INVESTIGATING IMPULSIVITY IN CEREBELLAR (DYS)CONTROL

By

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
AMY	Amygdala
ANOVA	Analysis of variance
AUC	Area under the curve
BIS-11	Barratt Impulsivity Scale version 11
BOLD	Blood oxygenation level-dependent
CCAS	Cerebellar Cognitive Affective Syndrome
CSA	Spinocerebellar ataxia
CT	Computed tomography
DA	Dopamine
DCN	Deep cerebellar nuclei
DREADD	Designer Receptors Exclusively Activated by Designer Drugs
EEG	Electroencephalogram
ET	Essential Tremor
FDR	False Discovery Rate
fMRI	Functional Magnetic Resonance Imaging
FrSBe	Frontal Systems Behavior Scale
FSL	FMRIB Software Library
FWHM	Full width at half maximum
GABA	Gamma-aminobutyric acid
GLM	General linear model
GRASE	Gradient and spin echo
HC	Healthy control
HIPP	Hippocampus
ICB	Impulsive and compulsive behavior(s)
LASSO	Least absolute shrinkage and selection operator
LC	locus coeruleus
MCL	Mesocorticolimbic (system)
MDS	International Parkinson and Movement Disorders Society
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
MPRAGE	Magnetization-prepared rapid gradient-echo
MRI	Magnetic Resonance Imaging
MSA	Multiple system atrophy
NAc	Nucleus accumbens
NINDS	National Institute for Neurological Disorders and Stroke
OFC	Orbitofrontal cortex
PET	Positron Emission Tomography
PD	Parkinson’s Disease
QUIP	Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease

QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale
RBD	REM sleep behavior disorder
RF	Radiofrequency
ROI	Region-of-interest
rs-fMRI	Resting state functional magnetic resonance imaging
SCA	Spinocerebellar ataxia
SNc	Substantia nigra pars compacta
SNP	Single nucleotide polymorphism
SPECT	Single-photon emission computerized tomography
TE	Time to echo
TMS	Transcranial magnetic stimulation
TR	Repetition time
SSRT	Stop-signal reaction time
UPDRS	Unified Parkinson's Disease Rating Scale
UPPS	Urgency-Premeditation-Perseverance-Sensation seeking Impulsive Behavior Scale
vmOFC	ventromedial orbitofrontal cortex
VTA	ventral tegmental area

CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 THE CEREBELLUM

The cerebellum is a structure located at the most posterior part of the brain below the temporal and occipital lobes and is highly recognizable by its highly foliated appearance (Fig. 1-1). It accounts for 10% of total brain weight, though it contains somewhere between 60-80% of the total number of neurons in the brain – equivalent to roughly 60 billion neurons (Herculano-Houzel, 2010; Sereno et al., 2020). In fact, the cerebellar cortex is much more tightly folded than the cerebral cortex, with a surface area that is estimated to be 10cm in width, but almost a meter in length (Sereno et al., 2020). Historically, the cerebellum has been considered a motor structure, these ideas developed due to patients with lesions within the cerebellum that produced noticeable impairments in motor control. Large numbers of reports from the last two centuries have cited both patient and animal research in which cerebellar lesions resulted in movement disorders such as ataxia, dysmetria, dysarthria, and other clinical features, including a landmark study showing loss of coordinated wing movements in pigeons with cerebellar damage (Dow & Moruzzi, 1958; Flourens, 1842; Grimaldi, 2013; Russel, 1894).

