disgust, empathy, and economical decision making (Benuzzi, Lui, Duzzi, Nichelli, & Porro, 2008; Britton et al., 2006; Craig, 2002; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Hein & Singer, 2008; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003; Singer, Critchley, & Preuschoff, 2009; Wicker et al., 2003). From socio-affective functions to perception and attention, the variety of functions assigned to the AI complicate the issue of what is the fundamental role of this brain region to cognition. To integrate these findings, it has been recently suggested that distinct subdivisions within the insular cortex are devoted to attention and affective processes (Chang, Yarkoni, Khaw, & Sanfey, 2012; Touroutoglou, Hollenbeck, Dickerson, & Feldman Barrett, 2012). In contrast to this point of view, a group of researchers (Menon & Uddin, 2010; Seeley et al., 2007) suggest that the primary role of the AI, in concert with anterior cingulate cortex (ACC), is to signal salience or behavioral relevance of sensory events to exert optimized cognitive control. They argue that the AI and ACC form a 'saliency network,' primarily signaling saliency of sensory inputs. According to this argument, the wide involvement of the AI in social, affective processing is because the stimuli arousing emotional feelings are intrinsically salient.

Another prefrontal region in the stimulus-driven attention network, inferior frontal junction (IFJ) (also called middle frontal gyrus), is also known to be involved in various cognitive processes. A large body of studies have consistently reported that the IFJ is activated by the occurrence of salient and behaviorally relevant events (Asplund, Todd, Snyder, & Marois, 2010; Corbetta et al., 2008; Corbetta & Shulman, 2002; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Sharp et al., 2010). This region may also play a role in resolving response conflicts and exerting executive control (Brass, Derrfuss, Forstmann, & von Cramon, 2005; Derrfuss, Brass, Neumann, & von Cramon, 2005).

Furthermore, this region is suggested as a core neural node of an attentional bottleneck that is responsible for the attentional blink (Han & Marois, 2013; Marois, Chun & Gore, 2000; Marois, Yi, & Chun, 2004; Todd, Han, Harriosn, & Marois, 2011) and psychological refractory period (Dux, Ivanoff, Asplund, & Marois, 2006; Dux et al., 2009; Tombu et al., 2011).

As briefly reviewed above, there is much evidence that a functional dissociation between each individual region might exist within the stimulus-driven attentional network. Consistent with this notion, a recent study (Asplund, Todd, Snyder, & Marois, 2010) demonstrates that the lateral prefrontal cortex (IFJ) can be functionally decoupled from the lateral parietal region (TPJ): even though the IFJ and TPJ were co-activated during the presentation of an oddball, when goal-directed behavior was performed, the IFJ activity decoupled from the TPJ activity. Instead, the IFJ activity became correlated with core components of the dorsal attention network, the IPS and frontal eye fields (FEF). The study concluded that the IFJ is involved in both goal-directed and stimulus-driven attention, whereas the ventral parietal cortex (TPJ) is specialized for stimulus-driven attention.

However, even though these findings provide direct evidence for a functional dissociation between the prefrontal and parietal areas, they do not specify how distinct processes associated with attention-capturing events – namely, orienting of attention towards the event, evaluation of the event, and reorienting of attention from the event back to the goal-relevant task – are implemented in these regions.

Summary of current studies and predictions

The goal of this dissertation is to identify neural substrates associated with each distinct process evoked by the presentation of a novel, salient stimulus. As mentioned above, neural activities specifically associated with the initial orienting of attention toward a salient (oddball) stimulus have not been distinguished from those related to evaluating the attended stimulus and the reorienting of attention towards the goal-directed behaviors. This is primarily due to the nature of the oddball stimuli used in many previous studies; brief and transient oddballs do not allow one to temporally dissociate the initial orienting activity from the immediately following evaluative and reorienting activity (Asplund Todd, Snyder, & Marois, 2010; Downar et al., 2000, 2002).

In this dissertation, using a novel paradigm with temporally extended oddballs and exploiting the temporal resolution of fMRI, I attempted to separately identify neural substrates of attentional orienting/reorienting and stimulus evaluation. In the presence of a temporally extended oddball, attentional orienting toward the oddball, which includes detecting and switching attention to the oddball, is expected to happen transiently at the onset of the stimulus to be attended (Braver et al., 2003; Downar et al., 2002; Konishi et al., 1998; Yantis et al., 2002). This is because orienting primarily refers to the shifting of attention, which is, by definition, a transient, dynamic process (Konishi et al., 1998).

By contrast, neural activity associated with stimulus evaluation should show a sustained pattern as the presentation of a stimulus to be evaluated is temporally extended. This is because stimulus evaluation is a process dependant on the nature of the attended stimulus. According to Kok (2001), stimulus evaluation refers to a process that precedes the selection and preparation of the appropriate response to a stimulus. This evaluative process includes stimulus identification and categorization, which typically requires matching a stimulus to templates stored in memory (Ciesielski et al., 1985; Courchesne et al., 1975; Polich, 2007). An ERP component, P300, has been associated with this evaluative process, based upon findings that its peak latency was delayed as it took longer for a given stimulus to be identified, categorized, or compared with internal representations (Coles et al., 1995; Courchesne et al., 1975; Kok 2001; Linden, 2005; McCarthy & Donchin, 1981). Given these findings, in the presence of a temporally extended oddball, evaluation of the stimulus will also be extended, thereby rendering it temporally dissociable from the transient orienting response with fMRI. In the same vein, transient activity related to reorienting of attention from the oddball back to goal-directed behavior should also be dissociable from the sustained activity associated with the evaluative process.

To preview the results of the experiments using temporally extended oddballs (see Chapter II), the AI and anterior cingulate cortex (ACC) responded only to the onset and offset of the temporally extended oddballs, while other regions in the stimulus-driven attentional network (IFJ & TPJ) showed sustained responses. Remarkably, when the demand for sustained, evaluative processes was minimized, the IFJ also showed transient patterns of responses to the onset and offset of the oddball, implicating this region in both the orienting and evaluative processes. These initial results indicate that the stimulus-driven attention network may be fractionated into several distinct functional components.

This finding of AI activation in the orienting process is also interesting in the context of the function of the AI. As mentioned above, the AI has been associated with a wide variety of social and affective processes, as well as other cognitive ones. Most studies arguing for social and affective function of the AI reported that the activity of this region was enhanced by the presentation of pictures or films depicting painful or disgusting situations, leading to the suggestion that this brain region is involved in the perception of empathy and disgust (Benuzzi et al., 2008; Britton et al., 2006; Gu, Liu, Van Dam, Hof, & Fan, 2013; Singer et al., 2009; Wicker et al., 2003). However, all of these studies are subject to an alternative interpretation; these social, affective events simply become more salient or potentially relevant for adaptive behaviors, and the AI is sensitive to salience or behavioral relevance in general (Menon & Uddin, 2010).

The extended oddball paradigm provides an ideal means to assess the affective and salience theories of AI function. This can be achieved by observing the response of the AI to the presentation of extended oddballs with disgust- or empathy-inducing content (see Chapter III). If the AI's function primarily consists in signaling salient changes in the environment, then it should only respond to the onset (and offset) of these oddballs. Conversely, if it is also involved in affective processing, then AI's response should be sustained throughout the duration of the oddball.

Chapter IV investigates which specific process is associated with the transient, orienting activity evoked by the onset of a salient stimulus. This transient orienting activity is further decomposed into detecting and switching activity (Friedman et al., 2001; Opitz, Rinne, Mecklinger, von Cramon, & Schroger, 2002; Molholm, Martinez, Ritter, Javitt, & Foxe, 2005). Using a well-established paradigm optimized to isolate the transient activity of attentional switching (Chiu & Yantis, 2009; Esterman, Chiu, Tamber-Rosenau, & Yantis, 2009; Tamber-Rosenau, Esterman, Chiu, & Yantis, 2011; Yantis et al., 2002), I probed the core regions found to be involved in attention orienting; namely, the AI, ACC, and IFJ. Furthermore, while participants were engaged in a goal-directed task, oddball stimuli were presented, which were followed either by another distinct oddball (dual oddballs), or by other task-related stimuli (single oddballs). In these oddball presentations, there is a transition either between an oddball and task-related stimuli (single oddball), or between two oddballs (dual oddball). This paradigm allowed me to assess how the prefrontal regions respond to transitions between task-irrelevant events and goal-oriented behavior – i.e. between oddball onsets/offsets and search task – and to transitions between two task-irrelevant events (i.e. between two oddballs). While the former type of transition is expected to affect attentional task settings, the latter is not. Thus, regions solely involved in detecting a salient change in the environment should be engaged by the transition between oddballs, whereas regions involved in attention switching should be solely recruited in the transition between oddballs and the goal-oriented task.

Taken together, the studies reported in this dissertation elucidate how the brain responds when attention is captured by a novel, salient stimulus in a stimulus-driven manner. By identifying the neural substrates associated with orienting (detecting and switching attention towards the oddball stimulus), evaluating that stimulus, and reorienting of attention, the functional decomposition of stimulus-driven attention into its core processing components can now be established, thereby paving the way towards an integrated picture of the mechanisms by which attention is captured.

Chapter II

TEMPORAL SEGREGATION OF ORIENTING ACTIVITY FROM EVALUATIVE AND REORIENTING ACTIVITIES

This chapter investigates how each individual node in the stimulus-driven attention network contributes to a series of cognitive operations evoked when a novel, salient stimulus (oddball) is presented. Presentation of such an oddball, even though it is not associated with any goal-directed behavior, captures attention in a stimulus-driven manner and undergoes an attention-demanding, evaluative process (Friedman et al., 2001; Kahneman, 1973; Sokolov, 1963). This evaluative process determines whether the attended stimulus should be further acted upon (or avoided), or whether it should be ignored. If the stimulus is deemed behaviorally inconsequential, attention will be redirected to other behaviorally significant events.

While the stimulus-driven attention network, consisting of the AI, IFJ, and TPJ, has been implicated in oddball processing (Asplund, Todd, Snyder, & Marois, 2010; Corbetta et al., 2008; Corbetta & Shulman, 2002; Downar et al., 2000, 2002; Marois, Leung, & Gore, 2000), it remains unclear how each of these regions contributes to distinct subcomponents of oddball processing. This is because many previous studies used too brief stimulus presentation to permit temporal separation of neural activities associated with such processes; neural activities associated with each distinct component of oddball processing are conflated with each other. In addition to these core nodes in the stimulus-driven attention network, I also examined other regions implicated in processing salient sensory inputs, anterior cingulate cortex (Menon & Uddin 2010; Seeley et al., 2007) and amygdala (Balderston, Schultz, & Helmstetter, 2011; Blackford et al., 2010; Kiehl et al., 2005;Rutishauser, Mamelak, & Schuman, 2006; Weierich, Wright, Negreira, Dickerson, & Barrett, 2010; Wright et al., 2003).

In this chapter, I tried to separate neural activity associated with orienting attention toward an oddball from that of evaluating the oddball. To achieve this, I devised a paradigm that contains temporally extended oddballs. In this paradigm, participants were required to search for pre-specified targets in a rapid serial visual presentation (RSVP) of distractors, and to make speeded responses to those targets. In some trials (about 12 % of the total), a temporally extended oddball was presented, which was unannounced to participants. Presumably, attention should be oriented to this surprising oddball, which is reflected by a transient pattern of neural activity to the onset of the oddball (Figure 2a). After the initial orienting, attention would be maintained on this oddball while the oddball is evaluated. This evaluative process would induce a sustained pattern of neural response throughout the presentation duration of the oddball (Figure 2b). Finally, attention should be once again re-oriented towards the main goal-oriented task at the offset of the oddball stimulus.

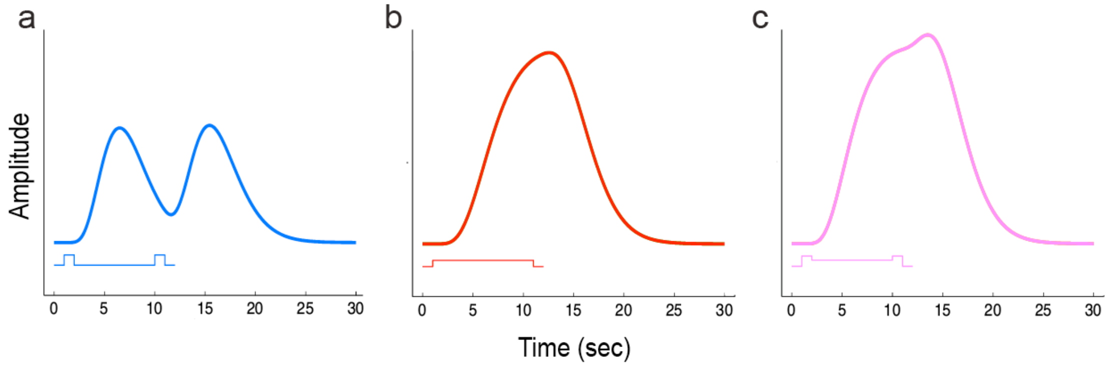

Figure 2. Predicted hemodynamic responses to the temporally extended oddball. Each hemodynamic response was constructed by convolving each boxcar function with a double gamma function (SPM2, http://www.fil.ion.ucl.ac.uk/spm). a) Predicted hemodynamic response of a region involved in the transient process of attentional orienting/reorienting, which should be sensitive to the onset and offset of a temporally extended oddball. The boxcar function represents transient neuronal response to the onset and offset of the oddball. b) Predicted hemodynamic response of a region related to sustained processes during the oddball presentation. The boxcar function represents sustained neuronal activity during the oddball presentation. c) Predicted hemodynamic response of a region associated with both the transient and sustained components of oddball processing. Note that the transient and sustained activities are summed up, yielding a sustained pattern of activity. The boxcar function represents the onset and offset activity, and also shows sustained activity between the onset and offset.

Experiment 1

Methods

Behavioral Experiments

Participants

Twelve adults (6 males, aged 18-24) participated for course credit or monetary compensation. The Vanderbilt Institutional Review Board approved the experimental protocol and written informed consent was obtained from each participant.

Design & Procedure

The task involved searching for targets (images of a dining room and a living room) in a rapid serial visual presentation (RSVP) of distractors (images of outdoor, indoor scenes, or buildings) presented at the center of the screen. Each image frame subtended 2º of visual angle, and lasted 125 ms. The RSVP lasted 18 seconds, consisting of forty images used with replacement (though no image was successively repeated). In each trial, participants detected and identified the targets in the RSVP by immediately pressing buttons assigned to each of the two targets.

There were a total of 120 trials, which were divided into three conditions: Long oddball-target (4 trials), Long oddball-no target (6), Search-target (110) conditions.

In the Long oddball-target and Long oddball-no target conditions, a temporally extended oddball was presented either 4 or 6 sec after the trial onset. The oddballs included ten, distinct 10-sec long movie clips. The oddball movies consisted of a car accident, an earthquake, fireworks, a building explosion, fast-moving roller coasters, overturning ships, moving toys, a remote-controlled vacuum cleaner, a dogfight of jet-fighters, and a laptop commercial. The movies were downloaded from the World Wide Web, and edited so that neither text, humans, nor animals were shown.

In the four Long oddball-target trials, a target was presented either at lag 2 or at lag 13 from the oddball offset. These trials served to demonstrate that attention was sustained on the oddball stimulus throughout its presentation duration. Given that there were only two pairs of Lag 2 and Lag 13 trials per subject, the effect of oddball presentation on target performance was assessed by applying non-parametric Cochran Q tests to each pair, separately. The remaining long oddball trials were identical to the Long oddball-target trials described above except that no target was presented after the oddball offset (Long oddball-no target trials).

In the remaining 110 trials which did not include any oddball stimulus, a variable number of targets (1, 2, or 3) were imbedded in the RSVP of distractors (Search-target condition). The first target (T1) was presented 2, 4, 6, 8, 10, or 14 sec after the onset of the trial. The second target (T2), when presented, followed the first target with a 4, 8, 10, or 12-second interval, while the third target (T3) was presented 15 sec after the trial onset.

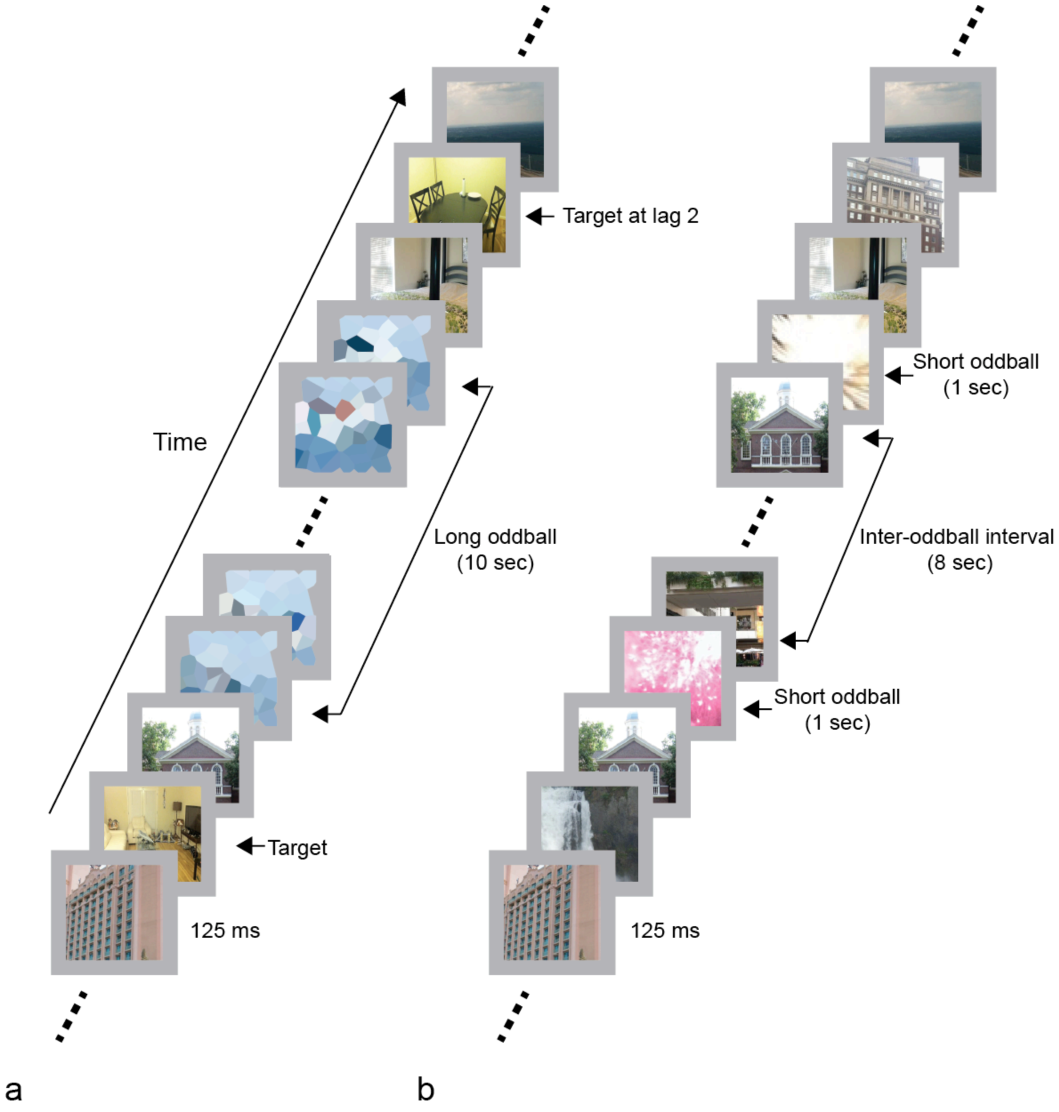

Figure 3. Examples of trials. The RSVP consisted of 40 images, each of which was presented for 125 ms. a) An example of a trial that contains the long oddball and targets (Long oddball-target trial). The target could be at lag 2 or lag 13 from the oddball offset. b) An example of a trial that contain two short oddballs separated by an 8-sec interval (Dual-short oddball trial, see fMRI Experiments). The Dual-short oddballs did not include targets. The trials containing short oddballs were included only in the fMRI experiment.

fMRI Experiment

Participants

Fourteen adults (5 males, aged 20-32) participated for monetary compensation. The Vanderbilt Institutional Review Board approved the experimental protocol and written informed consent was obtained from each participant.

Design & Procedure

A similar paradigm with the behavioral experiment was used except that there were a total of 180 trials, which were divided into six trial types; in addition to the same Long oddball-target (4 trials), Long oddball-no target (6), and Search-target (98) trials as in the behavioral testing, Dual-short oddball (6), Single-short oddball (6), and Search-no target (60) trials were included.

While the Long oddball-target trials served to replicate the findings of the behavioral experiment in the scanner, the Long oddball-no target trials were primarily used for fMRI analyses to examine the neural activity associated with the long oddball without contamination by target presentations or motor responses. In the trials containing the Long oddballs, the same set of oddball movies used in the behavioral testing were presented for ten participants, while the other four participants were shown another set of ten oddballs, composed of abstract animations (e.g. continuously transforming fractals or molecular polymerization) were used.

The six 'Dual-short oddball' trials included two 1-sec long oddballs (static abstract images) separated by an 8-sec interval, during which task-related stimuli (distractors) were presented. This Dual-short oddball condition was included to provide a reference for the hemodynamic response to be expected of a given brain region that responds to the onset and offset of the 10s-long oddballs but not to its sustained presentation.

Six other trials included a single presentation of a 1-sec long static abstract image as oddball (Single-short oddball condition). These trials served two purposes. First, they prevented the presence of a short oddball to predict the occurrence of a second one, thereby further ensuring that the second of the two oddballs in the Dual-short oddball trials (see above) was attention-grabbing. Second, they were used to define ROIs.

Finally, there were 60 trials in which neither oddball nor target was presented during the RSVP of distractors (Search-no target condition). This condition served to isolate the brain activity associated with goal-directed search without contamination by the target or motor responses.

fMRI methods

Anatomical 2D and 3D high-resolution T1-weighted images were acquired with conventional parameters on a 3T Philips scanner at the Vanderbilt University Institute of Imaging Sciences. For the functional scan, thirty-three 3.5 mm axial slices (0.5 mm skip; 3.75 x 3.75 mm in-plane) were taken parallel to the AC-PC line (TR, 2000 ms; TE, 35 ms; FA, 79^{o}; FOV, 240 mm), for a total of 191 brain volumes per fMRI run. There were 12 functional runs, each of which included 15 trials. Trials were separated by a blank interval of variable duration that follows an exponential distribution (9 trials x 4 sec, 4 trials x 8 sec, 2 trials x 12 sec) to facilitate deconvolution analysis of the BOLD responses (Serences, 2004). Imaging data were analyzed using Brain Voyager QX 2.3

and custom software written in MATLAB. Data preprocessing included slice scan time correction, 3D motion correction, linear trend removal, and spatial smoothing with a 6-mm Gaussian kernel (FWHM). All functional data of each participant were aligned to the first functional run, and co-registered to each individual's anatomical T1-weighted image. Functional and anatomical data were transformed into standardized Talairach space (Talairach & Tournoux, 1988).

To create statistical parametric maps (SPM) of BOLD activation, regressors were defined for each trial type and convolved with a double gamma function (SPM2, http://www.fil.ion.ucl.ac.uk/spm). Then, a group random effect contrast was run to isolate regions involved in oddball processing. Specifically, activity for the Single-short oddball trial was contrasted with activity for the Search-no target trial. The resulting SPM was corrected for multiple comparisons, using a cluster filter of 25 contiguous voxels, yielding a map-wise error rate of $p < .05$ (Forman et al., 1995). Each ROI was defined as the peak voxel and surrounding areas up to 1.33 cm^3 of the region (Dux et al., 2006).

Given that the group SPM contrast yielded significant activation only on the IFJ and TPJ, but none in other regions implicated in processing of salient stimuli, such as the AI, ACC, and amygdala (Blackford, Buckholtz, Avery, & Zald, 2010; Downar et al., 2002; Kiehl et al., 2005; Menon & Uddin, 2010; Seeley et al., 2007), I defined these regions individually for each participant. The AI and ACC were isolated from an SPM (q (FDR) < .05) created using a regressor detecting the target presentation. Each ROI was defined by the peak voxels and surrounding area up to 1.33 cm^3. This target regressor should be effective to localize not only the AI and ACC, but also the IFJ because they have been implicated in detecting infrequent, behaviorally relevant stimuli, and attentional control for target processing (Asplund, Todd, Snyder, & Marois, 2010; Corbetta et al., 2008; Downar et al., 2002; Eckert et al., 2009; Hampshire et al., 2010; Menon & Uddin, 2010; Seeley et al., 2007). The same regressor was also used to define the TPJ by associating negative beta weights with this region, given that the TPJ tends to be deactivated during goal-directed behaviors (Asplund, Todd, Snyder, & Marois, 2010; Greicius, Krasnow, Reiss, & Menon, 2003; Harrison et al., 2008; Raichle et al., 2001; Shulman et al., 2007; Todd et al., 2005). The group-defined and individually defined IFJs and TPJs yielded the same pattern of results. The amygdala was defined anatomically by manually tracing the border of the region, excluding the nearby structures (e.g. hippocampus and putamen). Given that only trials that contained neither long oddball nor dual-short oddball were included in the SPM analysis, the ROI selection is statistically independent from subsequent timecourse analyses.

In addition, regions included in the goal-directed attention network, frontal eye fields (FEF), and intraparietal sulcus (IPS) were also defined in the same was as the IFJ was defined.

For ROI analyses, event-related time courses of the BOLD signal for each participant and condition were estimated using a deconvolution anlaysis (using the 20 volumes immediately following the trial onsets). Then, the Beta estimates were averaged across participants, yielding group-averaged time courses. As no hemispheric difference was found (ps > .3), timecoures of bilateral ROIs were collapsed to increase statistical power (Asplund, Todd, Snyder, & Marois, 2010).

Given that oddball processing is carried out in the context of a goal-oriented behavior (target searching), to specifically isolate the brain response to the oddballs, we subtracted away any activity associated with the goal-directed search process. Specifically, the timecourse for search activity (Search-no target condition) was subtracted from the timecourse for the trials containing oddballs but no targets (Dual-short oddball) (Asplund, Todd, Snyder, & Marois, 2010). Even though it is presumed that there is no search-related activity during the extended oddball presentation, the same subtraction was also applied to the timecourse for the Long oddball-no target trial activity for consistency. Importantly, the subtraction did not change the temporal pattern (transient vs. sustained) of the Long oddball activity.

Once timecourses of the BOLD response to oddballs were constructed, I statistically assessed whether those responses were biphasic (transient) or monophasic (sustained) for the Dual-short oddball and Long oddball-no target trials. First, the peak volumes whose activities correspond to the onset and offset of the oddball were determined. The onset-related peak volume was defined as the volume with the greatest signal amplitude between the 3rd and 7th volumes immediately following the onset of the oddball (4-12 sec from the oddball onset) (Dux et al., 2006). The offset peak volume was also defined in a similar way except that the volumes following the offset of the oddball were used (14-22 sec from the oddball onset). The amplitudes of the onset and offset peak volumes were then compared with that of the volume corresponding to the middle point between those peaks, using paired t-tests. The middle point volume was determined by a volume whose volume number is the closest to the averaged volume number of the onset and offset peaks.

Results & Discussion

Behavioral Experiments

The results of the first behavioral experiment (n=12) are shown in Figure 4. Accuracy for the first (T1), second (T2), and third (T3) targets in the trials that contained no oddball (Search-target trials, see Methods) was comparable (p's > .3), suggesting that attention was constantly maintained throughout the RSVP. Importantly, when the target was at lag 2 from the oddball (the first Lag 2 trial), target accuracy was worse than when the target was at lag 13 (the first Lag 13 trial), suggesting that attention was sustained on the oddball, Q(1) = 6, p < .05 (Fig. 4a). One alternative interpretation to this result is that it is the transition between the oddball offset and RSVP task that impaired target processing rather than sustained attention to the oddball. This possibility could be ruled out because no such deficit was found when participants encountered the second pair of Lag 2 and Lag 13 trials, p > .56. This is presumably because participants became familiar with the instance that a target follows the oddball offset at lag 2.

To further confirm that the behavioral deficit was due to sustained attention on the oddball rather than its offset-transients, we ran a second behavioral experiment (n= 13) in which the same long oddball was repeatedly presented (10 times). Because its content became rapidly familiar to the participants, the repeated oddball should not sustain much of the participants' attention throughout its presentation, thereby leading to equivalent performance for Lag 2 and Lag 13 trials. By contrast, if the Lag 2 deficit in Experiment 1 was due to the perceptual/cognitive transition between the oddball and the RSVP, the Lag 2 deficit should still be as robust because that transition is still present in Experiment 2. Consistent with the former hypothesis, target accuracy was now similar for the Lag 2 and

Lag 13 trials, ps > .3 (Fig. 4b). Taken together, the results of these two behavioral experiments indicate that the presentation of oddball video clips engages the participants' attention throughout their 10 seconds duration.

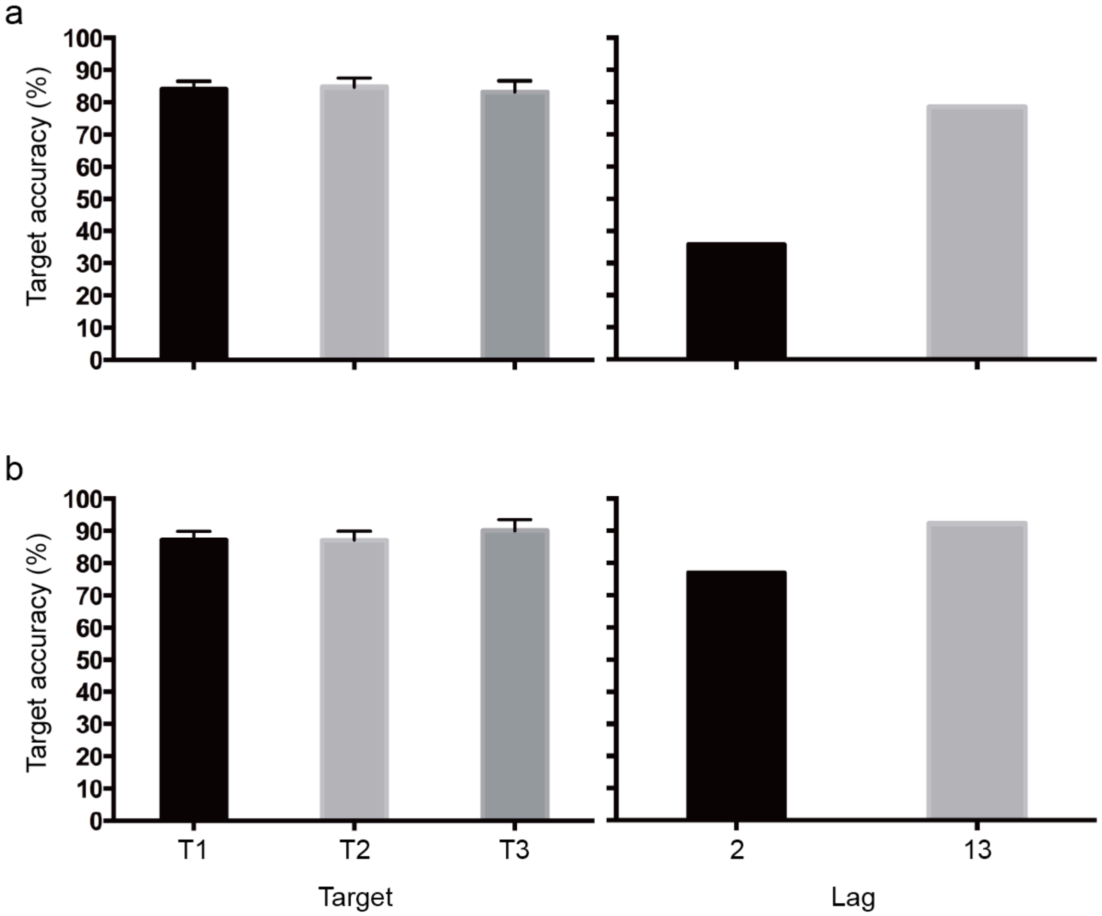

Figure 4. Results of behavioral experiments. Left, target accuracy in trials that contains no oddball. In a trial, there could be up to three targets distributed throughout the entire RSVP stream. Right, target accuracy of the first Lag 2 and Lag 13 trial, in each of which the target was at lag 2 and at lag 13 from the oddball, respectively. a) Results of the behavioral experiment with distinct oddballs. b) Results of the behavioral experiment with repeated presentation of a single oddball. T1 – the first target, T2 – the second target, T3 – the third target. Error bars represent standard errors of the mean.

fMRI Experiment

The fMRI experiment (n = 14) used a similar paradigm to the first behavioral experiment except that the Single-short, Dual-short oddball, and Search-no target trials were added (see Methods). Behavioral data acquired during the scans were very similar to those acquired outside the scanner; target accuracy in the Long oddball-target condition for the Lag 2 trials was worse than that for the Lag 13 trials, $Q(1) = 8$, $p < .005$. Moreover, such a difference was also found with the second pair of Lag 2 and Lag 13 trials $Q(1) = 4.50$, $p < .05$, unlike in the behavioral experiments. This is presumably because the fMRI experiment included more goal-directed search trials and short oddballs, increasing the relative salience of the long oddballs.

To examine the response of the core components of the stimulus-driven attention network to the presentation of oddballs, the AI, IFJ, and TPJ were functionally localized, and timecourses of activities to the oddballs were extracted from these ROIs (see fMRI methods and Table 1). In addition to these regions, anterior cingulate cortex (ACC) was also probed because this region has been suggested to form a ‘Salience network’ with the AI, implicated in processing of salient stimuli (Menon & Uddin, 2010; Seeley et al., 2007).

Table 1. List of ROIs in Experiment 1. The group-defined ROIs were isolated from the SPMs contrasting the Single-short oddball activity with the search activity, while the individually defined ROIs were isolated from each individual participant's SPM detecting activity associated with the onset of target. The group-defined and individually defined ROIs showed the same pattern of results.

Single-short oddball - Search-no target (group-defined ROI)

		Talairach Coordinates		
ROI name	Mean t Value	X	Y	Z
Left inferior frontal junction (IFJ)	3.17	-49	19	18
Right inferior frontal junction	3.13	45	14	19
Left temporo-parietal junction (TPJ)	3.05	-55	-46	13
Right temporo-parietal junction	3.04	49	-54	17

Open contrast of target presentation (individually defined ROI)

		Talairach Coordinates		
ROI name	Mean t Value	X	Y	Z
Left anterior insula (AI)	6.11	-30	15	3
Right anterior insula	4.87	32	13	2
Anterior cingulate cortex (ACC)	3.86	4	15	36
Left inferior frontal junction	3.23	-45	3	22
Right inferior frontal junction	5.16	44	5	26
Left temporo-parietal junction	-11.35	-48	-63	22
Right temporo-parietal junction	-9.25	48	-59	22
Left frontal eye field (FEF)	4.40	-27	-7	45
Right frontal eye field	4.32	32	-2	47
Left intraparietal sulcus (IPS)	4.71	-31	-58	43
Right intraparietal sulcus	4.56	31	-58	43

As shown in Figure 5, the IFJ and TPJ showed a sustained (monophasic) pattern of activity throughout the presentation of the long oddball. These sustained activities were not due to the sluggishness of the hemodynamic responses in these regions as transient patterns of activities were clearly observed in the Dual-short oddball trial. Specifically, the peak amplitudes related to each short oddball were significantly greater than the amplitudes of activities at the middle point between the two peaks for both regions, t’s(13) > 3.29, p’s < .005. Furthermore, there was no significant activity at the middle point, p > .18.

In stark contrast, the activities to the long oddball in the AI and ACC showed two separate peaks of the BOLD response, each corresponding to the onset and offset of the oddball. To statistically assess these bi-phasic patterns of activity, the amplitudes at the peak volumes related to the oddball onset and offset were compared with that at the middle point between those peaks (see Methods). The amplitude at the onset peak was greater than that at the middle point for both regions, t’s(13) > 4.71, p’s < 4.10 x 10^{-4}, as was the offset peak amplitude, t’s(13) > 5.94, p’s < . 4.87 x 10^{-5}. Moreover, the signal amplitude at the middle point was not significantly different from zero, p’s > .2, whereas the IFJ and TPJ showed robust activities, p’s < 9.46 x 10^{-4}. As expected, the AI and ACC also showed bimodal patterns of activity in the Dual-short oddball condition, that is, activities to the onsets of the first and second peaks were significantly greater than to the middle point, p’s < .008.

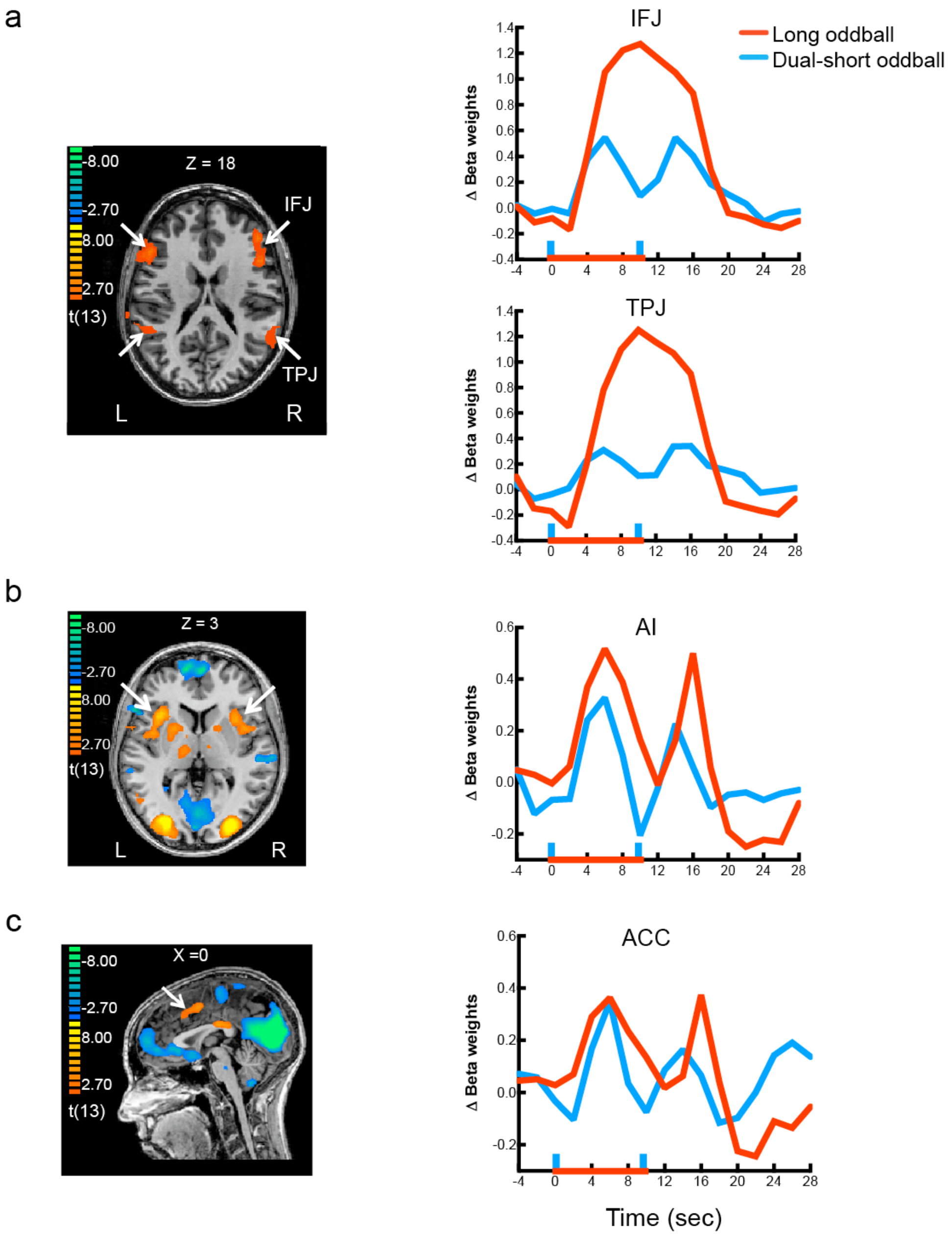

Figure 5. Results of the first fMRI experiment with distinct oddballs. a) SPM showing inferior frontal junction (IFJ) and temporo-parietal junction (TPJ), and timecourses of activity. B) SPM showing anterior insula (AI) and timecourses of activity. c) SPM showing anterior cingulate cortex (ACC) and timecourses of activity. All the SPMs were thresholded at the level of q(FDR) < .05. Each timecourse was constructed by subtracting the timecourse for goal-directed search (Search-no target trial) from the timecourse for trials containing oddballs (Long oddball-no target and Dual-short oddball trials). The first and second blue vertical bars (at time point zero and nine) in the timecourses indicate the first and second short oddballs which lasted 1 second in the Dual-short oddball condition. The red horizontal line indicates the presentation of 10-sec long oddballs.

Further analyses of transient activity in the AI and CC

While the transient activity patterns in the AI and ACC are dramatically different from those in the TPJ and IFJ, this finding rests on the assumption that this activity pattern truly reflects the underlying state of neuronal activity rather than being an artifact of the intrinsic, hemodynamic properties of these brain regions. Specifically, it is possible that the BOLD responses in AI and ACC are due to the rapidly adapting hemodynamic properties of these brain regions even under sustained neural activity. To test this possibility, I assessed whether this region can show a sustained BOLD response under conditions in which such response should be obtained. Specifically, capitalizing on the observation that the AI and ACC responds to targets (Downar et al., 2002; Eckert et al., 2009; Hampshire et al., 2010; Menon & Uddin, 2010; Seeley et al., 2007), simulations of the BOLD response (assuming canonical properties) suggest that this response should show a summated and sustained response when pairs of targets are presented at 4 sec interval, whereas they should show a clearly biphasic BOLD response when two targets are presented 8 seconds apart (see Fig. 6). Consistent with this prediction, analysis of the AI and ACC timecourses in trials containing two targets t showed a single, sustained monophasic response with the 4-sec interval but a biphasic response with the 8-sec interval. These results indicate that the AI can show a sustained BOLD response under conditions in which it is expected to do so, thereby ruling out the possibility that the transient activity obtained with the long oddball was the result of the rapidly adapting hemodynamic (but not neurophysiological) properties of this brain region.

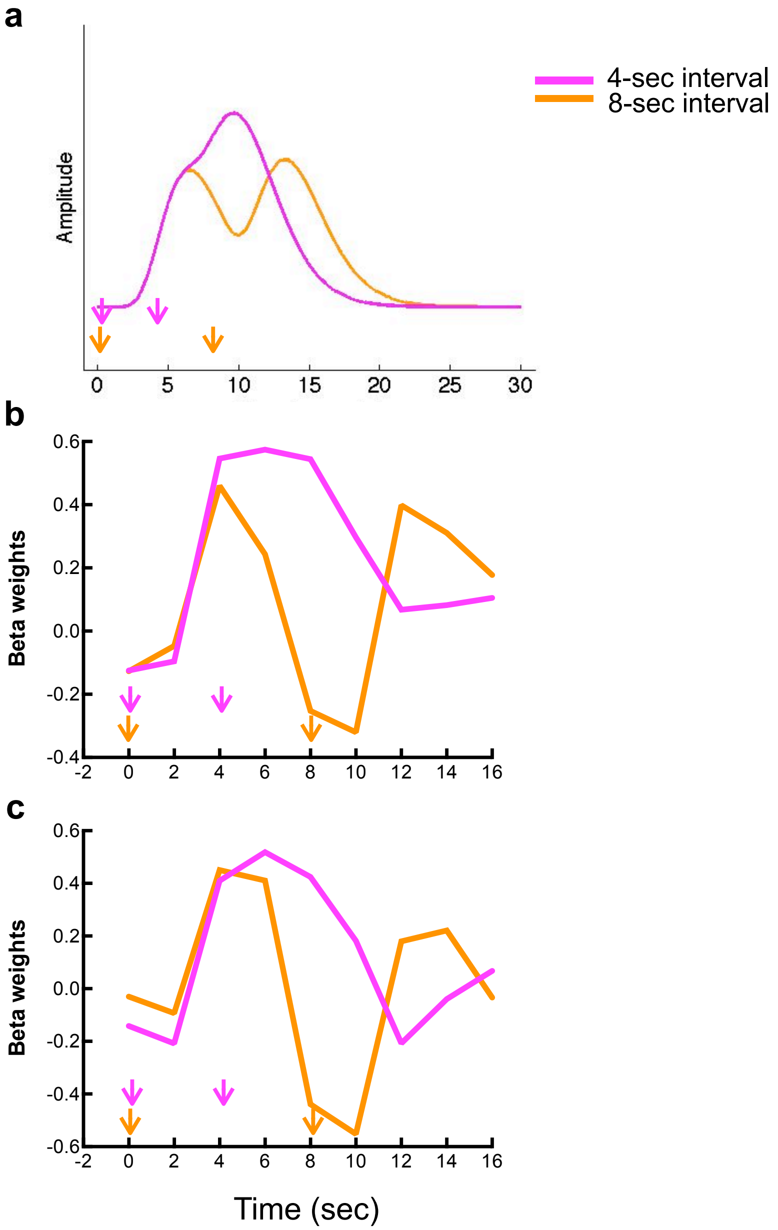

Figure 6. a) Modeled hemodynamic responses to targets separated either by a 4-sec or an 8-sec interval. b and c) Timecourses of activation of the AI (b) and ACC (c) with target presentations. The magenta and yellow arrows indicate the first and second targets when they were separated by a 4-sec and 8-sec interval, respectively. With the 8-sec inter-target interval, the signal amplitude dropped from the 3rd to 4th volume in the AI, while it dropped from the 4th and 5th volume in the ACC, p's < .01, whereas the signal persisted during the same period of time when targets were separated by 4 seconds, p's >.66.