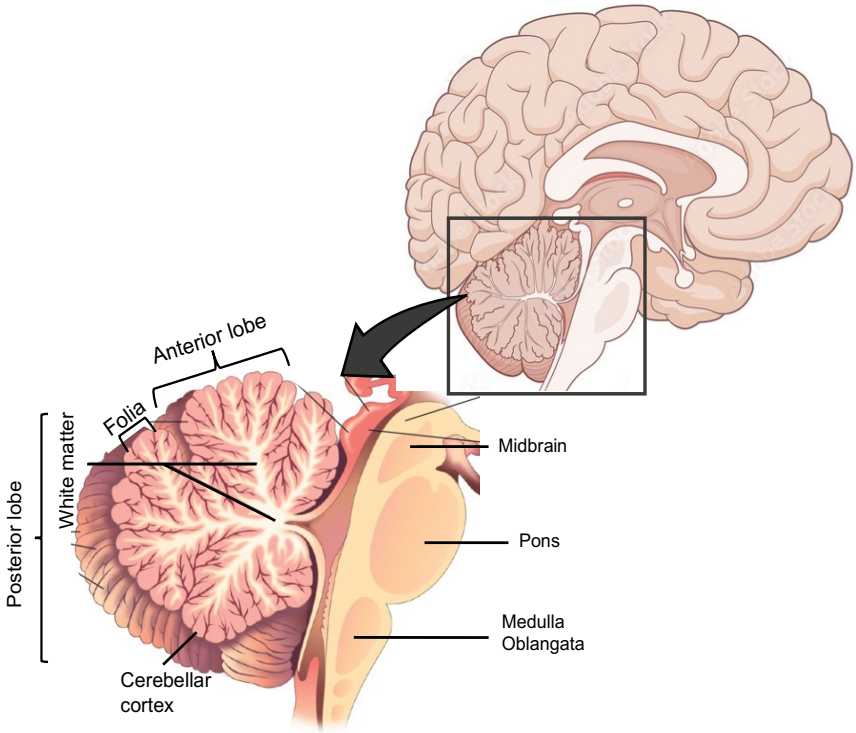


Figure 1-1. A sagittal view of the brain (top right) zoomed in to show the cerebellum and brainstem structures (bottom left). Image created from altered vector stock and Adobe photos. https://stock.adobe.com.

Anatomy & function

The cerebellum consists of two hemispheres, connected by the vermis, a central midline structure, and is traditionally sub-divided into three main lobes the anterior, posterior, and flocculonodular, based on two fissures that split the cerebellum horizontally (Fig. 1-1). The primary fissure separates the anterior and posterior lobes, while the posterolateral fissure separates the posterior and flocculonodular lobes. The cerebellum can also be phylogenetically classified into the vestibulocerebellum, spinocerebellum, and cerebrocerebellum (Fig. 1-2) (Purves et al., 2018). The oldest portion, the vestibulocerebellum, primarily receives input from the vestibular system and is important for maintaining balance. The phylogenetically intermediate portion are most medial part, the spinocerebellum, receives direct input from the spinal cord. The most recently developed part and most lateral, the cerebrocerebellum, receives input from various parts of the cerebral cortex. Processing information from many varied inputs requires a lot of computational power. Like the cerebrum, it has a highly convoluted surface of grey matter that surrounds a white matter core, which in turn surrounds the four pairs of deep cerebellar nuclei. The cortex contains three layers,

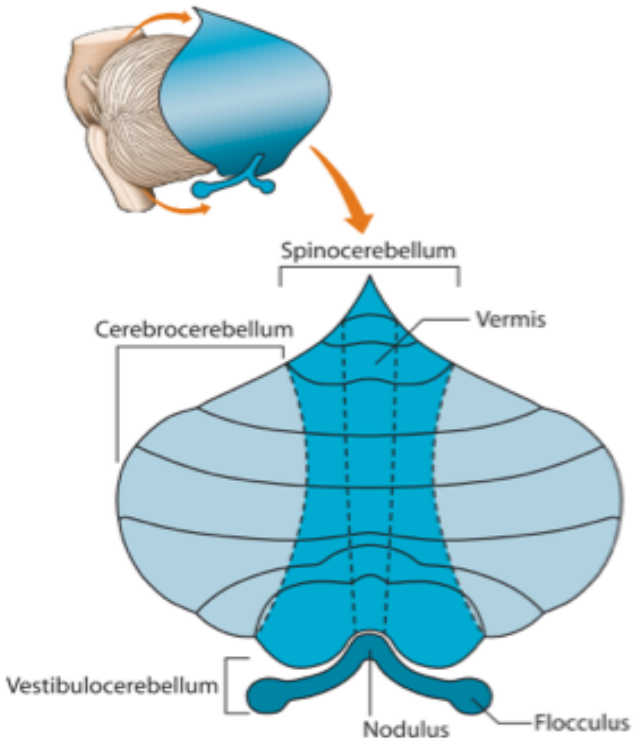


Figure 1-2. Phylogenetic breakdown of the cerebellum. Three divisions are shown in varying shades of blue. The cerebrocerebellum is shown in lightest blue color (most lateral) and is phylogenetically the newest. The spinocerebellum occupies the median and paramedian areas of the cerebellum and is shown in blue. The vestibulocerebellum is shown in the darkest blue. Located at the base of the cerebellum, it is phylogenetically the oldest part of the cerebellum.

the external molecular layer, the Purkinje cell layer (middle), and the internal granule cell layer. Incoming input from the cerebrum travels through climbing and mossy fibers to reach the cerebellar cortex where they eventually synapse onto Purkinje cells. The Purkinje cells then project in turn to deep cerebellar nuclei. These cells are the only output cells of the cerebellar cortex, and are GABAergic, meaning the output of the cerebellar cortex is solely inhibitory. This description of information though the cerebellar pathway is basic in nature and excludes significant interactions between interneurons and the nuances of interneuronal communication. However, it does underline one of the primary features of information processing within the cerebellum, which is to integrate and deconstruct incoming information from the body and the brain and then modulate the information to send in a feedforward fashion through the deep cerebellar nuclei. Thus, the cerebellum functions to continuously monitor, regulate, and fine-tune incoming information from various parts of the brain (Purves et al., 2018). For the most studied cerebellar role, motor movement, inputs from motor cortex, brainstem nuclei, and sensory receptors throughout the body are integrated, and the cerebellum then sends out new information on how to coordinate muscle contractions, joint positioning, tendon tension and force, etc. to maintain action, posture, balance, and allow for smooth coordinated movements. This is a complex process (and this example is solely in the context of motor control), which requires multi-level integration and synthesis to produce a refined output. If any component in this process breaks down, it will likely result in movement dysfunction, which can present itself through a wide variety of symptoms.

Cerebellar Dysfunction

There are a few ways that cerebellar disorders can be classified: 1. Congenital/developmental, 2. Acquired, 3. Inherited/Genetic, and 4. Degenerative (Roostaei et al., 2014; Valente et al., 2018). Congenital/developmental cerebellar diseases occur when parts of the cerebellum do not develop completely or correctly. Examples of these are Joubert syndrome in which the cerebellar vermis does

not completely develop, Dandy-Walker syndrome in which the cerebellum and fourth ventricle do not develop completely, and Chiari malformations, in which cerebellar tissue extends into the spinal canal due to a misshapen or atypically small skull. Acquired cerebellar diseases occur later in life, sometimes as a consequence of a previous infection, dysfunctional metabolism, traumatic brain injury, drug/toxin ingestion, or vascular damage, such as a stroke. Genetic cerebellar disorders can be caused by a variety of DNA alterations including single-nucleotide polymorphisms (SNPs), insertions or deletions, larger copy number variants, and nucleotide repeat expansions, X-linked, autosomal-recessive, or autosomal-dominant, both inherited and *de novo* (Valente et al., 2018). One of the most common autosomal dominant ataxias are spinocerebellar ataxias (SCAs). Finally, degenerative cerebellar diseases are those in which there is progressive loss of cells in the cerebellum that lead to worsening disease over time. Cerebellar symptoms can occur in isolation or as part of a larger neurological condition. Proper diagnosis of patient conditions requires a clinical examination including instructions to test a variety of motor-related tasks that the cerebellum is known to be responsible for including coordination, balance, smooth movements, and goal-directed actions.

The cerebellum is highly interconnected with the cerebral cortex and the classical view for how these areas interacted stated that information was projected from all four lobes (frontal, parietal, temporal, occipital), integrated within cerebellar circuits, then projected out through the ventrolateral nucleus of the thalamus where it was believed to only project to a single cortical area, M1 – primary motor cortex (Bostan & Strick, 2018). Therefore, prior views assumed cerebellar network connections with cerebral cortex served to integrate information across multiple cortical areas, perform a sensorimotor transformation based on the input, and then convey updated results to motor cortex to modulate movement. Further, given these views, any abnormal activity in this circuit would solely result in impairments to motor control. However, in the last few decades, emerging evidence is challenging this singular role of the cerebellum (Akkal et al., 2007; Ben-Yehudah & Fiez, 2008;

Ben-Yehudah et al., 2007; Bostan & Strick, 2018; Middleton & Strick, 1998, 2000; Strick et al., 2009).