Taken together, the above findings suggest a functional dissociation between core components of the stimulus-driven attention network following the presentation of a temporally extended oddball, with the AI's (and ACC's) transient activity at oddball onsets and offsets implicating it in attention orienting, and the IFJ's and TPJ's sustained activity associating them with the evaluative process.

Further analyses of sustained activity in the TPJ and IFJ.

An alternative interpretation for the TPJ's – and perhaps also IFJ's – sustained responses with the extended oddballs is that it reflects its known involvement in social attribution and mentalization (Frith & Frith, 2006; Hampton et al., 2008). That is to say, given that several of the oddball movie clips included human-based, real-world situations (e.g. aerial combat of fighter jets), participants may have engaged in inferring the mental states of the human agents that controlled the objects or events even if the agents were not visible in the movie clips. To address this issue, I separately analyzed the data from the four participants who were only exposed to non-meaningful abstract animations that were devoid of socio-affective content. These four participants (Fig. 7) still showed robust sustained activity in the TPJ and IFJ, suggesting that this activity is not caused by social evaluative or mentalizing processes.

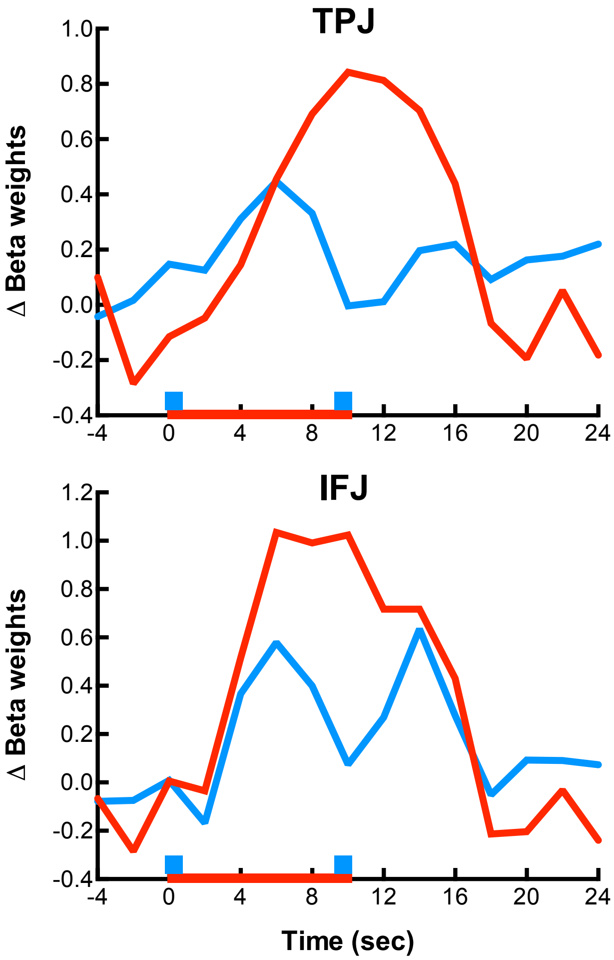

Figure 7. Activation timecourses of the TPJ and IFJ when the oddballs were abstract animations (n = 4). The first and second blue vertical bars (at time point zero and nine seconds) in the timecourses indicate the first and second short (1s) oddballs in the Dual-short oddball condition. Each timecourse was constructed by subtracting the timecourse for goal-directed search (Search-no target trial) from the timecourse for trials containing oddballs. The red horizontal line indicates the presentation of 10-sec long oddballs.

I also considered the possibility that the increased TPJ activity during the long oddball presentations simply reflected the release of suppression that is usually present in this region during goal-directed behavior (Greicius et al., 2003; Harrison et al., 2008; Raichle et al., 2001; Shulman et al., 2007; Todd et al., 2005) (No such suppression is present during goal-oriented behavior in IFJ; see e.g. Apslund, Todd, Snyder, & Marois., 2010 and Fig. 9 below). That is to say, because there was no goal-directed behavior during the long oddball presentations, the TPJ might have entered into a ‘default mode’ or resting state (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Greicius et al., 2003; Harrison et al., 2008; Raichle et al., 2001), thereby elevating its activity compared to search-related activity. This release from suppression could then be erroneously construed as activation in response to the oddball stimulus. To address this issue, I compared brain activity during long oddball presentations with that during the 12-sec inter-trial fixation periods. If the sustained TPJ activity to the oddball simply reflects a release from suppression, the activity of this region during the oddball presentation should be similar to that during the inter-trial fixation interval, as there is also no goal-directed behavior during that period. As shown in Figure 8, the TPJ activity during the long oddball presentation was far greater than that during the fixation period (12-sec inter-trial interval), $t(13) = 4.00$, $p = .0015$ (paired t-test between volumes with the greatest signal amplitude). This finding suggests that the sustained TPJ activity during the long oddball presentation does not simply reflect a release from suppression, but rather genuine activation associated with processing of the oddball stimuli.

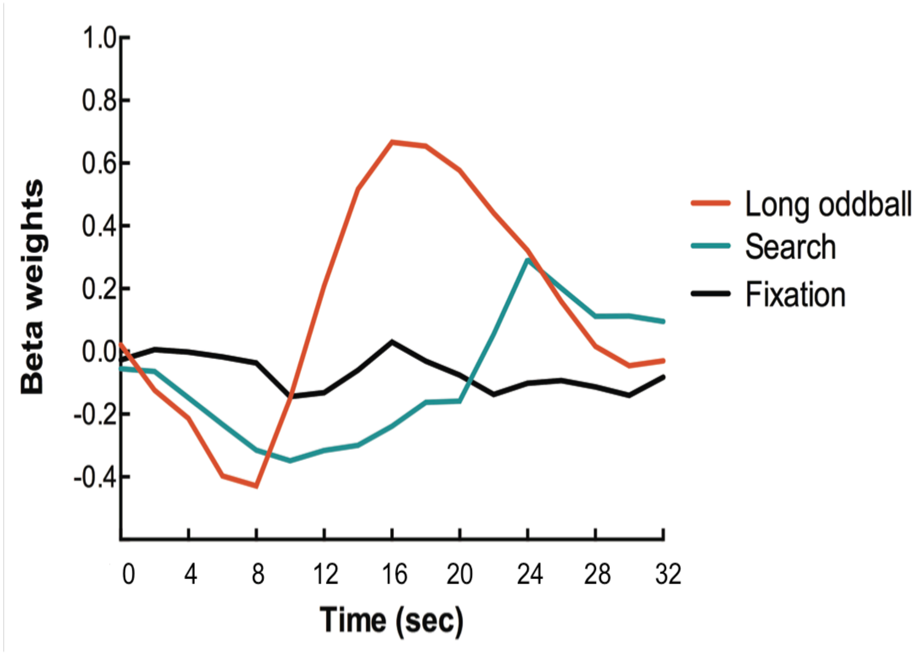

Figure 8. Timecourses of the TPJ activity in the Search-no target and Long oddball-no target conditions, and during the 12-sec fixation period. The onset of a trial or inter-trial interval (fixation period) is at time zero. The Search-no target timecourse was not subtracted from the Long oddball-no target timecourse, confirming that TPJ activity to the oddball (Figure 5) is not a byproduct of subtracting the search activity (which is suppressed relative to fixation baseline).

Another alternative interpretation for the TPJ's and IFJ's sustained activity is that it reflects attention to the stimulus event *per se*, rather than its evaluation. After all, evaluation of the temporally extended oddball likely requires that attention be maintained onto the stimulus, which complicates distinguishing the evaluative process from sustained attention. However, and as discussed above, it is well established that the TPJ is typically deactivated under sustained goal-directed attention (Greicius et al., 2003; Harrison et al., 2008; Raichle et al., 2001; Todd et al., 2005), a finding that is inconsistent with the present result of increased activity with long oddball presentations. Along the same vein, the sustained IFJ activity with long oddballs is also quite distinct from its typical response under sustained attention; its activity is typically only transient when attentional sets are sustained (Braver, Reynolds, & Donaldson, 2003; Chiu & Yantis, 2009; Konishi et al., 1998)

To directly test if the activation of the IFJ and TPJ with long oddballs can be solely explained by sustained attention, these regions were probed with data obtained from an experiment in which sustained attention was not confounded by the evaluative process (Asplund et al., in preparation). The task essentially consisted of a Posner endogenous cuing task with variable delays (1, 5, 9, or 13 sec) of sustained attention between the central cue presentation and peripheral target presentation (Fig. 9a). Such variable delays should facilitate the temporal isolation of the BOLD response associated with sustained attention from any cue- or target-related processes. As there is no evaluative process going on during that delay, any evidence of sustained activation would suggest that these two regions have a general role in attention *per se* rather than in evaluation specifically. Contrary to this prediction, the results of the cuing experiment showed that the TPJ is deactivated during sustained attention, while the IFJ is transiently activated by the onsets of the cue and target (Figure 9). These results corroborate the notion that sustained attention by itself cannot account for the sustained IFJ and TPJ activation with the long oddball presentations, bolstering the claim for their involvement in the evaluative process.

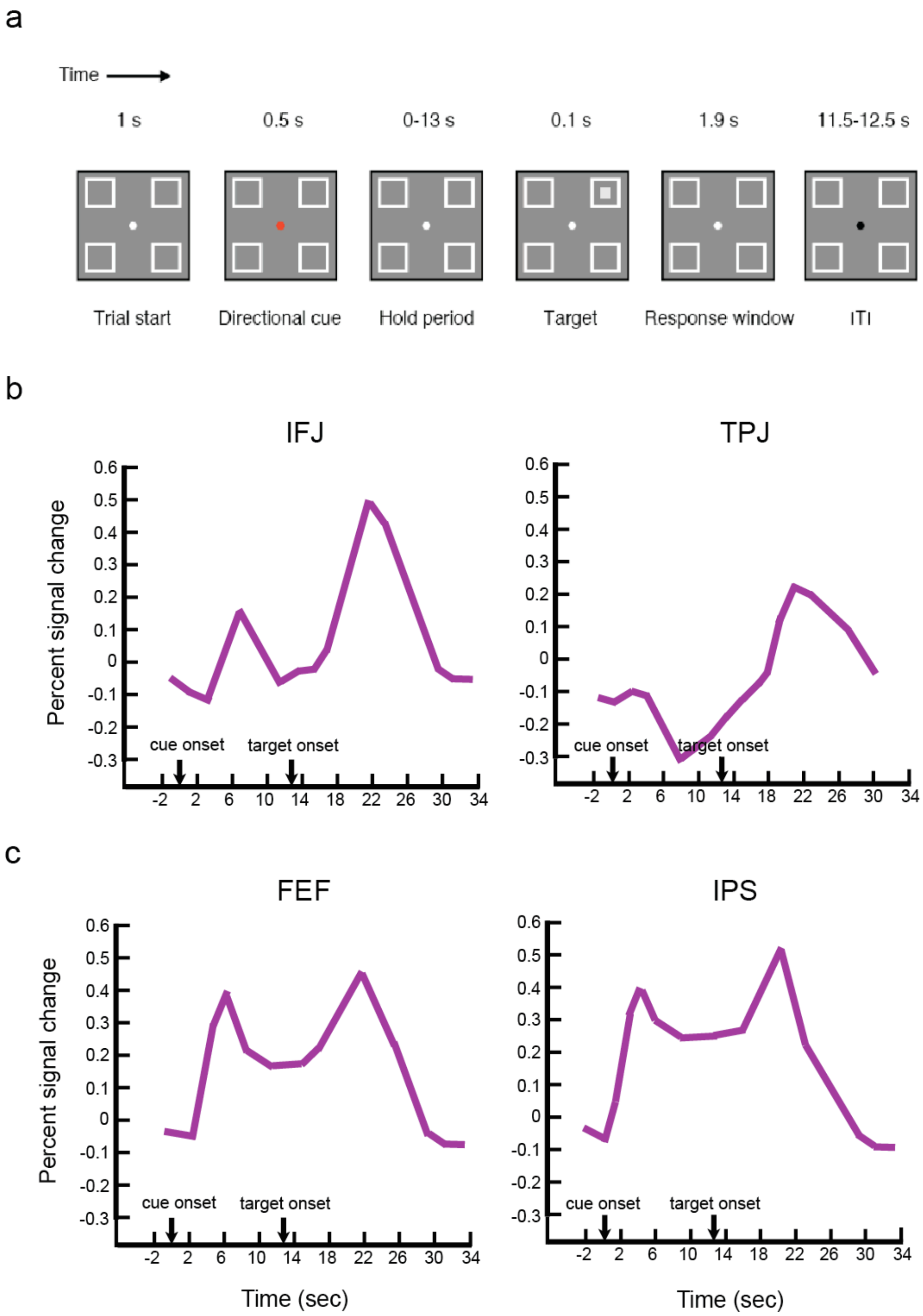

Figure 9. a) Trial design of a Posner cuing task in which the color of the central cue instructed subject to attend covertly to one of 4 peripheral boxes for target presentation after a variable delay. Activation timecourses of the IFJ and TPJ (b) and FEF and IPS (c) (Asplund et al., in preparation). The attentional cue was presented at the time of zero, while the target followed the cue with variable durations of delays. For simplicity, the results for 13-sec delay trials are plotted. There was no significant activity associated with the delay period for the IFJ and TPJ, whereas the FEF and IPS showed significant sustained activation.

Goal-directed attention network activation

In addition to the regions of the stimulus-driven attention and salience networks, core components of the goal-directed attention network – the FEF and IPS – were also examined (Table 1 and Figure 10) for their response profiles with oddball presentations. Given the behavioral evidence that the oddballs are attended throughout their presentation duration (see above), I predicted that presentation of the long oddballs would be associated with sustained activity in these dorsal regions. Consistent with this prediction, probing of the FEF and IPS showed sustained activity throughout the presentation duration of the long oddball stimuli, but bi-phasic activity following the presentation of the dual-short oddballs, p's < .05.

So far, the dorsal attention regions have the same activation profile as the IFJ and TPJ. However, they are dissociable from these lateral brain regions during the goal-directed sustained attention task described above (Asplund et al., in preparation). Specifically, and unlike the IFJ and TPJ, the IPS and FEF showed robust sustained activity during the delay period (see Fig. 9c). These results support the evidence that the IFJ and TPJ are involved in evaluating the oddball, whereas the IPS and FEF may be supporting the sustained attention to the oddballs.

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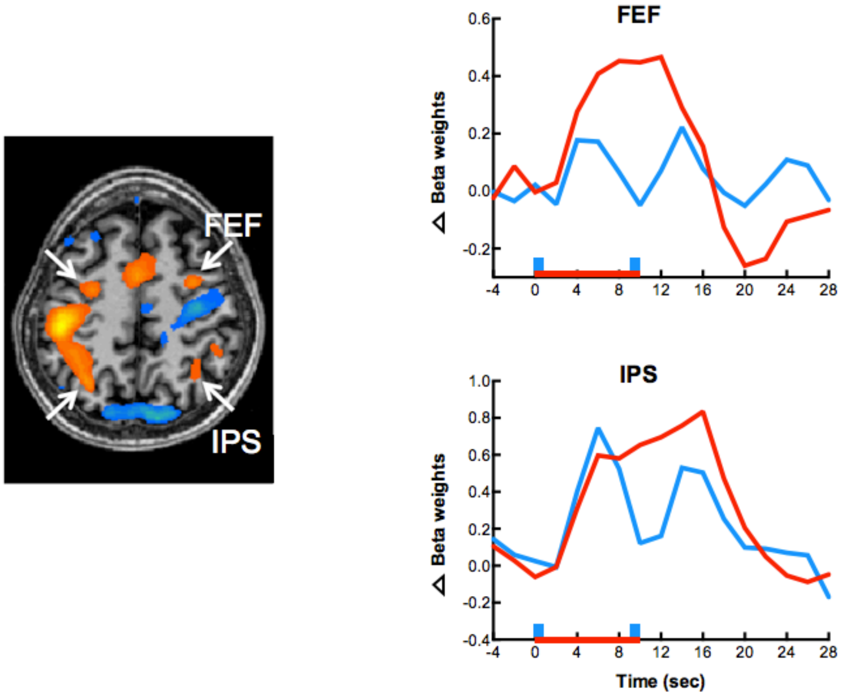

Figure 10. SPM (left) showing the frontal eye fields (FEF) and intraparietal sulcus (IPS), and timecourses (right) of each region. The SPM was created using the target regressor and thresholded at the level of q(FDR) < .05 (see Methods). Each timecourse was constructed by subtracting the timecourse for goal-directed search (Search-no target trial) from the timecourse for trials containing oddballs. The first and second blue vertical bars (at time point zero and nine) in the timecourses indicate the first and second short (1s) oddballs in the Dual-short oddball condition. The red horizontal line indicates the presentation of 10-sec long oddballs.

Experiment 2

Experiment 1 could successfully distinguish brain regions showing transient activity from those exhibiting sustained activity. However it does not reveal whether the latter brain regions show only sustained activity or both transient and sustained activity. This is because any transient activity would be swamped by the large sustained activity (Fig. 1c), thereby concealing the involvement of the brain region(s) in orienting/reorienting. To determine whether the IFJ and TPJ responded to the transient phases of the long oddball presentations in addition to responding to the sustained phase, Experiment 2 aimed at unmasking any transient BOLD response by using a manipulation that specifically attenuates the sustained activity. This can be achieved by repeatedly presenting the same long oddball throughout the experimental session, as such repeated presentation attenuates the requirement for a sustained attention-based evaluative process as the contents of the oddball become familiar with repeated iterations (see Fig. 4). However, given that this oddball still appears infrequently and non-predictively, attention should still be briefly captured by the onset of the oddballs. The offset should also capture attention because it is a behaviorally significant event, indicating the resumption of goal-directed search process. Hence, if the IFJ and TPJ are engaged by these transitory phases of oddball presentations, they should now be manifest.

Methods

Participants

Six adults (four males, aged 19-35) participated for monetary compensation. The Vanderbilt Institutional Review Board approved the experimental protocol and written informed consent was obtained from each participant.

Design & Procedure

All the behavioral and imaging protocols were identical to those of Experiment 1 except for the following modifications. The same long oddball was presented 20 times out of a total of 135 trials. Among these 20 oddball trials, there were ten Long oddball-no stimulus trials, in which a fixation period followed the offset of oddballs (see below). The remaining oddball trials were either Long oddball-no target trials (8 trials) or Long oddball-target trials (2). In the Long oddball-target trials, a target was presented at either Lag 2 or Lag 13 from the oddball offset. There were neither Single-short nor Dual-short oddballs in this experiment. The experiment did include, however, Search-target (65 trials) and Search-no target conditions (50 trials). Definition of ROIs for each individual participant, extraction of timecourse from ROIs, and statistical assessment of the pattern of activity were performed in the same way as in Experiment 1.

Participants could expect whether an oddball would be followed by the search task or by no task at all because in the first half of oddball trials, the oddballs were followed by the search task, whereas in the second half the oddballs were followed by a fixation period (4 sec – 12 sec) or vice versa (counterbalanced order across participants). This Long oddball-no stimulus condition was introduced to examine whether the oddball onset/offset activity is signaling any changes in environmental conditions (as would be expected at the offset of an oddball followed by a fixation period) or a change that is behaviorally relevant (as would be expected at the transitions between oddballs and the search task).

fMRI methods

The imaging parameters and preprocessing procedures were identical to those of Experiment 1. ROIs were defined for each individual participant in the same way as Experiment 1. Specifically, an SPM (q (FDR) < .05) was created using a regressor detecting the target presentation. Then, positive beta weights were associated with the AI, ACC, IFJ, FEF, and IPS, whereas negative beta weights were associated with the TPJ. The amygdala was defined anatomically by manually tracing the border of the region. The locations of ROIs are shown in Table 2.

Table 2. List of ROIs in Experiment 2. The ROIs were isolated for each participant from an SPM detecting activity associated with target presentation, similar with Experiment 1. Each ROI included the peak voxel and surrounding area up to 1.33 cm^3 of the activated region.

		Mean Talairach Coordinates		
ROI name	Mean t Value	X	Y	Z
Left anterior insula (AI)	5.85	-34	22	-4
Right anterior insula	7.27	30	23	0
Anterior cingulate cortex (ACC)	7.42	-4	14	41
Left inferior frontal junction (IFJ)	6.17	-42	2	31
Right inferior frontal junction	9.78	37	9	29
Left temporo-parietal junction (TPJ)	-5.34	-49	-57	22
Right temporo-parietal junction	-3.00	42	-57	30
Left frontal eye field (FEF)	5.33	-34	-7	55
Right frontal eye field	6.66	34	5	48
Left intraparietal sulcus (IPS)	6.32	-29	-63	40
Right intraparietal sulcus	12.73	25	-64	40

Results and Discussion

The results of Experiment 2 are shown in Figure 11. For comparison, activities of individually defined ROIs to distinct oddballs from Experiment 1 are also plotted. For both data sets, the oddball presentation was followed by task-related stimuli. Consistent with Experiment 1, the AI and ACC showed biphasic patterns of activations. That is, the amplitudes at onset and offset peak volumes were greater than that at the middle point volume, ps < .05. This result is consistent with Experiment 1: indeed, two-way ANOVAs with Time (from the oddball onset to 22 sec after the onset,) as a within-subject factor and Experiment (Experiments 1 & 2) as a between-subject factor revealed main effects of Time for both regions, p's < .005, but neither main effect of Experiment nor interaction, ps > .74. The TPJ activity was also similar with that of Experiment 1; it showed a monophasic response, although with markedly reduced amplitude and duration, p's < .005.

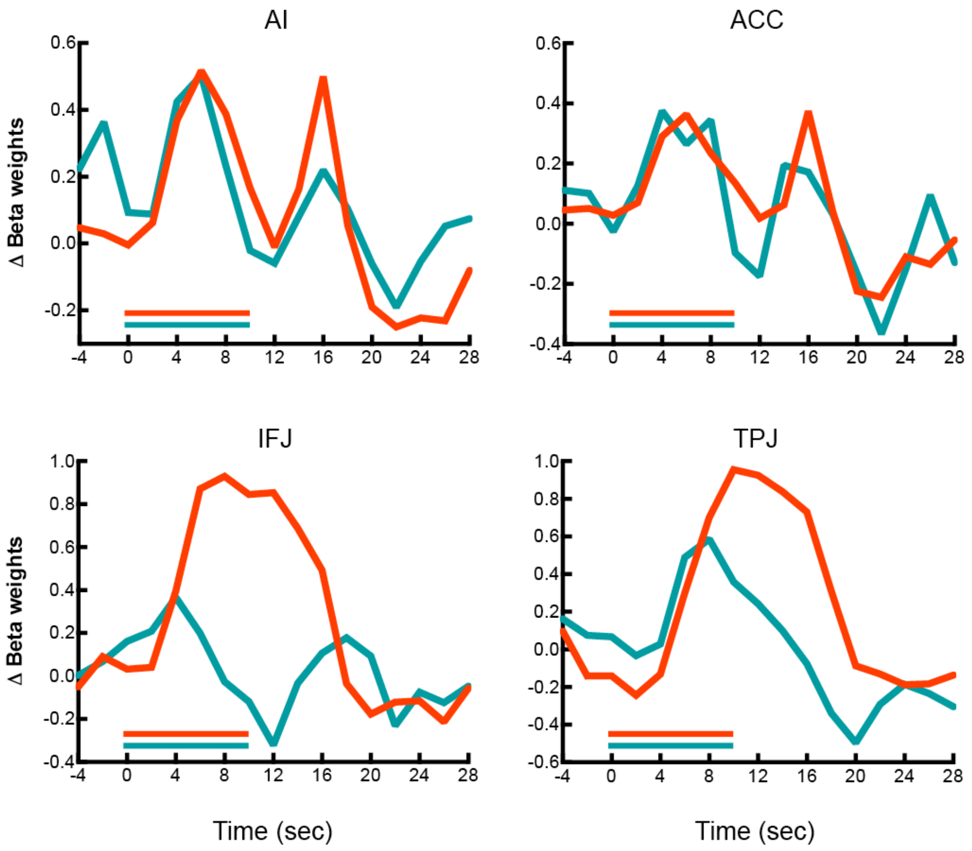

Figure 11. BOLD activity timceourses of the AI, ACC, IFJ, and TPJ to repeated presentation of the same oddball. For comparison, timecourses of activity to unrepeated,

distinct oddballs are also plotted. Each timecourse was constructed by subtracting the timecourse for goal-directed search (Search-no target trial) from the timecourse for trials containing oddballs. The horizontal lines in the timecourses indicate 10-sec long presentations of distinct (red) or the same (green) oddballs.

By contrast, the IFJ, which showed a sustained response to the presentations of distinct oddballs, now exhibited a biphasic response with the repeated presentation of the same oddball; the onset ($t(5) = 2.90$, $p < .05$) and offset ($t(5) = 2.84$, $p < .05$) peak amplitudes were greater than that at the middle point, which showed no significant activity above baseline, $p > .25$. This modulation of IFJ activity by repeated oddball presentations was further confirmed by the ANOVA across Experiments 1 and 2; there was an interaction between Time and Experiment, $F(10, 180) = 6.10$, $p < 5.64 \times 10^{-8}$, with a main effect of Time, $F(10, 180) = 7.00$, $p < 3.03 \times 10^{-9}$, and a marginal effect of Experiment, $p = .063$, while no such interaction was found in the AI and ACC activation, p's > .74. Furthermore, a 3-way ANOVA with Time and Region (AI, ACC, IFJ, and TPJ) as within subject factors and Experiment as a between subject factor yielded a significant 3-way interaction $F(30, 540) = 3.19$, $p < 6.05 \times 10^{-8}$, confirming differential patterns of activity to oddballs across regions.

Data from the dorsal attention regions were also analyzed in the same way as above. As shown in Figure 12, the FEF and IPS activities were significantly reduced, compared to when the oddball was not repeated; all these regions showed significant main effects of Experiment, Time, and Interactions, all p's < .05.

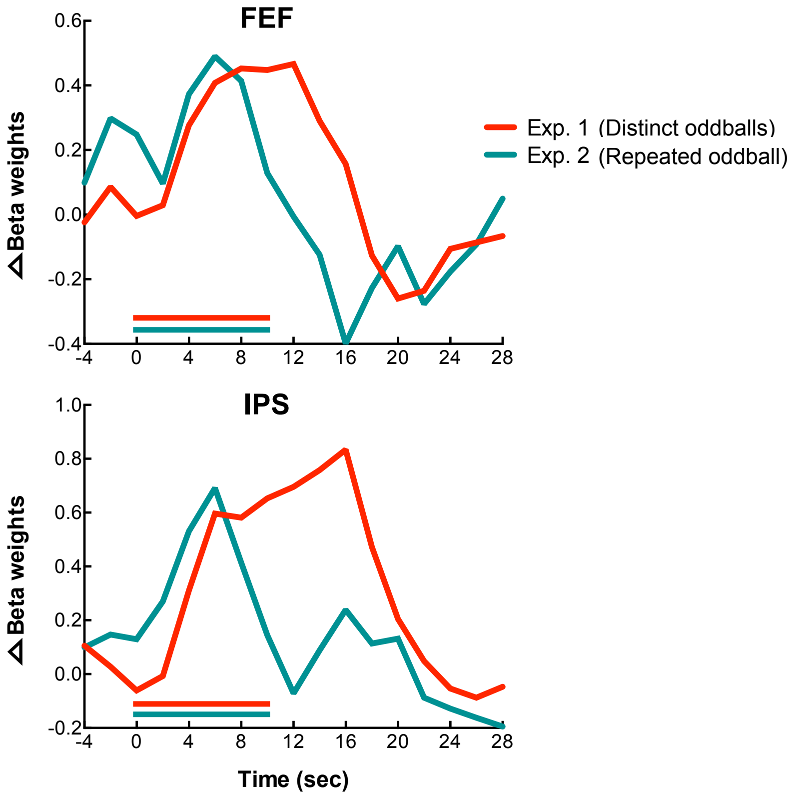

Figure 12. Activity to the distinct oddballs (Exp. 1) and the repeated oddball (Exp. 2) in the FEF and IPS. Each timecourse was constructed by subtracting the timecourse for goal-directed search (Search-no target trial) from the timecourse for trials containing oddballs. Without subtraction, the FEF and IPS showed robust activities to the offset of the oddball (data now shown). The horizontal lines in the timecourses indicate 10-sec long presentations of distinct (red) and (green) repeated oddballs.

With repetition of the same oddball, the demand for sustained evaluation of the stimulus was greatly diminished, and this was reflected in reduced and shortened TPJ activity (although this activity was not altogether eliminated, most likely owing to the need to evaluate the unexpected presentation of the oddball at its onset). Similarly, sustained attention to the oddball should be diminished, as reflected by reduced activation in the goal-directed attention network. Most importantly, diminished processing demand of the repeated oddball in Experiment 2 unmasked onset- and offset- related responses in the IFJ that were swamped by the sustained activation in Experiment 1. This finding implies that the IFJ is associated with both the transient and sustained components of oddball processing. By contrast, the AI and ACC activities were immune to the demand for sustained oddball processing, further confirming these regions' primary involvement in the transient processes evoked by salient sensory events.

Activations to the transition between oddballs and rest (fixation).

I also examined whether the oddball related activity would be influenced by changes in behavioral relevance at the oddball offset. Specifically, this stimulus condition allowed me to assess whether the oddball onset/offset activity is signaling any changes in environmental conditions (as would be expected at the offset of an oddball followed by a fixation period) or a change that is (potentially) behaviorally relevant (as would be expected at the offset of an oddball followed by the search task).

Activities to the Long oddball-no stimulus trials are shown in Figure 13. The results were generally similar with the results of trials in which the oddballs were followed by the search task (Fig. 11), with a monophasic response in TPJ but a bi-phasic one in IFJ, showing greater activities to the onset and offset of the oddball than to the middle point, p's < .05. Notably, contrary to the AI still showing a clear bi-phasic response, p's <.05, the ACC now displayed a monophasic response. This result suggests that whereas the AI may signal any changes in environmental homeostasis, the ACC may instead signal a change from or to a behaviorally relevant state. The potential dissociation between ACC and AI will be further addressed in Chapter IV. Finally, the FEF and IPS activation was not significantly above search-related activity; the peak amplitudes of oddball activities from which the search activity was subtracted were not significantly above zero, p's > .20 – likely reflecting the minimal demand for evaluating the repeatedly presented oddball – although it dropped precipitously when the trial was completed with the appearance of the fixation (Fig. 13).

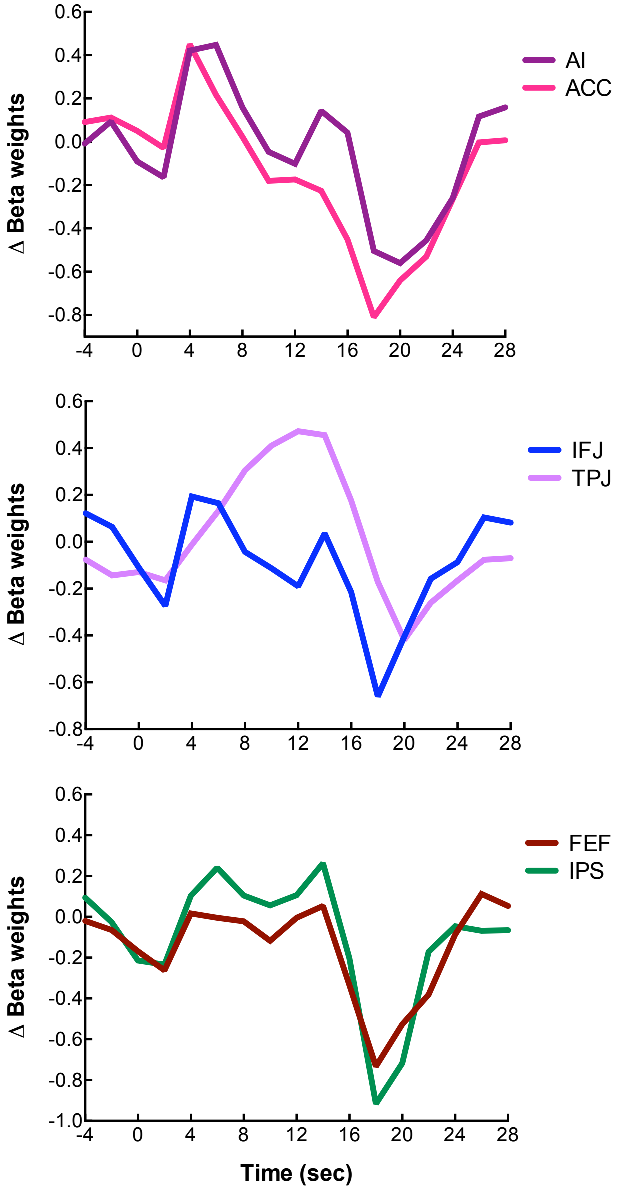

Figure 13. Activity to the repeated oddball followed by fixation. The offset of the oddball indicated the termination of that trial. Each timecourse was constructed by subtracting the timecourse for goal-directed search (Search-no target trial) from the timecourse for trials containing oddballs.

Amygdala activation to distinct oddballs and repeated oddball

While the amygdala is typically associated with emotion processing (Adolphs et al., 2005; Adolphs, Tranel, Damasio, & Damasio, 1994; Phelps & LeDoux, 2005), there is some evidence to suggest that it may be involved in processing of novel, salient stimuli as well (Balderston, Schultz, & Helmstetter, 2011; Blackford et al., 2010; Kiehl et al., 2005;Rutishauser, Mamelak, & Schuman, 2006; Weierich, Wright, Negreira, Dickerson, & Barrett, 2010; Wright et al., 2003). Moreover, when this brain region has been implicated in detecting novel stimuli, it is usually considered to reflect the arousal state evoked by the novel stimulus rather than cognitive evaluation of that stimulus (Kensinger & Schacter, 2006; Lewis, Critchley, Rotshtein, & Dolan, 2007). Given these prior findings, I have also examined the amygdala's response to the long oddballs, with the prediction that amygdala activation might be immune to the demands for cognitive evaluation of the stimuli.

The amygdala was defined anatomically in each individual participant for both fMRI experiments because none of the SPM analyses showed significant activation in the amygdala, Similar to the TPJ, the amygdala showed a monophasic pattern of response to the long oddball, $p < .05$ (paired t-test comparing the peak amplitude with zero). However, whereas the TPJ activity was strongly attenuated when the same oddball was repeatedly presented (see above), no such modulation of activity was found in the amygdala, p's > .9 (Fig. 14). A 3-way ANOVA with Region (Amygdala & TPJ) and Time as a within subject factor and Experiment as a between subject factor yielded a significant 3-way interaction, $F(10, 180) = p < 5.90 \times 10^{-6}$, further confirming the functional dissociation between these regions.

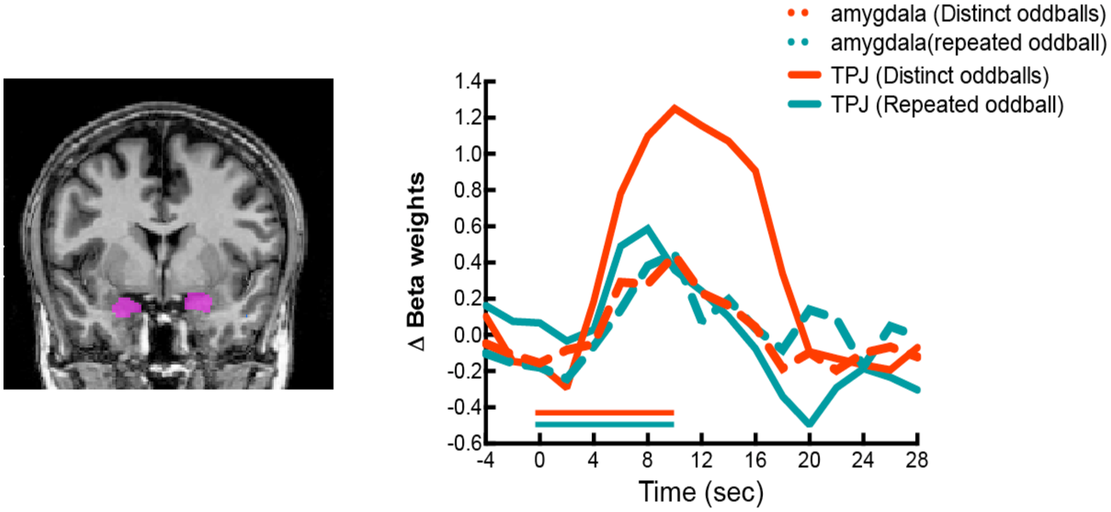

Figure 14. Anatomical location of amygdala of a representative participant (left) and group-averaged timecourses of activity to the long oddballs (right). Mean Talairach coordinates (x, y, z): -17, -4, -16 and 19, -3, -14 for left and right amygdala. For comparison, the TPJ activity is also plotted (See also Fig. 5). Solid lines indicate TPJ activity, while dotted lines indicate amygdala activity.

Discussion of Chapter II

The present studies provide clear evidence for a functional dissociation of each individual region implicated in stimulus-driven attention, and yields important insights into their specific cognitive computations.

The finding that the AI and ACC were activated only by the onset and offset of the extended oddballs implicate this region in the transient process of attentional orienting/reorienting. Due to its association with a plethora of behavioral functions, ranging from attention and perception to socio-affective processes, the AI's basic role in cognition has been extensively debated (Craig, 2002; Critchley et al., 2004; Downar et al., 2002; Menon & Uddin, 2010; Singer et al., 2009). One theory posits that the AI, in concert with the ACC, is primarily involved in a network signaling the appearance of salient sensory inputs (Menon & Uddin, 2010; Seeley et al., 2007; Sridharan et al., 2008). According to this salience account, socio-affective events or stimuli recruit the AI simply because they are particularly salient. While the current finding that the AI is primarily involved in attentional orienting during oddball presentations fits well with this salience account, additional studies are required to determine whether such account can accommodate the host of behavioral functions attributed to this brain region (see Chapter III). Moreover, while the repeated oddball experiment provides some evidence for a dissociation between the AI and ACC – with the former region being involved in signal any salient changes and the latter signaling any behaviorally relevant changes –further experimentations are required to strengthen that assertion (see Chapter IV).

Contrary to the AI and ACC, the IFJ, TPJ and amygdala showed sustained activity during the long oddball presentations. The extended goal-directed attention experiment (see Fig. 9) suggests that this activity does not simply represent sustained attention *per se*. Rather, we propose that, at least for the TPJ and perhaps also the IFJ, it reflects an evaluative process by which the oddball stimulus is identified and/or categorized. Based on other studies of TPJ function, we further surmise that the evaluative process specifically consists in comparing the continuously unfolding oddball event with internal representations in order to gauge its potential behavioral significance (Decety & Lamm, 2007; McCarthy & Donchin, 1981; Polich, 2007). This hypothesis is consistent with the markedly reduced activation observed in these brain regions as the oddball content becomes familiar with repeated presentations (see Experiment 2). Further testing of this hypothesis will be especially valuable considering that, like the AI, the TPJ has been associated with widely disparate functions (Cabeza et al., 2012; Decety & Lamm, 2007; Meyer, Spunt, Berkman, Taylor, & Lieberman, 2012; Mitchell, 2008).

Like the TPJ, the amygdala showed monophasic patterns of response to the long oddballs across the two fMRI experiments. However, the amygdala activity was immune to the demand for the evaluative process of the oddball contents, which the TPJ activity was strongly sensitive to. This finding suggests that the amygdala's response to the oddballs should be primarily associated with arousal or physiological response to rare, salient stimuli (Glascher & Adolphs, 2003; Weierich, Wright, Negreira, Dickerson, & Barrett, 2010), rather than to the cognitive evaluation of the stimuli.

Finally, the IFJ was the only region that showed both transient and sustained activity. Considering that this brain region has been involved in task switching and attention orienting (Asplund, Todd, Snyder, & Marois, 2010; Braver et al., 2003; Chiu & Yantis, 2009), the transient activity likely reflects the attention shifts between the goal-directed task and oddball stimuli. While the sustained activity is consistent with an involvement in the evaluative process, a more parsimonious explanation is that it reflects sustained attention towards the oddball stimuli, especially given the evidence that this brain region can show characteristics that are common to the dorsal goal-directed attention regions (Asplund, Todd, Snyder, & Marois, 2010). Regardless of the specific computations performed by the IFJ, the finding that this brain region plays multiple roles in stimulus-driven attention is broadly consistent with the propositions that this lateral prefrontal region acts as a central hub for attentional processing and cognitive control (Asplund, Todd, Snyder, & Marois, 2010; Brass et al., 2005; Braver et al., 2003; Konishi et al., 1998; Marois & Ivanoff, 2005). Indeed, we propose that the IFJ may coordinate or integrate the transient and sustained processes going on in the AI and the TPJ during stimulus-driven attention. In that framework, the AI is associated with attentional orienting, the TPJ is involved in evaluating attended stimuli, while the IFJ acts to integrate information across these brain regions.

CHAPTER III

THE FUNCTION OF THE ANTERIOR INSULA

In this chapter, I investigate the function of the anterior insula (AI). A growing number of studies have focused on the issue of what is the role of the AI in human information processing (Chang et al., 2012; Craig, 2009, 2011; Hein & Singer, 2008). This is primarily because this region has been implicated in an explosively wide range of emotional, affective and cognitive processes (Menon & Uddin, 2010; Singer et al., 2009).

AI activity has been associated with experiencing disgust and pain, as well as with body awareness, mood, and addictive behaviors (Adolphs, 2002; Craig, 2009; Critchley et al., 2004; Greenspan & Winfield, 1992; Phillips et al., 1997). Remarkably, this region is not only activated when people feel disgust or pain themselves, but it also shows robust activity when one observes other people experiencing disgust and pain (Chen et al., 2009; Gu et al., 2013; Kipps, Duggins, McCusker, & Calder, 2007; Phillips et al., 1997; Singer et al., 2009; Wicker et al., 2003). These findings imply that the AI plays a role in empathy, which refers to one's ability to infer and understand another person's emotional experience, desire, or intention (Hein & Singer, 2008). More broadly, this region is thought to play a key role in social cognition and economical decision-making (Caruana, Jezzini, Sbriscia-Fioretti, Rizzolatti, & Gallese, 2011; Sanfey et al., 2003; Singer et al., 2009)

Besides various social, emotional and affective processes, the AI has also been implicated in more elementary cognitive processes. In particular, the AI was found to be activated when people are confronted by salient events in many studies (Corbetta et al., 2008; Crottaz-Herbette & Menon, 2006; Downar et al., 2000, 2002; Linden et al., 1999), which suggests that this region could play a role in detecting and switching attention to a salient stimulus. Indeed, the AI is commonly included in two prominent networks implicated in the processing of salient stimuli: the stimulus-driven attention network (Corbetta et al., 2008) and saliency network (Seeley et al., 2007).

Besides processing salient stimuli, the AI has also been associated with perceptual decision-making, and attention and executive control (Dosenbach et al., 2006; Ploran et al., 2007; Sridharan et al., 2008; Eckert et al., 2009; Nelson et al., 2010; Tombu et al., 2011). In line with these findings, the AI is considered a core region of the multiple demand network, which exerts cognitive control to allow flexible behaviors (Duncan, 2010; Woolgar, Hampshire, et al., 2011; Woolgar, Thompson, et al., 2011).

To account for this plethora of functions ascribed to the AI, ranging from attention and perception to social, emotional, and affective processing, a group of researchers (Menon & Uddin, 2010; Seeley et al., 2007) has suggested that the AI is a core region of a ‘saliency network’, composed of the AI and anterior cingulate cortex. According to this account, the findings that the AI is associated with social, cognitive, and affective function originates from its primary role in signaling salience or behavioral relevance of sensory events. They argue that the AI does not subserve all the processes listed above, and that emotional and affective stimuli are particularly salient are particularly salient or behaviorally significant, to which the AI strongly responds. For example, the presentation of painful and disgusting stimuli is of much behavioral significance, rendering them highly salient.

One potential reconciliation of the saliency and affective accounts of AI processing is that distinct subregions of the anterior insula process salient and affective stimuli. Precisely, such an account has been suggested based on recent meta-analyses and resting-state functional connectivity analyses. According to this account, the dorsal part of AI is implicated in attention and cognition, the ventral AI is suggested to play a role in emotional, affective processing (Chang et al., 2012; Deen, Pitskel, & Pelphrey, 2011; Nelson et al., 2010; Touroutoglou et al., 2012), and the posterior insula is specifically involved in experiencing emotions such as pain (Benuzzi et al., 2008; Chang et al., 2012).