Cerebellar Neurocognition

The cerebellum was considered for many years to only be responsible for motor function, balance, and coordination, but as mentioned earlier, the cerebellum contains more than half of all the neurons in the brain, so it was unlikely that such a structure would solely be relegated to motor control. In fact, there were anecdotal mentions of behavioral symptoms in early reports investigating cerebellar diseases, with the earliest reports from France in the mid 1800s, but they lacked pathological verification, and the attention stayed on cerebellar contributions to motor rather than non-motor function (Andral, 1848; Combettes, 1831; Knoepfel & Macken, 1947; J D Schmahmann & Sherman, 1998; Jeremy D. Schmahmann, 1991). In the 1980s, a few studies published findings that patients with cerebellar degeneration or cerebellar stroke presented with cognitive dysfunction directly related to the cerebellar disease (Bracke-Tolkmitt et al., 1989; Kish et al., 1988; Henrietta C. Leiner et al., 1986). Then, over the course of the next decade, studies continued to show relationships between cerebellar dysfunction and cognitive deficits, including, but not limited to, increased planning times, poor verbal fluency, visuospatial deficits, impaired linguistic processing and expression, and abnormal mood/affect (Appollonio et al., 1993; Botez-Marquard & Botez, 1993; Grafman et al., 1992; H C Leiner et al., 1993; Henrietta C. Leiner et al., 1986; Levisohn et al., 2000; Molinari et al., 1997; Wallesch & Horn, 1990). These findings spanned a variety of ages, disease states, and neuropsychological testing paradigms, and were not widely accepted enough to expand the role of the cerebellum to include non-motor behaviors. Finally, a landmark study in 1998 by Schmahmann and Sherman was performed to test patients with diseases specific to the cerebellum to assess whether there were clinically relevant cognitive and behavioral changes in these patients using a combination of neurological examinations, bedside mental status testing, and neuropsychological evaluations

(Schmahmann & Sherman, 1998). Their results revealed a pattern of behavioral abnormalities, which they termed the 'cerebellar cognitive affective syndrome' (CCAS) and included many of the previously described impairments, such as visuospatial deficits, personality change with blunted affect or disinhibited behavior, language production difficulties, and a variety of executive dysfunctions in planning, set-shifting, abstract reasoning, verbal fluency, working memory, and attention (Schmahmann & Sherman, 1998). This study laid the groundwork for future investigations into the precise mechanisms by which the cerebellum contributes to cognition and behavior. Lesion studies along the midline of the cerebellum in a rodent model showed that those with lesions had increased perseverative behaviors, deficits in attention, especially to novel stimuli, and an increase in disinhibited impulsive-like behaviors further implicating the cerebellum in modulating behavioral actions (Bobée et al., 2000). The next step was to track down what area(s) of the cerebellum were important for behavioral regulation, and how those were interconnected with other areas of the brain. A study by Bostan et al., (2010) used retrograde transneuronal transport of a rabies virus to investigate the origins of some multi-synaptic inputs to the cerebellum. They found that the subthalamic nucleus, a dopamine rich region of the midbrain (and the origin spot of the nigrostriatal pathway), has a disynaptic projection to the cerebellar cortex that is topographically organized and likely forms a highly integrated functional network. Another study showed direct dopaminergic projections from the ventral tegmental area (VTA; the origin spot for the mesocorticolimbic system) to the cerebellum and found detectable levels of dopamine in the posterior lobules of the cerebellum (Glaser et al., 2006). Further research implicating a role for the cerebellum in dopaminergic pathways showed that, in humans, dopamine D1-3 receptors, tyrosine hydroxylase (a dopamine precursor), and dopamine transporter mRNA were all found of the vermis of the cerebellum in post-mortem brains of normal individuals (Hurley et al., 2003). Interestingly, when comparing the amount of mRNA expression to Parkinson's patients, they found that Parkinson's patients had significant reductions in D1 and D2 receptor mRNA in lobule IX, and significant reductions in tyrosine hydroxylase in lobule X,

suggesting that dopaminergic dysfunction in Parkinson's disease extends beyond the basal ganglia into the cerebellum. Furthermore, it was shown that cortical regulation of striatal activity, a region highly associated with impulsive behaviors, could be modulated by the cerebellum (Moers-Hornikx et al., 2009). This modulation could be regulated through a few cerebellar afferent pathways: 1. Indirect cerebellar connections to the VTA through the reticulotegmental and pedunculopontine nuclei (Carbo-Gas et al., 2014) 2. Indirect connections to the VTA that first pass through the mediodorsal and ventrolateral nuclei of the thalamus (Rogers et al., 2011), and 3. Direct projections from deep cerebellar nuclei to the VTA (Carta et al., 2019; Watabe-Uchida et al., 2012). These findings collectively implicated the cerebellum in dopaminergic pathways. Cerebellar connections with the VTA provide a pathway for cerebellar modulation/influence on the major pathway in the brain thought to be responsible for reward, motivation, salience, and social behaviors – all contributing factors in disinhibited and impulsive actions (Bromberg-Martin et al., 2010; J. W. Dalley & Roiser, 2012; Koob & Volkow, 2016; Volkow et al., 2019, 2017; Wise & Rompre, 1989).