Even though the saliency account provides a parsimonious explanation for the findings that the AI is involved in various cognitive and affective processes, no direct evidence supporting the claim has been found. The extended oddball paradigm provides an ideal means to assess the saliency account of AI functions. Specifically, by presenting 10-sec movies with contents that arouse the feelings of disgust, pain, and empathy, it can be determined whether the AI is particularly sensitive to those affective processes, or whether it simply responds to salient changes in in the environment. As shown in Chapter II, the AI responded only to the onset and offset of the temporally extended oddballs, suggesting that a primary role of this region is detecting and switching attention to salient sensory events. This was so regardless of whether the oddballs were always novel (Experiment 1) or always the same (Experiment 2; see Fig. 11). Because novel oddballs are more salient and yet do not lead to a greater response than repeated oddballs, the results of the first two experiments argue that the AI is primarily involved in signaling a *saliency change* in the environment – as would occur at oddball onsets and offsets – rather than saliency *per se*. If this hypothesis is true, then the AI should still show such transient response to the onset and offset of emotionally laden oddballs. By contrast, if the AI is involved in affective processing, it should show a sustained pattern of response throughout the presentation duration of the affective oddballs. Moreover, by carefully probing subregions of the AI, the present study can assess whether different subdivision of the insular cortex responds distinctly to salient and/or affective stimuli.

Experiment 3

Methods

Participants

Ten adults (2 males, aged 23-33) participated for monetary compensation. The Vanderbilt Institutional Review Board approved the experimental protocol and written informed consent was obtained from each participant.

Design & Procedure

Most of the details were similar to those of Experiment 2 except that there were 20 distinct oddballs (10-sec long movie clips) presented. Half of the oddballs were non-meaningful, abstract ones used in Experiment 1 (non-affective oddballs), whereas the other half were affective oddballs, which were movies depicting either people suffering pain, people expressing disgust, wounded human body parts, or repulsive insects (e.g. cockroach, spider) crawling over human body parts (affective oddballs). These types of stimuli, when briefly presented, are known to engage the AI (Benuzzi et al., 2008; Britton et al., 2006; Gu et al., 2013; Singer et al., 2009; Wicker et al., 2003). In four of the oddball trials (2 each for affective and non-affective oddballs), a target followed the oddball offset either by a 125-ms or 1500-ms interval, during which distractors were presented. In the remaining oddball trials (16 trials), there was no target. The rest of trials consisted of Search-target (65 trials) and Search-no target (50) trials. No short oddball was included.

fMRI methods

All the imaging parameters and preprocessing procedures were identical to those of the previous experiments. ROIs was defined in the same way to Experiments 1 and 2. The AI, ACC, and IFJ were isolated from a group random effect SPM (q (FDR) < .05) created using a regressor detecting target presentation. The same regressor was also used to define the TPJ by associating negative beta weights with this region. To assess the extent to which the ROIs defined above are similar to those responding to oddballs, I constructed another SPM by defining regressors for each trial type and contrasting activity to all oddballs (non-affective and affective oddball trials) with goal-directed search activity (Search-no target trials). This SPM showed significant activation in the similar IFJ and TPJ. Furthermore, the amygdala, ventral AI (vAI), and posterior insula (PI) were also significantly activated, while they were not activated in Experiment 1. This is presumably because the current experiment used more oddballs (18 Long oddballs) than Experiment 1 (6 Single-short oddballs).

For ROI analyses, the IFJ and TPJ defined using the target regressor were used because the AI was also defined using this regerssor (see also Experiment 1 and 2). As mentioned above, the amygdala, vAI, and PI were defined running the contrast between the oddball trials and goal-directed search trials. The anatomical locations of ROIs are shown in Table 3.

ROI analyses were performed in the same way as Experiments 1 and 2. Event-related timecourses of the BOLD response were constructed by a deconvolution analysis for each condition. Then, the timecourse for search activity (Search-no target condition) was subtracted from the timecourse for the trials containing oddballs (affective and non-affective oddballs). Once timecoures of activities to the oddballs were constructed, I statistically assessed whether those activities were transient or sustained in the same way as in Experiments 1 and 2.

Table 3. List of ROIs in Experiment 3. The ROIs were isolated either from the SPM contrasting the oddball activity with the goal-directed search activity, or. from the SPM detecting activity associated with target presentation.

Affective & Non-affective oddballs vs Search trials

		Talairach Coordinates		
ROI name	Mean t Value	X	Y	Z
Left inferior frontal junction (IFJ)	5.20	-47	8	18
Right inferior frontal junction	6.80	45	12	18
Left temporo-parietal junction (TPJ)	8.94	-41	-62	18
Right temporo-parietal junction	10.91	48	-47	17
Left amygdala	7.51	-20	-9	-9
Right amygdala	6.78	23	-3	-11
Left ventral anterior insula (vAI)	5.71	-30	18	-10
Right ventral anterior insula	5.89	23	16	-10
Left posterior insula (PI)	4.49	-38	-10	-6
Right posterior insula	4.65	31	-15	-4

Open contrast of target presentation

		Talairach Coordinates		
ROI name	Mean t Value	X	Y	Z
Left anterior insula (AI)	5.67	-28	22	1
Right anterior insula	6.49	28	21	1
Anterior cingulate cortex (ACC)	4.42	0	11	45
Left inferior frontal junction (IFJ)	3.63	-41	7	25
Right inferior frontal junction	3.33	37	10	25
Left temporo-parietal junction (TPJ)	-3.77	-48	-60	23
Right temporo-parietal junction	-3.81	47	-57	24
Left frontal eye field (FEF)	3.31	-37	-2	38
Right frontal eye field	2.25	23	4	38
Left intraparietal sulcus (IPS)	4.96	-23	-56	38
Right intraparietal sulcus	3.55	24	-55	38

Results & Discussion

Insular region

The AI defined in the current study corresponds well to the dorsal AI (Talraich coordinates, x/y/z: 33/18/5) suggested to be primarily involved in attention and cognition (Touroutoglou et al., 2012). As shown in Figure 15a, the AI showed biphasic patterns of responses to the extended oddballs, regardless of its contents. For both the affective and non-affective oddballs, the amplitudes of activities at the onset peaks were greater than those at the middle points, t's(9) > 4.84, p's $< 9.14 \times 10^{-4}$, as were the offset peak amplitudes, t's(9) > 4.61, p's < .005. However, remarkably, there was sustained activity during the presentation of the affective oddballs, t(9) = 3.30, p < .01 (one-sample t-test comparing the peak amplitude with zero), but not during the presentation of the non-affective oddballs, p > .90. Consistent with this, the activity at the middle point was greater for the affective oddballs than for the non-affective ones, t(9) = 2.29, p < .05. This differential activation pattern across the types of oddball contents was further confirmed by a two-way ANOVA with Time (9 volumes from the oddball onset) and Oddball type (Affective vs. Non-affective) as within subject factors, which showed a significant interaction between these two factors, F(8, 72) = 2.18, p < .05.

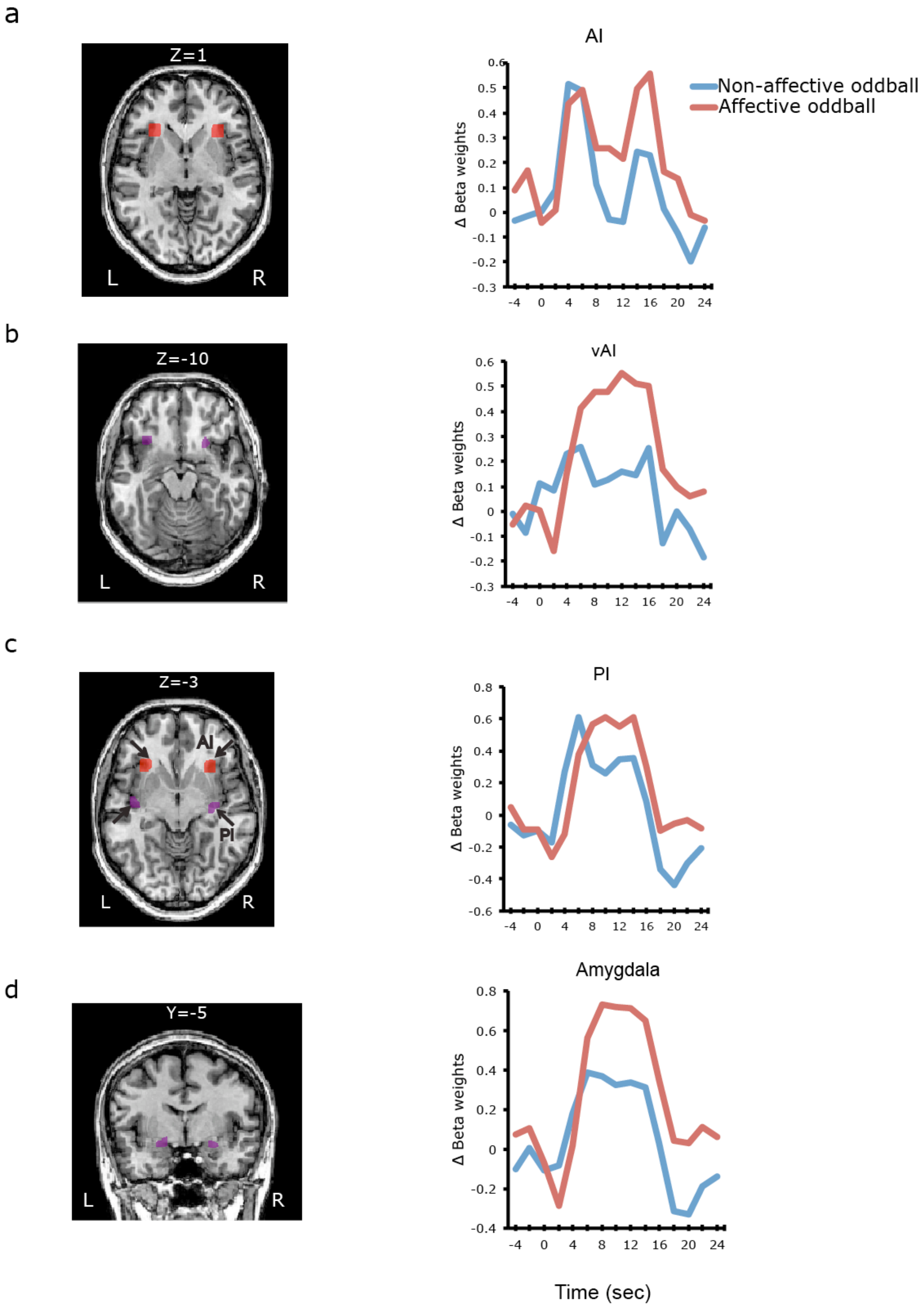

Figure 15. ROIs implicated in affective processing and their activation timecourses with affective and non-affective oddballs. a) Group-defined anterior insula (AI). This region corresponds well to the dAI. b) Group-defined ventral anterior insula (vAI). c) Group-defined posterior insula (PI). For comparison, the AI is also shown on the SPM. d) Group-defined amygdala. Timecourses were constructed by subtracting the timecourse for goal-directed search (Search-no target condition) from the timecourse for trials containing (affective or non-affective) oddballs. The oddball onset is at time point zero.

In contrast to the AI, other subregions in the insular cortex – the vAI and PI – showed no significant biphasic responses to the affective and non-affective oddballs; activities at the peaks associated with the onset and offset of the oddball were not significantly grater than at the middle point , p's > .15 (Figure 15b & c), though the affective oddballs elicited a greater response, p < .05.This differential pattern of activity across subdivisions within the insular cortex (the AI, vAI, and PI) was confirmed by an interaction between time (9 volumes from the oddball onset) and Region (AI, vAI, and PI) as within subject factors in a two-way ANOVA (F(16, 144) = 3.13, p < .001 for non-affective oddballs, and F(16, 144) = 3.41, p < .001 for affective oddballs).

These results imply that distinct subregions of the insular cortex exert different functions. Specifically, the AI primarily responds to salient changes in the environment, whereas the vAI and PI preferentially signal arousing or affective events. These finding are generally consistent with the recently suggested functional dissociation of the insular cortex (Chang et al., 2012; Deen et al., 2011; Touroutoglou et al., 2012) in which the AI supports attention and cognitive functions and the vAI and PI mediate affective processing. Importantly, however, the present results indicate that such dissociation is only relative; the AI showed clear evidence of a sustained response during the affective oddball presentations, suggesting that this brain region is also engaged in affective processing.

As a reference frame for the activations observed in the insular cortex, I probed the amygdala as it plays a prominent role in emotional, affective processing (Adolphs et al., 2005; Adolphs, Tranel, Damasio, & Damasio, 1994; Phelps & LeDoux, 2005). As expected, this region showed sustained activities to both types of oddballs (Fig. 15), with stronger activity to the affective oddball than to the non-affective oddball, t(9) = 2.54, p < .05 (paired t-test of peak amplitudes).

Other attention brain regions.

Having shown that the presentation of affective stimuli modulated activation of brain regions implicated in affective processing, I probed other regions in the saliency and stimulus-driven attention networks (Figure 16). The ACC – which, along with the AI forms the saliency network (Seeley et al., 2007; Menon & Uddin, 2010) – showed a transient response to the non-affective oddball without sustained activation, consistent with the results of Experiment 1 and 2, p's < .005. However, unlike the AI, it also showed only a transient response to the affective oddballs, p's < .05, with no sustained activity, p > .49. This region also showed a marginally greater response to oddball offset than onset, p = .078. Thus, unlike the AI, the ACC may be playing a cognitive function that is not modulated by the emotional contents of the material (Bush, Luu, & Posner, 2000).

The IFJ showed a biphasic pattern of responses to the non-affective oddball, p's < .01, as well as sustained activation, t(9) = 3.32, p < .01, which is also consistent with the results of Experiments 1 and 2. Its response to the affective oddballs was greater than that to the non-affective oddballs. Specifically, a two-way ANOVA with Time (9 volumes from the oddball onset) and Oddball type (Affective vs. Non-affective) as within subject factors yielded a significant interaction between the two factors, F(8, 72) = 3.17, p < .005. This result is consistent with previous findings that the lateral prefrontal cortex shows greater response to affective stimuli than to neutral, non-affective ones (Gu et al., 2013; Wicker et al., 2003), presumably because these are more attention-engaging.

Finally, the TPJ showed pronounced monophasic activities to both types of the oddballs. Notably, the affective oddballs elicited far greater activity than non-affective oddballs, t(9) = 4.23, p < .005 (paired t-test of peak amplitudes). This is presumably because the affective oddballs contained human faces or other body parts, to which the TPJ robustly responds (Frith & Frith, 2006; Hampton et al., 2008).

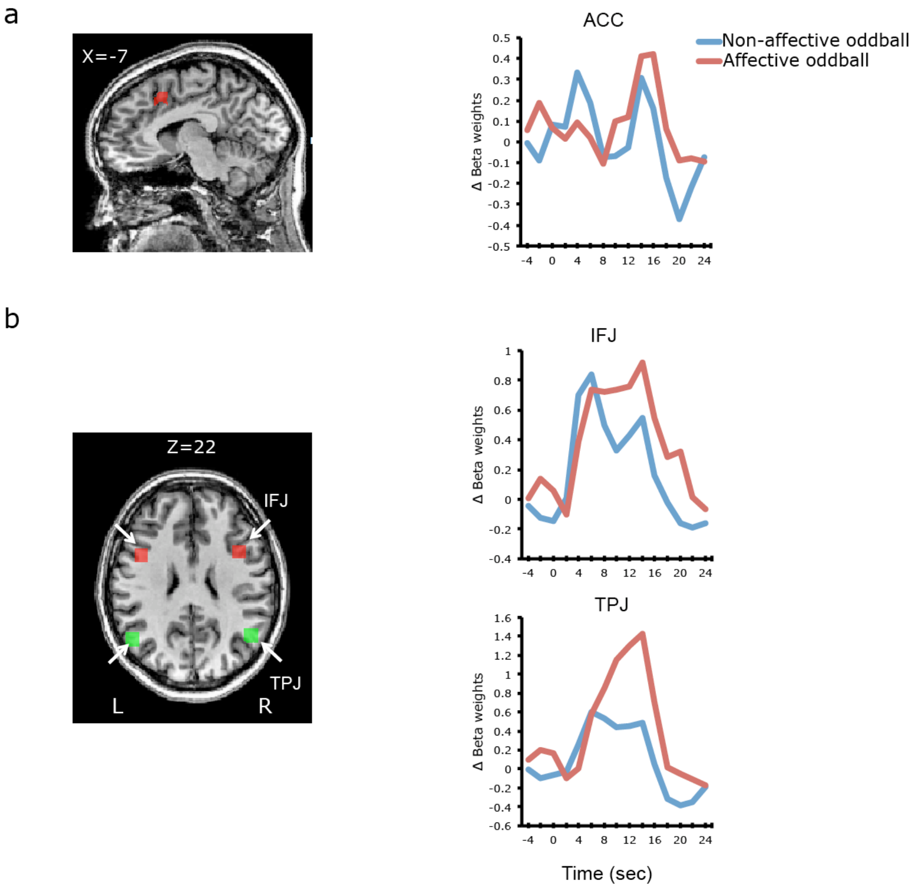

Figure 16. ROIs included in saliency and stimulus-driven attention networks and their activation timecourses. a) Group-defined anterior cingulate cortex (ACC). b) Group-defined IFJ and TPJ. Each timecourse was constructed by subtracting the timecourse for goal-directed search (Search-no target condition) from the timecourse for trials containing oddballs (affective and non-affective oddballs). The oddball onset is at time point zero.

Finally, I probed the FEF and IPS, core regions of the dorsal goal-directed attention network (Figure 17). For the non-affective oddballs, these regions showed stronger activities at the onset and offset of the oddballs than at the middle point p’s < .05. Importantly, the activities at the middle point were above baseline, p’s < .01, suggesting that attention was sustained on the oddball, as in Experiments 1 and 2. Remarkably, the presentation of affective oddballs neither increased activation, nor yielded sustained activation, compared to the non-affective oddballs (see also ACC activation in Figure 15). Rather, their responses were either transient (IPS, p’s < 05), or greatest at the offset of affective stimuli (FEF, p < .01). Given the complex response patterns of the dorsal attention ROIs to the affective oddballs, it is difficult to ascertain their specific involvement with these oddballs. Nevertheless, I surmise that the FEF and IPS show robust activation with the non-affective oddballs because they captivate attention in a sustained manner. By contrast, it is possible that some subjects may have averted their attention from the affective oddballs because they were uncomfortable or that they were easier to evaluate their meanings. In other words, while a broad set of brain regions increase activation in the face of affective stimuli, the dorsal attentional network (and ACC) seems to be preferentially engaged during the attention-demanding process of stimulus evaluation.

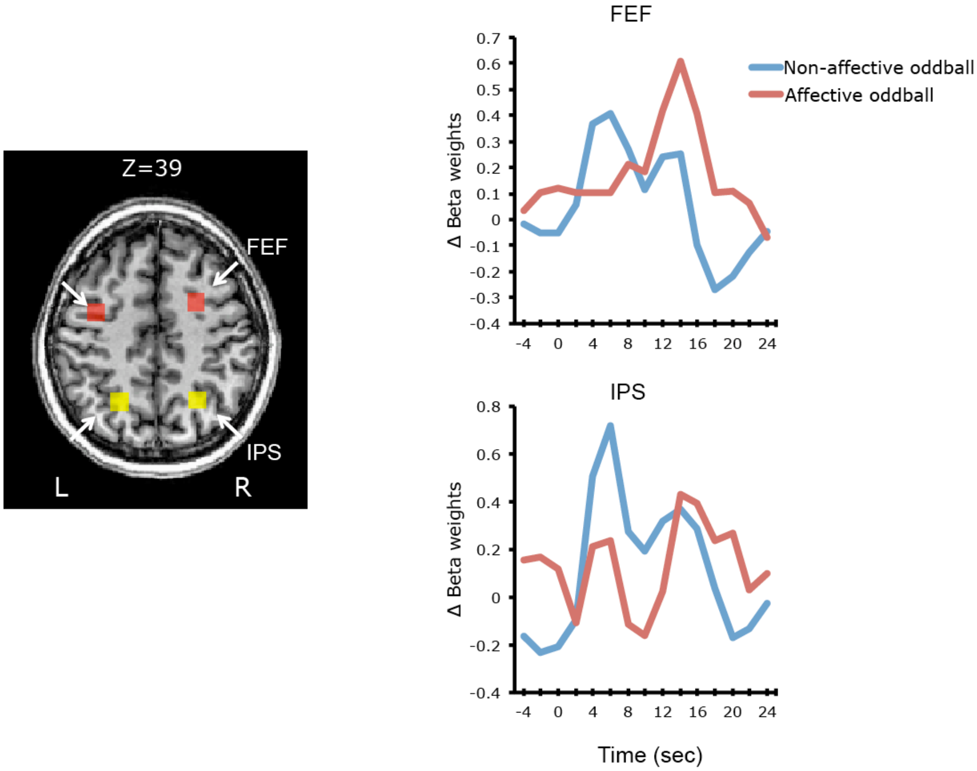

Figure 17. Group-defined frontal eye fields (FEF) and intra-parietal sulcus (IPS) and timecourses of activity. The oddball onset is at time point zero. Due to the large size of activational foci, ROIs were confined to the peak voxel and surrounding area of 1.33 cm^3 to preserve signal to noise ration.

Discussion of Chapter III

The experiment in this chapter yielded several important results. Most importantly, the AI, which corresponds to the dorsal AI (Touroutoglou et al., 2012) showed a sustained response to the affective oddball. This sustained activation cannot be easily explained by the possibility that the stimuli arousing emotional responses are particularly salient or more attention-engaging than the non-affective stimuli. This is because Experiments 1 and 2 demonstrated that the AI only showed transient activity regardless of whether the oddballs were always novel or always the same. Had the AI been generally sensitive to attention or saliency, it should have shown a sustained response to the novel oddball condition compared to the identical oddball condition. Yet, no such difference was found (Fig. 11). I therefore conclude that the present results indicate the functional involvement of AI in affective processing. This involvement would be above and beyond that of detecting a salient change in the environment, as evidenced by the robust activation of this brain region to oddball onsets and offsets. While this finding is consistent with the salience network account of the AI (Menon & Uddin, 2010; Seeley et al., 2007), the sustained response with the affective oddball stimuli suggests that this account is incomplete; the AI seems to be involved in both attentional orienting toward a salient stimulus and affective processing.