Although further research is needed to fully understand the role of the cerebellum in impulsivity and behavioral regulation, there exists a working hypothesis for how these networks are functioning. Cerebellar dysfunction results in an increase in striatal-cerebellum activity while decreasing prefrontal-cerebellar activity which results in an overactive "go" system at the expense of top-down "no-go" inhibitory control (Miquel et al., 2019). The cerebellum is thought to be critical in restraining ongoing actions by adjusting prefrontal activity in response to new and continued input of sensory information that is integrated in the cerebellar cortex. This hypothesis is supported by studies in both animals and humans, in which electrical and non-invasive stimulation of cerebellar activity resulted in a modulatory effect on prefrontal cortical activity (Forster & Blaha, 2003; Schutter et al., 2003; T. C. Watson et al., 2014). Current hypotheses presented by Miquel and colleagues predict that inhibiting activity in the cerebellar cortex (invasively via designer receptor exclusively

activated by designer drugs (DREADDs) or non-invasively with transcranial magnetic stimulation) should increase impulsive and compulsive symptomatology (Miquel et al., 2019). Conversely, stimulation of the cerebellar cortex should improve behavioral inhibitory control. It's important to note that these hypotheses are strictly related to cerebellar cortical manipulation; opposite predictions are suggested for direct manipulations in the deep cerebellar nuclei (DCN), since these nuclei receive tonic inhibition from the cerebellar cortex. In this dissertation, I will assess contributions of the cerebellum to frontal behaviors, with an emphasis on dopamine-related behaviors such as impulsivity and disinhibition.

1.2 MOVEMENT DISORDERS

Parkinson's Disease

Epidemiology - This disease is found worldwide, and is present across multiple subgroups of race, ethnicity, geography, environment, and genotypes, though in varying amounts. For example, rates of Parkinson's Disease are higher in Israel (perhaps reflecting the higher prevalence of genetic mutations in this population, particularly Ashkenazi Jews (Chillag-Talmor et al., 2011), while the incidence of PD diagnoses are higher in men of Japanese descent living in Hawaii compared to Japanese men living in Japan, supporting the idea that environment plays a role (Morens et al., 1996). PD is not sex linked and can be found in both sexes, though the male sex can be more likely to develop PD than females, with a couple of studies finding that men were diagnosed at a rate twice as high as females (Baldereschi et al., 2000; Gillies et al., 2014), although incidence in males vs. females may depend on ethnicity (Jellinger, 2014). It's likely that in most PD cases, there are complex interactions between environmental factors and genetic background that occur to produce the disease state. Two forms of PD are recognized: a familial, or early-onset form of PD in which a genetic mutation, usually one of the 'PARK' family, DYT5 or SCA mutations are present, and an idiopathic, or sporadic form, also known as late-onset PD, which is the most common form and does not have a

direct genetic component. Although there have been several genetic and experimental models that have been studied over the years, there is no completely optimal model of this disease, and the precise etiology still remains elusive. The overall estimated prevalence for PD is 1-3% of the population over age 65, increasing to 4% over age 80, totaling to roughly 7-10 million people worldwide (Jellinger, 2014). With increasing life expectancies of the general population, it is likely we will see both the occurrence and prevalence of PD rising in the next couple of decades.

Neuropathology

Parkinson's Disease (PD) is a known progressive neurodegenerative disorder that selectively target dopamine neurons in the brain, particularly in the substantia nigra, which can be seen clearly via imaging techniques such as magnetic resonance imaging (MRI) and on autopsy (Fig 1-3). The degeneration of these neurons leads to a decrease in the overall level of dopamine in the brain, which is responsible for several functions, but has a primary role in motor movement.

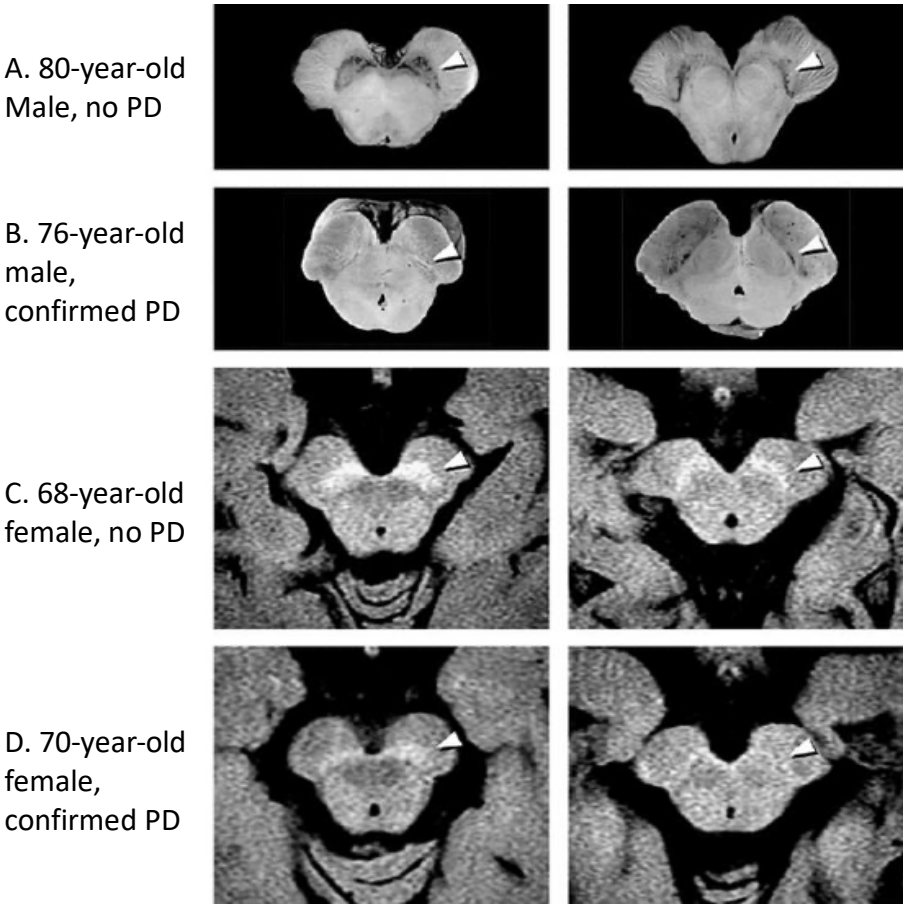


Figure 1-3. Macroscopic specimens (rows A, B) and neuromelanin magnetic resonance imaging (MRI) sections (rows C, D) of the substantia nigra pars compacta (SNc). (A) Macroscopic specimens from the brain of an 80-year-old male cadaver without Parkinson's disease (PD) or other central nervous system disorder. (B) Macroscopic specimens from the brain of a 76-year-old man with pathologically proven PD. The neuromelanin pigment of the SNc (white arrowheads) is greatly reduced in row C compared to row B, owing to neuronal depletion. (C) Neuromelanin MRI of pons and midbrain of a 68-year-old healthy woman. Hyperintensity areas are found at locations corresponding to the SNc (white arrowheads), in close correlation with the findings in (A). (D) Neuromelanin MRI of pons and midbrain of a 70-year-old woman with PD. The hyperintensity areas indicating the SNc (arrowheads) do not stand out, presumably because of decreased neuromelanin content resulting from neuronal depletion. Edited from Sasaki et al., 2006.

Additionally, these patients present with Lewy body inclusions, which are abnormal α-synuclein protein aggregates that reside inside neuronal cells. The Lewy body pathology is observed in particular brain areas, particularly affecting cholinergic and monoaminergic neurons in the brainstem

and olfactory areas, but as the disease progresses are also seen in limbic and frontal cortical areas, which is a distinctly different pattern of progression from other synuclienopathies such as Alzheimer's which tends to be more concentrated in the limbic brain regions (Jellinger, 2014; Kon et al., 2020; Wakabayashi et al., 2013).

Although most of the pathophysiology of PD has been studied in the substantia nigra and in the striatum, a few studies have investigated the cerebellum as a target for PD pathology. A rodent study investigating mutations in proteins associated with familial PD found α-synuclein in the cerebellum granule cell layer and dentate nucleus, regions not directly associated with Parkinson's disease (Solano et al., 2000). In a human model, Piao et al. (2003) found that in some PD patients, α-synuclein aggregates could be seen in the molecular layer of the cerebellar cortex. A recent study found both neuronal and oligodendroglial α-synuclein aggregates in the cerebella of twelve PD subjects with no α-synuclein aggregates seen in control cerebella. The cerebellum is not included in normal Braak staging of Parkinson's disease, however, given the inclusion of α-synuclein aggregates in multiple studies, a new staging model that includes cerebellar involvement may be warranted (Braak et al., 2003; Visanji et al., 2014).