Another important finding is that distinct subdivisions of the insular cortex were activated differently by the presentation of affective stimuli. The dorsal AI, ventral AI, and posterior insula commonly showed greater responses to the affective stimuli than to the non-affective stimuli, suggesting that the insular cortex plays a role in affective processing. However, the temporal patterns of activity to affective stimuli were different across distinct subdivisions. The dorsal AI, even though it showed sustained response to the affective oddballs, showed transient, biphasic response to the oddball. By contrast, other subdivisions showed only sustained responses. This finding that the dorsal AI is particularly sensitive to behaviorally significant sensory transitions is consistent with the claim that the dorsal part of the AI is specialized in attention and cognition, whereas the ventral AI and PI are primarily involved in affective processing (Britton et al., 2006; Chang et al., 2012; Deen et al., 2011; Touroutoglou et al., 2012). However, the functional dissociation within the insular cortex does not seem to be in an all-or-none manner, given that the dorsal AI, presumed to be a cognitive region, was also sensitive to the affective contents of the stimuli.

While the presentation of affective stimuli evoked greater activations than non-affective stimuli in several ventral and lateral cortical regions, the ACC and regions of the dorsal attention network (FEF & IPS) did not show such enhanced activation by the affective stimuli. Hypothetically, this is because the presentations of affective oddballs primarily engage affective brain regions rather than those (e.g. ACC, FEF, and IPS) involved in sustained attention and stimulus evaluation.

Taken together, the results of this affective oddball experiment provide important insights about the function of the AI. Most importantly, the results suggest that in addition to detecting and switching attention to a salient sensory event, this region is involved in affective processing. Furthermore, a functional dissociation exists within the insular cortex, such that the dorsal AI plays a greater role in attentional orienting, while the ventral AI and PI are more specialized in affective processing.

CHAPTER IV

ROLES OF THE PREFRONTAL REGIONS IN ATTENTIONAL ORIENTING

The experiments reported here showed that in the presence of temporally extended oddballs, the AI and ACC were transiently activated by the onset and offset of the oddballs, as was the IFJ when the demand for evaluating the oddballs decreased. These results implicate the prefrontal regions in the transient process of attentional orienting, which includes detecting and switching attention to a stimulus (Posner, 1980). A question that remained unanswered is whether these two subcomponents of orienting are subserved by separate neural substrates.

Even though the AI and ACC have been found to be involved in various tasks that require switching of attentional sets, it remains unclear whether those findings reflect the involvement of these brain regions in switching, or in detecting an event signaling the need to switch (Kim, Johnson, & Gold, 2012; O'Doherty, Critchley, Deichmann, & Dolan, 2003; Pessoa & Ungerleider, 2004; Sridharan et al., 2008; Woodward, Metzak, Meier, & Holroyd, 2008). For example, a prominent theory of the ACC function argues that it is primarily involved in detecting a significant event (e.g. response conflict, error) to trigger cognitive control or attentional switch (Cohen, Botvinick, & Carter, 2000; Kerns et al., 2004; Liston, Matalon, Hare, Davidson, & Casey, 2006; Yeung, Botvinick, & Cohen, 2004; Woodward et al., 2008), whereas other studies propose that it is also involved in the switching process (Hyafil, Summerfield, & Koechlin, 2009; Kim, Johnson, Cilles, & Gold, 2011; Kim et al., 2012; Menon & Uddin, 2010; Swainson et al., 2003).

Similar to the AI and ACC, the IFJ also shows increased activation when attentional switching is required (Braver, Reynolds, & Donaldson, 2003; Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Hyafil et al., 2009; Kim, Johnson, Cilles, & Gold, 2011; Konishi et al., 2998; Nagahama et al., 2001; Rossi, Pessoa, Desimone, & Ungerleider, 2009). However, the role of the IFJ does not seem to be confined to attentional switching. The IFJ is not only implicated in resolving response conflicts and distractor interference (Banich et al., 2000; Brass et al., 2005; Derrfuss et al., 2005; Gehring & Knight, 2002), but also in response selection and general attentional control limitations (Han & Marois, 2013; Marois & Ivanoff, 2005; Tombu et al., 2011). Furthermore, in line with a recent finding that it is a core region for coordination of stimulus-driven and goal-directed attention (Asplund, Todd, Snyder, & Marois, 2010), the experiments reported in Chapter II showed that the IFJ has multiple roles in stimulus-driven attention, particularly in both the transient and sustained components of oddball processing.

Given these findings, it is unlikely that the IFJ might be specifically associated with attentional switching, per se (Hikosaka & Isoda, 2010; Hyafil et al., 2009; Gehring & Knight, 2002; Johnston, Levin, Koval, & Everling, 2007). Instead, it might play a central role in adapting to dynamically changing task demands (Banich et al., 200; Braver et al., 2003; Dove et al., 2000; Kim et al., 2012; Leber, Turk-Browne, & Chun, 2008; Parris, Thai, Benattayallah, Summers, & Hodgson, 2007; Rossi et al., 2009; Roth & Courtney, 2007). Hypothetically, its primary role seems to be to establish a task set and implement the necessary control to perform the task. Hence, whenever the implementation/maintenance of task set is challenged by distractor interference or frequently changing task demands, stronger control should be exerted, with increased IFJ activation (Banich et al., 2000; Dreher & Berman, 2002; Gehring & Knight, 2002; Gold et al., 2006; Han & Marois, 2013; Hyafil et al., 2009; Nagahama et al., 2001; Kim, Johnson, Cilles, & Gold, 2011; Parris, Thai, Benattayallah, Summers, & Hodgson, 2007).

In this chapter, I investigate whether the AI, ACC, and IFJ are differentially involved in detecting and switching attention to salient sensory events. To do so, I employed two manipulations within the same experiment. Firstly, I adapted a well-established paradigm to isolate a transient response that is specific to switching (Chiu & Yantis, 2009; Esterman et al., 2009; Tamber-Rosenau et al., 2011; Yantis et al., 2002), and examined which of the prefrontal regions (AI, ACC, and IFJ) show switching-related activity. Specifically, a cue (task cue) was presented to inform participants which task set should be established. Another type of cue instructed them either to hold the current task set or to switch to the other set. The presentation of both the Hold and Switch cues should evoke activity related to detecting stimuli of behavioral relevance. However, regions involved in attentional switching should show greater activity to the switch cue than to the hold cue, whereas a region primarily involved in detecting would not show any differential activity to the hold and switch cues. Given that this paradigm isolated a transient, switch-related activity in the medial superior parietal lobule (mSPL) (Chiu & Yantis, 2009; Esterman et al., 2009; Tamber-Rosenau et al., 2011; Yantis et al., 2002), I also probed this region to validate the use of the current paradigm to search for the switching activity.

The second manipulation served to determine whether the transient responses of the AI, ACC and IFJ to oddball onsets and offsets simply indicate a salient change in current environmental settings, or whether they reflect a switch from and/or to goal-directed behavior (see also Experiment 2). Unbeknownst to participants, 10-sec long oddball movies were included during the experiment. Importantly, an oddball was followed by either another oddball (dual long oddballs), or by other task-related stimuli (single long oddballs). If the prefrontal regions are primarily involved in detecting salient changes, regardless of whether they are behaviorally relevant or not, then they should be activated at the transition phase between two unrelated oddballs. If, on the other hand, these regions are involved in switches of goal-relevant attentional sets, they should only be activated at the transitions between the goal-directed task and the oddballs.

Experiment 4

Methods

Participants

Ten adults (3 males, aged 25-33) participated for monetary compensation. The Vanderbilt Institutional Review Board approved the experimental protocol and written informed consent was obtained from each participant.

Design & Procedure

The experiment was programmed in Python using Psychopy software (Peirce, 2007) and run on a MacBook Pro laptop. The task was to judge the magnitude (M) or parity (P) of digits imbedded in a rapid serial visual presentation (RSVP) of letters. Some letters (‘M’, ‘P’, ‘S’, and ‘H’) were cues to inform participants which task should be performed, whereas other letters (‘F’, ‘K’, ‘B’, ‘G’, ‘Q’, ‘W’, ‘X’, and ‘Y’) were distractors. The height of each stimulus was 2°. Each stimulus (cue, target, and distractor) was presented singly for 500 ms at fixation with no inter-stimulus interval.

As shown in Figure 18, in the beginning of an fMRI run, a task cue, either ‘M’ or ‘P’, was presented, instructing participants to either judge the parity (odd or even digit) or magnitude (digit higher or lower than 5) of the digit targets. Participants responded to the targets by pressing one of two finger responses from the right hand. The H and S cues instructed the participants to maintain the current task set or to switch to the other task set (e.g., to now perform the P task instead of the M task on any subsequently presented targets), respectively. To ensure that participants pay attention to all cues, they were instructed to make a response to the task (M, P) and S and H cues with their left index fingers. The 500-ms presentation of a cue or target was followed by a 3.5-sec period – during which distractors were presented. This was to ensure that participants have enough time to make responses before the next event of interest occurs. The cue/target presentation and the immediately following 3.5-sec period comprised an event of interest. These different types of 4-sec long events of interest were intermixed randomly under a constraint that no more than two Hold/Switch cues events appear in succession. That is, if two Hold/Switch cues appeared in succession (e.g. two Hold cues, two Switch cues, Hold followed by Switch, or Switch followed by Hold), the next event of interest would be a target or task cue.

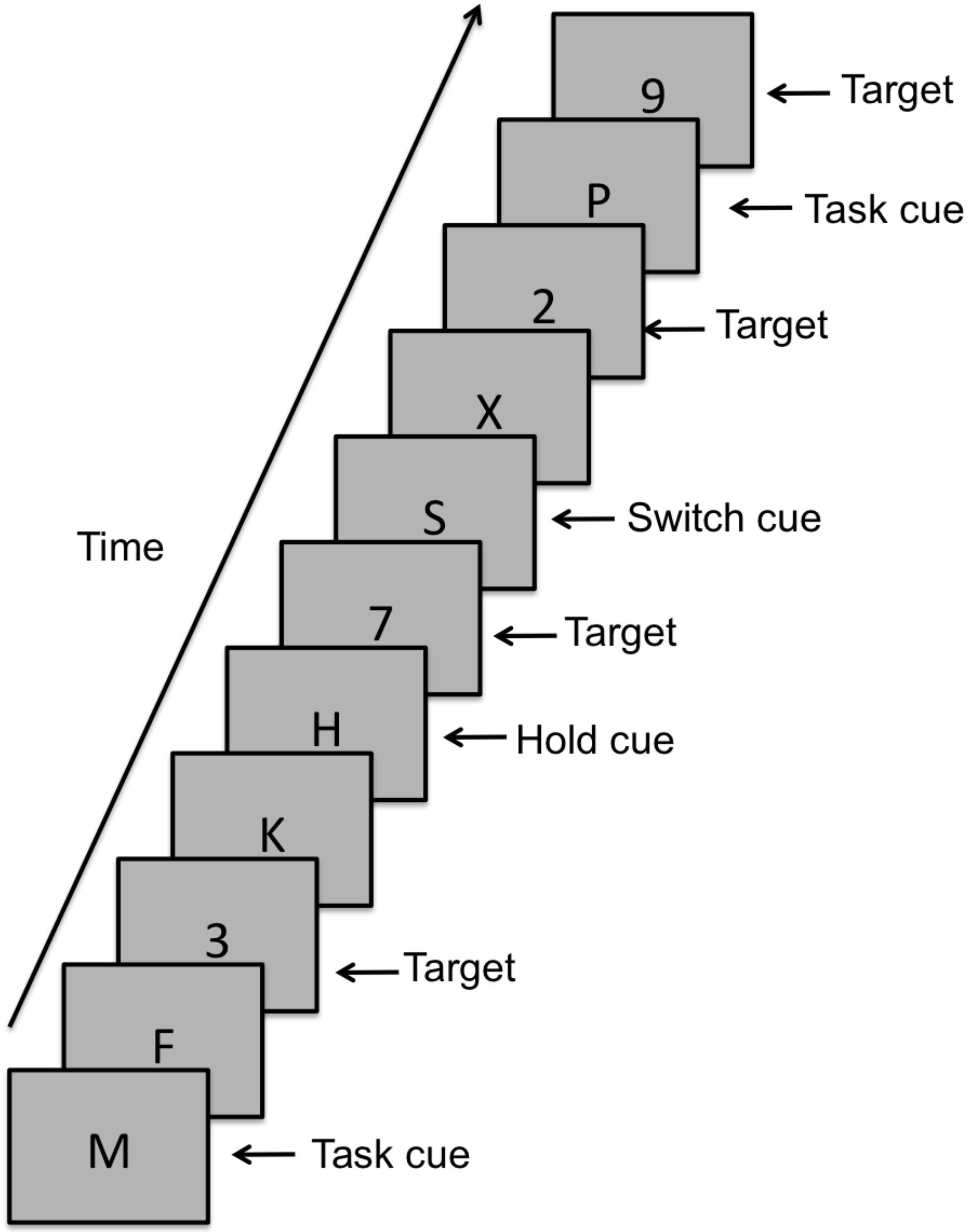

Figure 18. Detection vs. Switching task of Experiment 4. The 'M' and 'P' cue denotes the magnitude judgment and parity judgment tasks, respectively. In the face of an'H' cue, the task to be performed remains the same. In the face of an 'S' cue, the task should be switched to the other.

In addition to the events of interest described above, there were two types of oddball events: single and dual oddballs. The single long oddball included a 10-sec long movie composed of abstract animations (e.g. continuously transforming fractals or molecular polymerization). The dual oddball consisted of two such movies presented in succession with no gap between the oddballs. While the contrast between the switch and hold cue activity reveals neural substrates of goal-directed task switching, the presentation of oddballs should evoke stimulus-driven, involuntary switching. Notably, having dual oddballs allow me to compare neural activity to the transition between two task-irrelevant oddballs with activity to the transition between task-irrelevant oddballs and goal-directed task stimuli. Oddballs were shown to eight of the ten participants.

An RSVP that lasted 382 seconds comprised an fMRI run. In each run, there were a total of 48 events of interest, consisting of 8 task cues (M and H), 12 hold cues, 12 switch cues, 14 targets, and 2 oddballs. Each event of interest was separated by variable durations of interval that follow exponential distribution (3 events X 8 sec, 6 events X 6 sec, 12 events X 4 sec, 27 events X 2 sec) to facilitate deconvolution of hemodynamic responses evoked by events of interest. Distractors were also presented during these inter-event intervals.

fMRI methods

All the imaging parameters and preprocessing procedures were identical to those of the previous experiments. To create SPMs, regressors were defined for each event type, convolved with a double gamma function (SPM2, http://www.fil.ion.ucl.ac.uk/spm). Then, an SPM was constructed using an open contrast assigning regression coefficient of 1 to all the events of interest, excluding the oddball events. From this open contrast SPM, thresholded at the level of q(FDR) < .05, the AI, ACC, and IFJ were defined as all contiguous supra-threshold voxels of distinct activation foci. Medial SPL, implicated in attentional switching (Chiu & Yantis, 2009; Esterman et al., 2009; Tamber-Rosenau et al., 2011; Yantis et al., 2002), was also defined. Given that this region is associated with switching of attentional set, probing this region will evaluate whether the current paradigm is powerful enough to detect the typical switching-related activity. The anatomical locations of ROIs are shown in Table 4

For ROI analyses, event-related time courses of the BOLD signal for each participant and each event type (M, P, H, and S cues and targets) were estimated using a deconvolution analysis (using the 8 volumes immediately following the event onsets). The Beta estimates for each volume were converted to % signal change relative to the mean Beta value of their run. The normalized Beta estimates were averaged across participants, yielding group-averaged time courses (Han & Marois, 2013).

To statistically compare BOLD responses for the Hold and Switch cues, BOLD amplitudes at the peak volume were contrasted using paired t-tests. The peak volume was derived by collapsing the timecourses of all the conditions and participants and determining the time point of greatest signal amplitude in the averaged response for each ROI (Han & Marois, 2013; Todd & Marois, 2004).

Activations in response to oddball presentations were investigated with a separate GLM analysis. Specifically, I defined regressors for the two types of oddballs (single and dual oddballs). Then, timecourses of activity to the single and dual oddballs were extracted from the prefrontal and parietal ROIs, using a deconvolution analysis. Given that the duration of oddball presentation was either 10 sec or 20 sec, I used 20 volumes immediately after the event onsets to deconvolve the hemodynamic responses. Group-averaged timecourses were derived in the same way as described above.

In addition to these univariate GLM analyses, I also performed event-related multivariate pattern analysis (MVPA) of BOLD responses (Esterman et al., 2009; Tamber-Rosenau et al., 2011) in some of the ROIs. The goal of this MVPA was to determine whether a given brain region encoded cue information (e.g. task implementation differences between H and S) even if that region did not exhibit differential BOLD response amplitude to the cues. MVPA is useful to detect difference in spatial activation patterns from a given ROI that reflect differences at the sub-voxel level, (Kamitani and Tong, 2005; Esterman et al., 2009), which univariate GLM analyses fail to detect. This MVPA has been extensively used to reveal how different cognitive operations or mental states are represented within a region (Haynes & Rees, 2006; Norman, Polyn, Detre, & Haxby, 2006)

The MVPA analyses were performed as in previous studies (Esterman et al., 2009; Tamber-Rosenau et al., 2011) using OSU SVM toolbox (adaptation of libsvm: http://www.csie.ntu.edu.tw/~cjlin/libsvm/) for MATLAB and custom MATLAB software. Briefly, the signal in each voxel was z-transformed relative to the entire timecourse within each run. Independently for each ROI, participant, and TR, all but one run of data was used to train a linear support vector machine that was then tested on the held out run; this process was iterated until all runs had served as the test data once. Given the typical pattern of hemodynamic responses, decoding accuracy should peak at 4-6 seconds after the event onset. To prevent that mean difference in BOLD amplitude across the cue types biases MVPA results, the mean of activity of all the voxels for each type of event was subtracted from each voxel for that type (Esterman et al., 2009; Tamber-Rosenau et al., 2011).

Importantly, given that the ROIs were defined using an orthogonal contrast (open contrast of all events of interest) to the contrast of interest (Hold vs. Switch), the ROI analyses (univariate GLM analyses and MVPA) were statistically independent from the ROI selection.

Table 4. List of ROIs in Experiment 4. The ROIs were isolated using the open contrast of events of interest. The AI here corresponds to the dorsal AI implicated in cognition and attention (Touroutoglou et al., 2012).

		Mean Talairach Coordinates		
ROI name	Mean t Value	X	Y	Z
Left anterior cingulate cortex (ACC)	6.00	-8	10	43
Right anterior cingulate cortex	5.86	5	10	42
Left inferior frontal junction (IFJ)	5.04	-42	5	21
Right inferior frontal junction	4.01	41	7	26
Left anterior insula (AI)	5.23	-29	19	2
Right anterior insula	5.01	29	17	7
Medial superior parietal lobule (SPL)	4.62	-6	-63	43
Left frontal eye field (FEF)	5.81	27	3	49
Right frontal eye field	4.78	-32	-1	42
Left intraparietal sulcus (IPS)	7.02	30	-55	43
Right intraparietal sulcus	4.32	-28	-48	40

Results & Discussion

The behavioral data acquired during the scan showed that participants performed the task as instructed. Subjects almost always responded to the Hold (94.2 %) and Switch

(97.2 %) cues, with no difference between these two performances ($p > .19$). Similarly, there was no RT difference between the switch (904 ms) and hold (929 ms) cue responses, $p > .26$. Accuracy of target responses was 81.1%, and the mean RT for correct target responses was 1303 ms. The latter RTs did not differ depending on which cue preceded the target, $p > .26$.

Prior to probing the prefrontal regions, I verified that the current approach successfully isolated switching-related activity from a region well known for its role in attentional switching, the medial superior parietal lobule (mSPL). Specifically, mSPL activity was far greater to the Switch cue than to the Hold cue (Figure 19a), $t(9) = 5.54$, $p < 3.61 \times 10^{-4}$. This is a replication of a well-established finding reported by studies employing a similar paradigm (Chiu & Yantis, 2009; Esterman et al., 2009; Tamber-Rosenau et al., 2011; Yantis et al., 2002). Then, I examined which of the prefrontal regions sensitive to the presentation of behaviorally relevant events would show greater switching activity. Among the AI, ACC and IFJ, only the ACC significantly greater activity to the Switch cue than to the Hold cue, $t(9) = 4.34$, $p < .005$. By contrast, the AI and IFJ showed no difference in activation for the two types of cues, p's > .15 (Figure 19b & c).

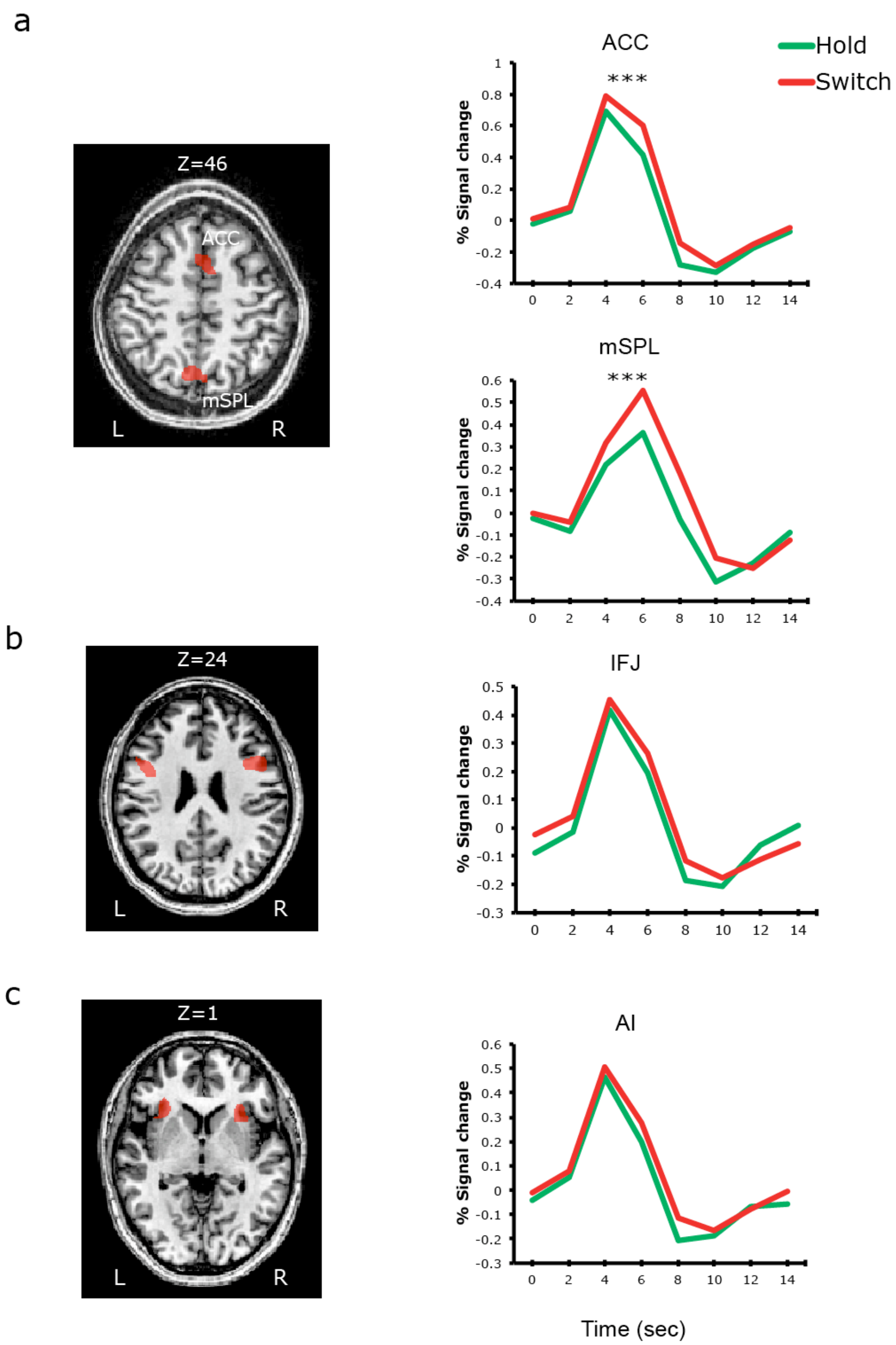

Figure 19. Group-defined ROIs and their timecourses of activation. a) Medial superior parietal lobule (mSPL) and anterior cingulate cortex (ACC). b) Inferior frontal junction (IFJ). c) Anterior insula (AI). The AI well corresponds to the dorsal, cognitive subdivision of the insular cortex (Touroutoglou et al., 2012). The ACC and mSPL showed greater activity to Switch than to Hold cues. *** denotes statistical significance, $p < .005$.

Furthermore, when another SPM was created contrasting activity to the switch cue with activity to the hold cue, significant activational foci were found only in the ACC and mSPL, consistent with the ROI analyses (Figure 20).

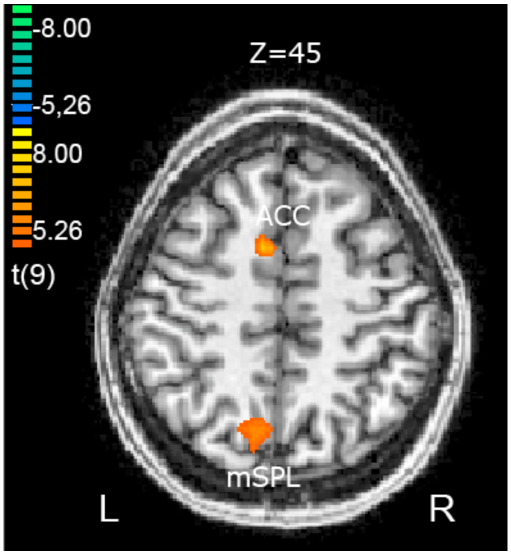

Figure 20. SPM of Switch vs Hold activity (q(FDR) < .05).

The univariate GLM analyses indicate that only the ACC (and mSPL) exhibit greater activity when attentional sets are switched than when they are maintained. By contrast, there was no activity difference in AI and IFJ for Switch and Hold cues. While it is reasonable to conclude that the latter brain regions do not make the distinction between switching and maintaining task sets, it is also possible that distinct neuronal subpopulations within the AI and IFJ encode the Switch and Task rules, a pattern that would not be detectable with univariate analyses. To address this issue, I applied multivariate pattern analysis (MVPA) to examine whether switching and holding rules could be decoded from activation patterns in the AI and IFJ.

As shown in Figure 22, switching and holding rules could be successfully classified in IFJ, but not in AI. Specifically, only the event-related MVPA timecourse for the IFJ showed a pattern compatible with the typical hemodynamic response function; decoding accuracy peaked above 50% chance level ($p <. 01$) at 6 seconds after the event onset. A repeated measure ANOVA with time as a factor (7 volumes immediately after the event onset) showed a main effect of time, $F(6, 54) = 3.20$, $p < .01$. By contrast, the AI did not show such pattern, $p > .15$. This dissociation in decoding accuracy between the IFJ and AI is further confirmed by the interaction term ($F(6,54) = 2.41$, $p < .05$) in a two-way repeated measure ANOVA with time (7 volumes immediately after the event onset) and region (AI and IFJ) as factors.

Finally, when applied to the ACC and mSPL, MVPA yielded successful decoding of Switching and Holding rules (Figure 23). The peak classification accuracy for both regions was greater than chance (50%), p's< .005, and the timecourses of decoding accuracy showed the typical hemodynamic response pattern, p's < .01. These results are not altogether surprising given that Switch related activity could already be distinguished from Hold related activity with Univariate statistics in these two brain regions.

In sum, the univariate and multivariate analyses of this experiment suggest that mSPL and ACC primarily instantiate task switching, that IFJ encodes the task rules for Switching and Holding, and that AI only detects the presence of behaviorally-relevant cues.

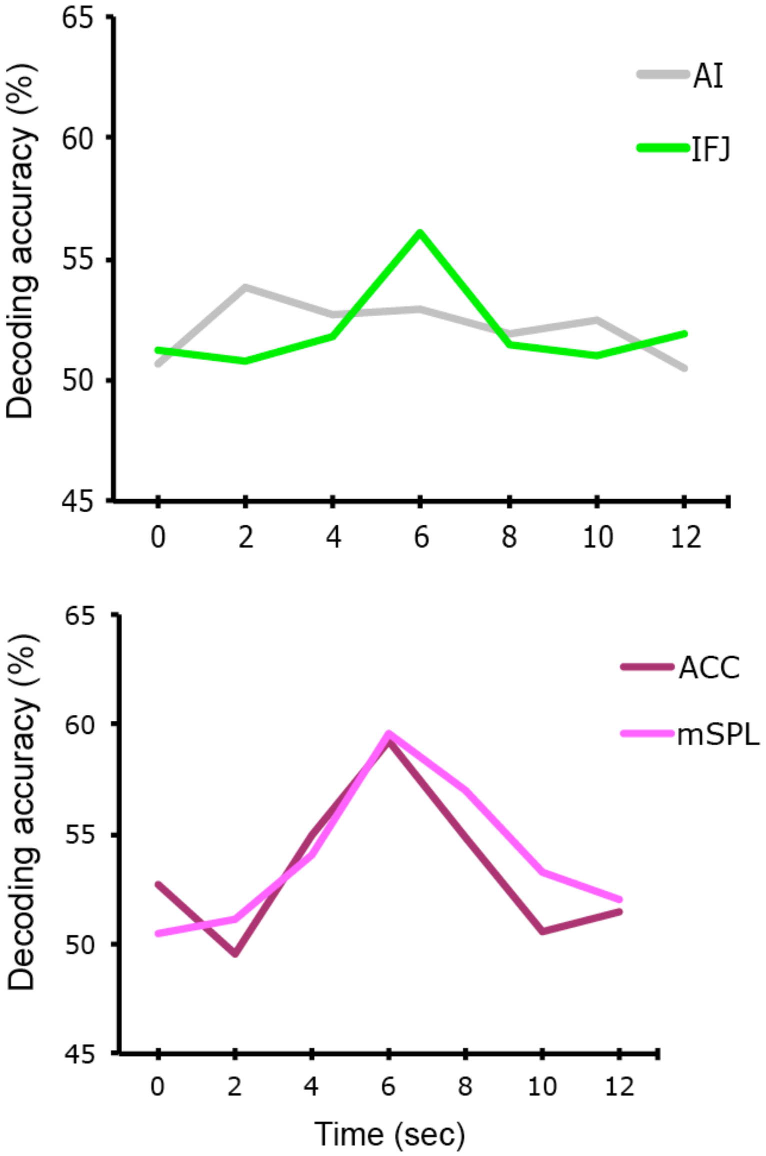

Figure 21. Event-related MVPA results for decoding accuracy of the cue type (Switch or Hold) in the AI, IFJ, ACC, and mSPL. The event onset is at the time of zero.

The oddballs provide a means to test the hypothesis that the AI is primarily sensitive to detecting salient changes in the environment. If this hypothesis is correct, then the AI should be activated not only at the transition between oddballs and the goal-oriented task, but also at the transition between two distinct, task-irrelevant oddballs. By contrast, brain regions that encode goal-relevant task sets should be specifically engaged when an oddball affects a task set. According to that account, these brain regions should show little activation in the transition between two task-irrelevant oddballs because such transition does not impact any goal-directed task sets.

The BOLD responses of the ACC, IFJ, AI, as well as mSPL, to the single and dual oddballs are shown in Figure 21. For the single oddball, all the prefrontal regions showed transient responses to the onset and offset of the oddball; the peak amplitudes associated with the onset and offset of the oddball were greater than that at the middle point between the two peaks, p's < .05.

The BOLD responses of these regions to the dual oddballs are remarkable. The ACC only responded to the onset of the first oddball and offset of the second oddball, p's < .05, with no response to the transition between the two oddballs, p >.37. By contrast, the AI and IFJ activities were sensitive to such transition between the two oddball stimuli, as well as to the transition between the oddball and task-related stimuli. Specifically, for both regions, the signal amplitudes for the first (first oddball onset) and second peak (transition between oddballs) were greater than that at the middle point between the two peaks, p's < .05. The third peak (offset of the 2nd oddball) amplitude was also greater than that at the middle point between the second and third peaks, p's < .05. For both of these regions, the oddball transition response was nevertheless smaller than that at transitions between oddballs and goal-oriented task.

Finally, while the mSPL showed robust activities to the offset of the oddballs, p's < .01, the BOLD responses to the onset and to the transition between oddballs for the dual oddball were not significant, p's > .20. This is presumably because this region is particularly sensitive to an event calling for switching of attention toward goal-directed tasks.

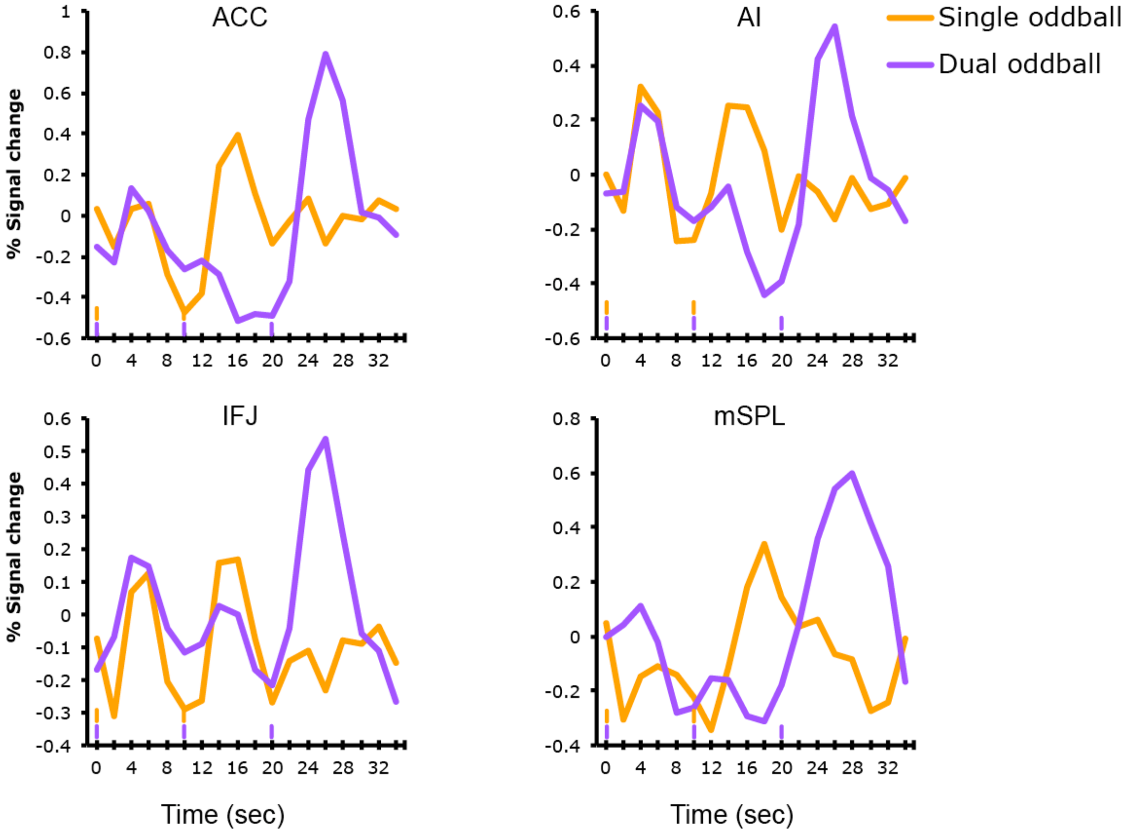

Figure 22. Timecourses of activity to the single and dual oddballs. The first and second orange bars in the plots denote the onset and offset of the single oddballs, respectively. The first, second, and third purple bars denote the onset of the first oddball, the transition between oddballs, and the offset of the second oddball in the dual oddballs.

In sum, the results of the oddball analysis suggest that while all prefrontal (and parietal) regions probed responded to the transitions between oddballs and the goal-relevant task, the AI and IFJ also signaled saliency changes between two-task irrelevant events.

Finally, I also examined what are the roles of the FEF and IPS in attentional switching. These regions were also defined from the open contrast SPM (see Methods).

Consistent with their roles in attentional control (Corbetta, 1998; Corbetta et al., 1998; Corbetta, Shulman, Miezin, & Petersen, 1995; Kastner & Ungerleider, 2000; Serences et al., 2005; Serences & Yantis, 2007; Szczepanski, Konen, & Kastner, 2010), the FEF showed increased activity when attention set should be switched. While the IPS also showed a similar pattern, it did not reach significance, p > .15 (Fig. 23).

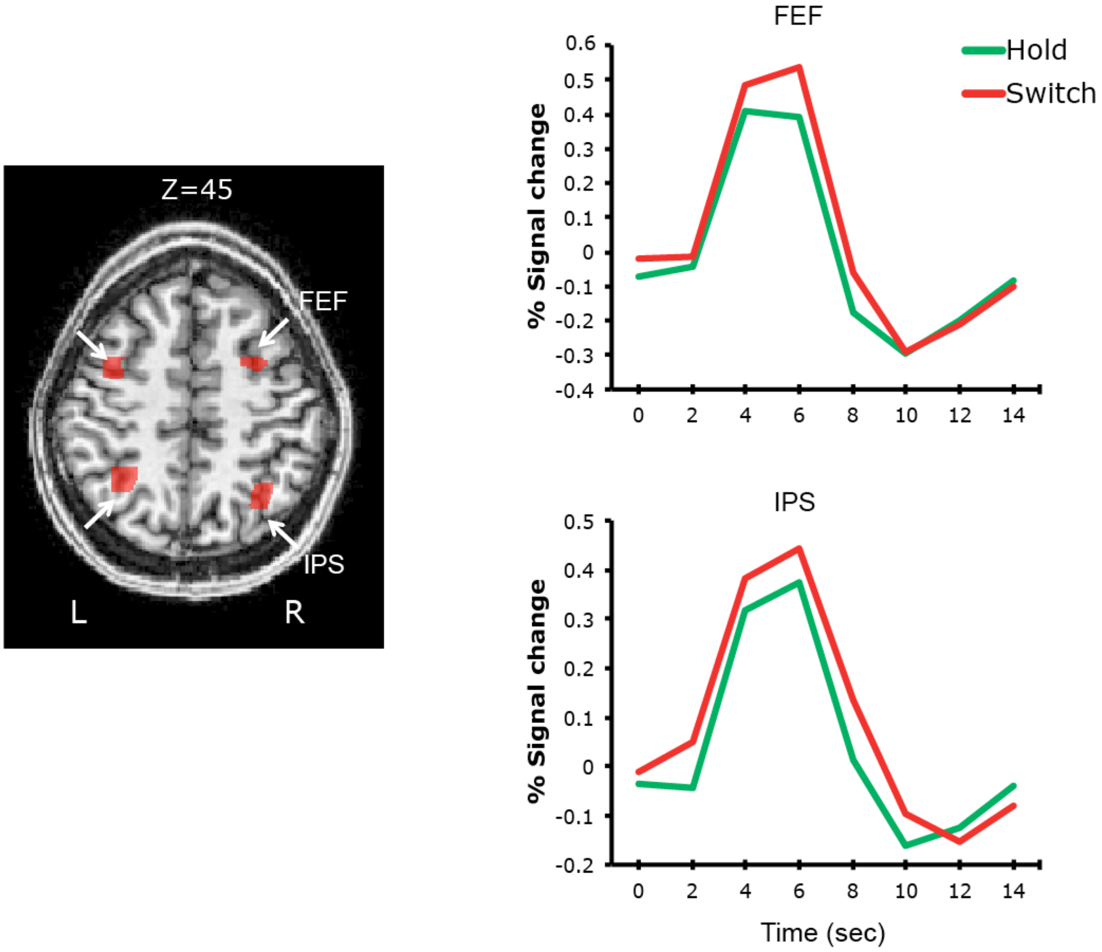

Figure 23. Group-defined FEF and IPS and their timecourses of activation

Similar with other regions that showed increased activity to the Switch cue (ACC, mSPL), the MVPA results of the FEF and IPS showed that activation patterns in these regions discriminated the switching process from the detecting process, p's < .01 (Fig. 24).

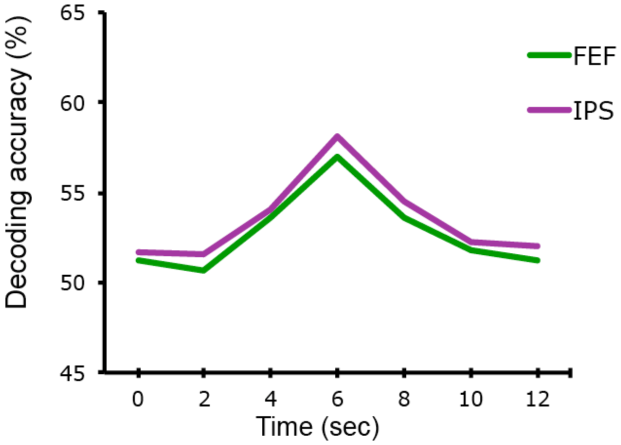

Figure 24. Event-related MVPA results for the FEF and IPS. The event onset is at the time of zero.

The BOLD responses of the FEF and IPS were similar to those of the prefrontal regions implicated in the switching process. Specifically, there was significant activity only at the transition associated with the initiation of goal-directed task, p's < .05, but no activity at the transition between two task-irrelevant oddballs, p's > .20.

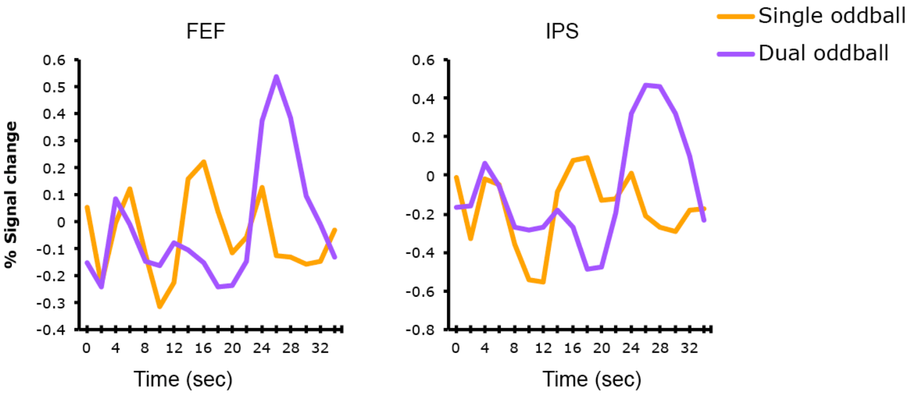

Figure 25. Timecourses of the FEF and IPS activities to the single and dual oddballs

Discussion of Chapter IV

The experiment in this chapter clarified how the prefrontal regions contribute to the transient process of attentional orienting, consisting of detecting and switching attention to a salient, behaviorally relevant event. All the prefrontal regions probed here (the AI, ACC, and IFJ) showed robust activities when behaviorally significant events or salient oddballs were detected. However, only a subset of these regions were found to be preferentially related to attentional switching. Specifically, the ACC, like mSPL, showed greater activity when a behaviorally relevant event was detected and the attentional set was switched than when the significant event was detected but no switching ensued. By contrast, the AI and IFJ showed similar BOLD responses to cues that instructed subjects to hold or switch attentional sets. However, the IFJ, but not the AI, encoded the task rules to Switch or Hold attention sets. This finding, together with the one that AI encoded the transition between two task-irrelevant oddball events suggest that this brain region is particularly sensitive to salient changes in the environment.

The finding that AI is primarily involved in detecting salient changes in the environment fits well with previous studies showing that this region is transiently activated by the occurrence of salient, behaviorally relevant sensory events. However, these studies could not distinguish whether the transient activities reflect detecting or attentional switching to those events (Downar et al., 2000, 2002; Menon & Uddin, 2010). The current results clearly show that the AI is more specialized in detecting, rather than in switching.

Another important result regarding the functional role of AI is that it responded to the transition between task-related stimuli and oddballs, as well as the transition between two oddballs. By contrast, the ACC, implicated in attentional switching, was activated only by the transition between the task-related stimuli and oddballs. Given these findings, the AI seems to universally respond to different kinds of sensory transitions, while the ACC is sensitive to transitions associated with goal-directed tasks.

It is also notable that the IFJ did not show increased activity when attentional switch was required. This finding seems to be inconsistent with numerous studies showing that IFJ activation increases when attentional sets are switched (Asplund, Todd, Snyder, & Marois, 2010; Brass et al., 2005; Braver et al., 2003; Derrfuss et al., 2005; Hampshire et al., 2010; Hyafil et al., 2009; Johnston et al., 2007; Kim et al., 2012; Konishi et al., 1998). However, this discrepancy is likely due to differences in experimental paradigm, as in most of these other studies switching attentional sets imposed more processing demands than the conditions including no switching (Badre & Wagner, 2006; Dreher & Berman, 2002; Hyafil et al., 2009). By contrast, the current paradigm removes any confound related to processing load, task difficulty, or time on task, and isolates activity specifically related to switching (Chiu & Yantis, 2009; Esterman et al., 2009; Tamber-Rosenau et al., 2011; Yantis et al., 2002). Indeed, accounts positing that the primary role of IFJ is attentional switching cannot easily explain its ubiquitous activation in a variety of tasks, which do not necessarily involve switching of attentional sets. I suggest that attentional switching often increases processing demand, which increases activation of the IFJ (Han & Marois, 2013; Marois, Chun, & Gore, 2000). Likewise, when the implementation and maintenance of task sets is challenged by distractor interference or rapidly changing task demands, activation of this region should also increase.