Diagnosis and symptomatology - Dopamine depletion from increasing disease burden results in the commonly seen symptoms in PD grouped under the acronym TRAP: Tremor at rest, Rigidity (stiff and inflexible muscles), Akinesia (or bradykinesia, which can include slow movement, micrographia, small voice, and a decreased arm swing), and Postural instability. These four cardinal symptoms were described by James Parkinson in 1817, for whom the disease has been named, although recent evidence has emerged that this disease and its four hallmark signs were described more than 120 years earlier by a Hungarian by the name of Ferenc Pápai Páriz (Bereczki, 2010; Parkinson, 2002). Clinical criteria for diagnosis have been established by the UK Parkinson Disease Society Brain Bank, Movement Disorder Society, and the National Institute of Neurological Disorders and Stroke

(NINDS), which allows for reliable and confident diagnoses (S. E. Daniel & Lees, 1993; Goetz et al., 2008). In addition to the cardinal motor features, a majority of PD patients experience non-motor symptoms (Antonini et al., 2017; Fengler et al., 2017a; Hlavatá et al., 2020; O'Callaghan & Lewis, 2017b; W Poewe, 2008; Weintraub & Mamikonyan, 2019; D. J. Zgaljardic et al., 2003). Non-motor symptoms can affect a wide variety of functions, including sleep disorders such as REM sleep behavior disorder (RBD), autonomic dysfunction (e.g., orthostatic hypotension, urogenital dysfunction, and constipation), sensory dysfunction (mostly loss of smell), cognitive dysfunction (e.g., memory impairment, frontal executive deficits, dementia), and behavioral changes, including impulsive-compulsive behaviors (ICBs) which will be expanded upon further later in this chapter. Understanding the role of non-motor symptoms is critical because these can antedate the presentation of classical motor symptoms by years, or even decades (Poewe et al., 2017). Further, many medication and treatment regimens consist of either dopamine replacement therapy and/or a dopamine agonist (see Table 1-1 for commonly used medications). While these medications provide relief from the motor symptoms of this disease, they have been found to be the most important risk factor for developing impulsive-compulsive behaviors (Maréchal et al., 2015; Weintraub et al., 2010).

Unfortunately, currently, there is no cure for Parkinson's Disease, and early diagnosis and clinical treatment are the best ways to increase longevity and quality of life in this patient population. The biggest challenges for modern medicine are developing novel biomarkers in the preclinical disease stages and development of putative disease-modifying therapies to stop or even prevent neurological damage from occurring.

Table 1-1. Common medications used to treat Parkinson's Disease

Medication name	Description
Carbidopa/Levodopa	The most commonly prescribed dopamine replacement therapy, also called L-dopa. This medication provides the chemical precursor for dopamine, which can then be converted to dopamine once it reaches the brain. This medication is particularly good at controlling/mitigating bradykinesia, and stiff or rigid body parts, though it is associated with wearing off and dyskinesia between doses, which can result in some discomfort for patients. Some of this can be eased by using extended-release forms of this type of medication. As the disease progresses, both dose strength and frequency tend to increase, which can result in appearance or increase in hallucinations, delusions, motor complications, and orthostatic hypotension side effects.
Dopamine Agonists: Pramipexole Ropinirole Rotigotine (transdermal) Apomorphine Hydrochloride (injection)	These are also commonly prescribed and function by mimicking the action of dopamine at dopamine receptors. These can be useful for patients who are worried about dyskinesias, want something other than an oral option (transdermal or subcutaneous agonists are available), or who want less frequent dosing schedules, although they can be used in concert with levodopa therapy as well. Use of these medications early-on in the disease can delay the need for levodopa, which has the added benefit of delaying exposure to levodopa-induced dyskinesia. Additionally, most are available in an extended-release option. However, these drugs tend not to offer the same amount of symptom relief as levodopa and come with their own side effects to consider. Peripheral edema, orthostasis, psychosis, drowsiness, and importantly, impulse control disorders are well documented potential side effects.
Monoamine oxidase (MAO) inhibitors: selegiline rasagiline	These drugs work by preventing the breakdown of dopamine, increasing the time spent in the extracellular space, which can increase the chance it will bind to receptors. There is some evidence that taking either selegiline or rasagiline can slow the progression of Parkinson's, but this needs further investigation (Pålhagen et al., 2006; Olanow et al., 2009; Hoy and Keating., 2012). Selegiline has reported side effects including nausea, dizziness or fainting, and stomach pain, while rasagiline's side effects can include headache joint pain, indigestion, and/or depression.
catechol-o-methyltransferase (COMT) inhibitors: entacapone tolcapone	These drugs work by inhibiting an enzyme (catechol-o-methyltransferase) from breaking down levodopa in the periphery, which allows a higher concentration to cross the blood-brain barrier to be converted to dopamine. When used in combination with levodopa therapies, these can help increase a patient's time with controlled symptoms with less "wearing off" effects.