Even though IFJ activity was equivalent between Hold and Switch cues, the multi-voxel pattern of activation within this region suggests that it encodes the Hold and Switch rules. This is a remarkable difference between the AI and IFJ. While the amplitude of their BOLD responses were equivalent for holding and switching attentional sets, only the latter encodes these processes. This finding provides further evidence supporting the claim that the AI primarily serves to detect any kind of environmental transitions, while the IFJ plays a central role as an integrator and coordinator of potentially relevant information.

In sum, the results of the Rules (Switch/Hold) and Oddballs analyses are strikingly consistent with one another in dissociating the brain regions involved in detecting salient events in the environment and switching attention from or to these events. Specifically, both sets of analyses point to the AI as a detector of salient changes in the homeostatic environment. By contrast, these analyses suggest that the ACC and mSPL are primarily involved in implementing attentional switches. Finally, the IFJ appears to integrate information about both detecting salient events and switching attention between such events. More broadly, these results provide support for the notion that orienting of attention to novel events can be fractionated into detecting and attention switching subcomponents (Friedman et al., 2001; Opitz, Rinne, Mecklinger, von Cramon, & Schroger, 2002; Molholm, Martinez, Ritter, Javitt, & Foxe, 2005), and reveal that different nodes of the stimulus-driven attention network make distinct contributions to each of these two subcomponents.

CHAPTER V

CONCLUSION

Most of human behavior is either planned and goal-directed or a reaction to dynamic changes in the environment. For example, while an individual is engaged in planned behavior to accomplish a certain goal kept in mind, his or her attention may be quickly switched from the task at hand to a novel, unexpected and salient event. This is so even though those events are completely irrelevant to the originally planned behavior. The individual then attempts to interpret the attended event to determine whether it is of any behavioral significance and worth modifying the planned course of action (Kahneman, 1973; McCarthy & Donchin, 1981; Posner, 1980; Pritchard, 1981; Sokolov, 1963). If that event is evaluated to be behaviorally relevant, a necessary action will be selected and executed. Otherwise, attention will be reoriented to the original goal-directed behavior.

The present research aimed at delineating the neural substrates underlying the cognitive processes evoked by the presentation of a novel, salient stimulus (oddball), namely attentional orienting/reorienting and stimulus evaluation. Specifically, I examined how those processes are implemented in the stimulus-driven attention network, consisting of the AI, IFJ, and TPJ, as well as in goal-oriented dorsal structures (FEF, IPS, and mSPL). To address this issue, I devised an experimental paradigm, in which a novel, unexpected and salient stimulus is presented to participants in a temporally extended manner to distinguish neural substrates associated with each distinct component of oddball processing.

Chapter II reported findings from experiments that used the extended oddball paradigm. In the face of temporally extended oddballs, the AI, in concert with the ACC, responded only to the onset and offset of the oddball, whereas the IFJ and TPJ showed sustained activation throughout the presentation duration of the oddball. Remarkably, when the contents of the oddball became familiar, thereby decreasing the demand of stimulus evaluation, the IFJ showed transient responses to the onset and offset of the oddball. These results suggest that the AI and ACC are involved in attentional orienting/reorienting, whereas the TPJ plays a role in stimulus evaluation, and the IFJ seems to be involved in both processes (Figure 26).

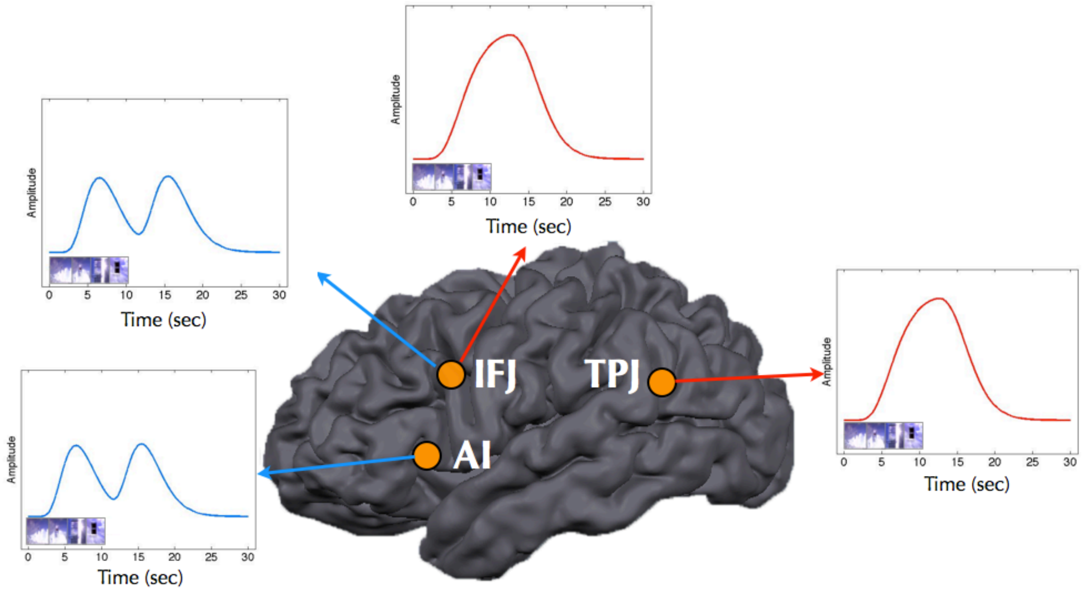

Figure 26. Brain regions comprising the stimulus-driven attention network and their modeled timecourses of activites to the temporally extended oddball. The image in the plots illustrates the 10-sec long presentation of an oddball. The AI shows a transient, double-peaked response, each peak corresponding to the onset and offset of the oddball, whereas the TPJ shows a sustained, single-peaked response. The IFJ is associated with both the transient and sustained components of oddball processing.

The finding that the TPJ showed sustained activation during the oddball presentation is remarkable because it provides an important constraint on understanding the cognitive function of this region. Similar to the AI, the TPJ has been associated with widely disparate functions (Cabeza et al., 2012; Decety & Lamm, 2007; Meyer et al., 2012; Mitchell, 2008). To integrate these findings, a recent theory posits that the TPJ is activated when salient sensory inputs or those related to internal representations capture attention in a bottom-up way (Cabeza et al., 2012). This bottom-up attention account of the TPJ function fits well with numerous findings that this region is often either deactivated during goal-directed behaviors, or activated transiently by the presentation of a salient stimulus (Cabeza et al., 2011; Corbetta et al., 2008; Downar et al., 2000, 2002). However, it fails to accommodate the sustained TPJ activity to the oddball; if the TPJ had been primarily involved in bottom-up attention capture, its response to the oddball would have been transient as the AI was.

Another prominent model of the TPJ function also posits that the TPJ is primarily involved in the transient process of orienting/reorienting of attention toward a behaviorally relevant stimulus (Corbetta et al., 2008; Shulman et al., 2007). In line with this proposition, the TPJ activity is particularly strong when a salient stimulus shares features with the target being searched for (contingent capture) (Serences et al., 2005). However, this orienting/reorienting account is not consistent with sustained TPJ activation observed in the present study. I surmise that involvement of the TPJ in contingent capture can also be accounted for by the notion that the TPJ evaluates the behavioral relevance of the (target) stimulus.

As reviewed in Chapter I, there is ample evidence suggesting that the primary role of the TPJ is stimulus evaluation, which refers to the process of identifying and categorizing a given stimulus to determine its functional significance, rather than attentional orienting or attention capture. Given that stimulus evaluation is often accomplished via matching the stimulus to internal representations (Ciesielski et al., 1985; Courchesne et al., 1975; Decety & Lamm, 2007; Delplanque et al., 2005; Donchin & Coles, 1988; Doricchi et al., 2010; Geng & Mangun, 2011; Polich, 2007), this account fits well with previous studies showing that this region is involved in the memory retrieval process (Bledowski et al., 2006; Cabeza et al., 2011; Uncapher, Hutchinson, & Wagner, 2011). This account also easily relates the TPJ to social cognitive processes; in a context of social interaction, one should identify and categorize another's intention and feeling to determine how to interact with the person one faces (Frith & Frith, 2006; Hein & Singer, 2008; Singer et al., 2009).

Another notable finding of my studies regarding the TPJ function is that the TPJ involved in stimulus-driven attention was found to be sensitive to stimulus properties evoking mentalizing processes. The TPJ activity was far greater to the stimuli arousing empathy, which is a crucial component of social cognition. Recently, it has been extensively debated whether the ventral parietal region, including the TPJ, subserves a core process underlying social, attention, and memory processes, or distinct regions in the ventral parietal cortex are devoted to different (mentalization, attention) processes (Cabeza et al., 2012; Decety & Lamm, 2007; Hutchison et al., 2013; Mitchell, 2008; Uncapher, Hutchinson, & Wagner, 2011). While the current studies do not directly address the issue of functional dissociation within the lateral temporo-parietal region, my findings are consistent with the account that this region cortex broadly subserves a core, fundamental process underlying social cognition, memory retrieval, and stimulus-driven attention. Specifically, I propose that this function consists in matching stimuli or events (whether targets, novel stimuli or social interactions) to internal representations for the purpose of understanding its behavioral significance (Doricchi et al., 2010; Geng & Mangun, 2011;Polich, 2007). Furthermore, given that stimulus evaluation requires matching a stimulus to information stored in memory (Ciesielski et al., 1985; Courchesne et al., 1975; Decety & Lamm, 2007; Delplanque et al., 2005; Donchin & Coles, 1988), the TPJ can be linked to memory retrieval, as well (Cabeza et al., 2012).

The finding that the AI transiently responded to the onset and offset of the extended oddball is consistent with a large body of studies suggesting that this region is involved in detecting salient, behaviorally significant events (Downar et al., 2000, 2002; Eckert et al., 2009; Menon & Uddin, 2010; Seeley et al., 2007). Furthermore, the ACC showed a similar pattern of response with the AI, supporting the claim that the AI and ACC form a saliency network signaling saliency of sensory inputs (Menon & Uddin, 2010; Seeley et al., 2007). Notably, while the salience network was derived from resting state functional connectivity analyses (Seeley et al., 2007; Sridrahan et al., 2008), the current study provided the first direct evidence that these two regions respond to a salient stimulus in a similar (though not identical) way.

The results that the AI and ACC responded only to the onset and offset of the temporally extended oddball, regardless of whether its contents were novel or familiar, also raised an important question. Are these regions completely immune to the contents of oddballs? This is an important issue especially because the AI has been implicated in various social, emotional, and affective processes (Adolphs, 2002; Brooks & Tracey, 2007; O'Doherty et al., 2003; Singer et al., 2009; Valentini, 2010). Indeed, the salience network account suggests that the finding that the AI was associated with affective processing is because stimuli that evoke affective processes are particularly salient ones, which the AI strongly responds to (Menon & Uddin, 2010; Seeley et al., 2007). Chapter III directly assessed this claim. The results of Experiment 3 showed that when the oddball contained contents arousing disgust, empathy and pain – which are known to activate the AI – this region showed sustained response during the oddball presentation. Even though the AI still showed pronounced, transient responses to the onset and offset of the oddball, it was clearly sensitive to the affective contents of the oddballs. A potential interpretation of these findings is that affective stimuli are so salient that they can lead to maintained AI activation throughout their presentation. However, if the sustained saliency account is correct, then I would have expected the presentation of novel oddballs to evoke sustained activity in AI compared to the repeated presentation of the same oddball (see Expt 1 & 2), as novel oddballs should be significantly more salient. Yet, there was no sustained AI activation with novel or repeated oddballs. It remains possible that our emotional oddballs were far more salient than the standard oddballs, which could account for why sustained AI activation is observed with affective oddballs only. In any event, it is clear that the AI is sensitive to the affective contents of task-irrelevant stimuli.

The IFJ has an activation profile to long oddball presentations that is distinct from both the AI and TPJ. This region was found to be involved in both attention orienting and in stimulus evaluation, and thus to integrate the type of information that is processed in AI and TPJ. This finding is consistent with previous studies suggesting that this region acts as a coordinator of other brain regions (Asplund et al., 2010b; Bledowski et al., 2004). Presumably, such coordinator plays a role in determining the value or behavioral relevance of a stimulus, and in mapping the appropriate response to that stimulus. All these findings support the proposition that this lateral prefrontal region acts as a central hub for stimulus-driven and goal-directed attention (Asplund, Todd, Snyder, & Marois, 2010) and for cognitive control, more generally (Brass et al., 2005; Braver et al., 2003; Konishi et al., 1998; Marois & Ivanoff, 2005).

In Chapter IV, I decomposed the orienting activity observed in the prefrontal regions into activities related to detecting and switching attention to a salient stimulus. Using a well-established paradigm that isolates transient activity specifically related to attentional switching, I found that ACC activation increased when attentional sets should be switched, whereas the AI and IFJ showed equivalent activation for attentional switching and detecting behaviorally relevant stimuli. Similarly, the ACC showed a robust response at the transitions between task irrelevant oddballs and goal-oriented behavior, but not between oddballs (Fig. 22) or between oddballs and a fixation period (Fig. 13), whereas the AI and IFJ were engaged by all transitions. These findings imply that the transient activities of the ACC to the onset and offset of the temporally extended oddball are related to switching attention between task-related stimuli and oddballs, while such transient pattern of AI activity seems to be related to detecting salient stimuli. As such, the present studies have functionally partitioned the two core components of the salience network.

To be noted, even though the IFJ showed no differential activity to detecting and switching, similar with the AI, the interpretation that the IFJ is primarily involved in detecting but not in switching is not likely. First, many previous studies showed that IFJ activation is involved in attentional switch (Asplund, Todd, Snyder, & Marois, 2010; Brass et al., 2005; Braver et al., 2003; Derrfuss et al., 2005; Hampshire et al., 2010; Hyafil et al., 2009; Johnston et al., 2007; Kim et al., 2012; Konishi et al., 1998). Most importantly, I also found that distinct neuronal populations in this region selectively coded the detecting and switching processes.

A more plausible account is that the IFJ plays a central, integrative role in human cognition, as demonstrated in Chapter II and previous studies (Asplund, Todd, Snyder, & Marois, 2010). Specifically, while other prefrontal regions are specialized in the processes of detecting or attentional switching, the IFJ coordinates and integrates outcomes of such processes to implement task sets and exert cognitive control. Hence, whenever the implementation of a task set is challenged by rapidly changing task demands or distractor interference, stronger task control is required, which recruits IFJ activation.

A Neural Network model of stimulus-driven attention

Taken together, the studies reported here provide important insights regarding how each individual node in the stimulus-driven attention network contributes to orienting responses. In particular, when integrating all of the findings derived from my thesis work, I propose the following model of attention capture by a novel, salient event (Fig. 27).

When an unexpected, salient stimulus appears in one's view, the AI, along with the IFJ, elicits a response that signals the presence of a salient change in the homeostatic environment of the observer. This change is rapidly accompanied by a shift in attentional resources to the oddball stimulus, provided primarily by the dorsal medial structures (mSPL and ACC). Based on the MVPA findings, I suggest that it may be the IFJ that instructs or co-ordinates the shift of attention implemented by the ACC and mSPL. Together, these steps represent the neural basis of orienting of attention to a novel stimulus. Following such orienting, an attention-based evaluative process takes place in the TPJ (as well as in the IFJ) and supported by the dorsal attention structures (FEF/IPS) in order to identify and categorize the oddball, possibly by a matching process between the external stimulus and internal representations (Ciesielski et al., 1985; Courchesne et al., 1975; Decety & Lamm, 2007; Delplanque et al., 2005; Donchin & Coles, 1988; Doricchi et al., 2010; Geng & Mangun, 2011; Polich, 2007). Finally, when the oddball event is terminated or is deemed behaviorally irrelevant, re-orienting of attention to the goal-oriented behavior would ensue, a process that would recapitulate the neural cascade associate with attention orienting with perhaps a greater contribution of medial structures in the re-orienting process (Fig. 27).

It is important to stress that this model does not imply strict compartmentalization of each computation in their respective nodes. Rather, it is assumed that much information sharing occurs across nodes, thereby ensuing that integrated and coherent information processing is taking place throughout this network. Finally, it is worth emphasizing the central role that the posterior lateral prefrontal cortex (IFJ) may play in stimulus-driven attention, as it appears to be involved in all of the individual computational components described above, once again driving the point of its pivotal position as a central hub for attention control (Asplund, Todd, Snyder, & Marois, 2010; Brass et al., 2005; Braver et al., 2003; Derrfuss et al., 2005; Han & Marois, 2013).

The proposed model of stimulus-driven attention makes some specific predictions. According to this framework, the IFJ, a hub region, should be functionally connected to all of the other brain regions of the network. By contrast, the model predicts that the AI and IFJ would be much more weakly connected with one another than each of them would be with IFJ. I would also expect the functional connectivity to be dynamically adjusted to processing demands. For example, the connectivity between IFJ and TPJ should be weaker when the oddball is always the same compared to when it is always different.

The model makes also specific predictions about the temporal flow of information processing, predictions that are difficult to test given the limited temporal resolution of fMRI. In particular, it would be expected that following the presentation of a novel salient stimulus, the AI and IFJ may be the first brain regions activated (perhaps via a low-level signal of saliency from visual cortex), to be quickly followed by activation in the dorsal attention switching structures. The TPJ would then become engaged as the stimulus is evaluated. While no electrophysiological studies have clearly mapped out the spatio-temporal dynamics of all of these brain regions, there is at least some evidence that the lateral prefrontal cortex may be activated just prior to the parietal cortex under stimulus driven conditions (Delplanque et al., 2005; Friedman et al., 2001). Clearly, more studies using high temporal resolution approached are warranted.

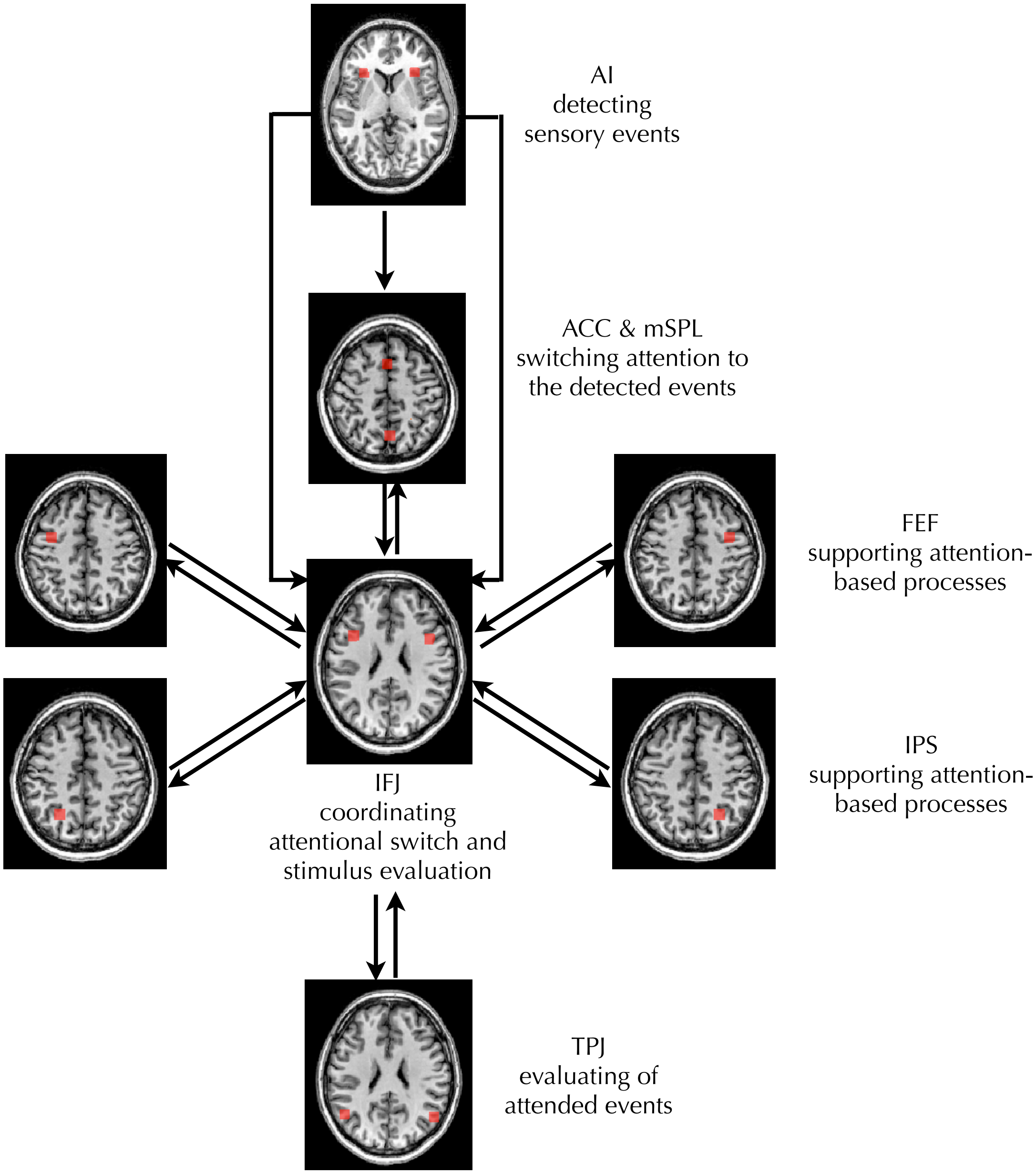

Figure 27. Neural network model of stimulus-driven attention. The AI, ACC, and TPJ are primarily involved in specific cognitive operations. The IFJ coordinates activities of those brain regions, and determines which stimulus should be attended and which process should be implemented. In this model, the IFJ may ultimately determine the value of a given sensory input and select the appropriate response. The dorsal attention regions (FEF and IPS) may be associated with the attentional demands of processes implemented in the network.

Regardless of the extent to which this model will turn out to be correct, in the process of this investigation many important findings were obtained that significantly constrain the extant theories regarding the roles of the prefrontal and parietal cortex in attention and cognition. These findings were obtained by the explanatory power of time resolved fMRI in fractionating a behavior into its basic neuro-computational constituents. Even though these studies primarily focused on stimulus-driven attention, the findings of the studies ultimately provide an integrative picture of how external sensory events are registered/encoded, analyzed/interpreted, and reacted in a context-appropriate manner to optimize coherent behavior.

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