Essential Tremor

Epidemiology - Essential tremor (ET) is a common movement disorder, and the most common cause of action tremor with an estimated worldwide prevalence of 3.2 cases per 1,000 individuals, with the incidence increasing with age, rising to 28.7 cases per 1,000 individuals over the age of 80 (Welton et al., 2021). It tends to be characterized by an action tremor, usually of an upper limb, without other neurological signs, through a wide range of symptoms can accompany ET. It is defined according to clinical characteristics rather than etiology, as no single marker or test alone is sufficient to identify ET. Therefore, there has historically been an inconsistent application of diagnostic criteria, which could lead to inaccurate reports of the prevalence. For example, the inclusion of individuals with mild tremor as ET have likely contributed to high prevalence (55% of individuals over the age of 40) in Finland (Rautakorpi et al., 1982). It's currently considered a 'tremor syndrome' according to a 2018 consensus statement by the task force on tremor of the International Parkinson and Movement Disorder Society (MDS), although it doesn't appear that any epidemiological studies have used the MDS criteria for tremor yet. Like PD, essential tremor has a familial and sporadic type. Familial ET has a heritable component and tends to have a younger age at onset, while sporadic ET has an older age at onset comparatively but tends to have a more rapid disease progression. Interestingly, more than half of patients with ET have a positive family history of this disorder, and those with a first-degree relative with a positive diagnosis are nearly five times more likely to have ET than those without a family history (Elan D. Louis, Ford, et al., 2001; Sullivan et al., 2004). There does not seem to be any obvious sex differences in prevalence, though women tend to have a high incidence of head tremor, and more severe head tremor, while men tend to have more severe postural tremor (Hardesty et al., 2004; Hubble et al., 1997; Elan D Louis et al., 2003).

Neuropathology - As mentioned above, diagnosing essential tremor was usually based on clinical presentation of symptoms and possible family history rather than reliance on specific etiology, and until recently, there was wide consensus that there were no identifiable pathological changes in the brains of ET patients (Elan D. Louis & Vonsattel, 2008; Welton et al., 2021). One of the likely reasons this view was popular, was because ET is pathologically heterogeneous. Studies have demonstrated two common differing pathologies 1. Patients who have degenerative changes in the cerebellum, making up some ~75% of cases and 2. A smaller proportion of patients who have Lewy body pathology in the brainstem, particularly in the locus coeruleus (LC) (Hallett, 2012; Helmich et al., 2013; Elan D. Louis, 2009; Elan D. Louis, Barnes, et al., 2001; Elan D. Louis & Faust, 2020). The more common form of cerebellar ET is marked by morphological changes in Purkinje cells and overall reduction in number of Purkinje cells. In both cases, the symptoms tend to progress and there is data showing a modest increased risk of mortality in ET (E D Louis et al., 2007) Taken together, this profile would indicate that ET is a neurodegenerative disease, but a review of the literature by Rajput et al. (2012) suggests that there are no consistent abnormalities reported across ET neuropathology research, with some patients showing Purkinje cell dysmorphia and some not, and it cannot be classified as a neurodegenerative disorder. Interestingly, imaging findings showing functional abnormalities with increased activity in cerebellar connections using positron emission tomography (PET) have been published (Jenkins et al., 1993; Wills et al., 1995). Additionally, a decrease in cerebellar volume using voxel based morphometry has also been observed (Bagepally et al., 2012). Although the precise mechanisms of ET pathology are still being investigated, it seems the prevailing opinion is that the cerebellum is implicated in ET disease and continued advances in imaging and pathology technology will help clarify this disease etiology.

Diagnosis and symptomatology – Although heterogeneous in nature, in fact, there is a paper published by a prominent ET researcher entitled ‘Essential Tremor: A family of neurodegenerative

disorders?' (Elan D. Louis, 2009), there is a core common feature of essential tremor, tremor. To further prove that this disease is heterogenous, the tremor profile is multi-faceted, including kinetic, postural, intention tremor, and tremor at rest (Cohen et al., 2003; Koller & Rubino, 1985; Elan D. Louis, 2009; Rajput et al., 2012). Kinetic tremor tends to be more severe than postural tremor, and frequently presents in the arms, head, and/or jaw. There is also an increasing body of literature that shows a variety of non-motor symptoms as well. A portion of the non-motor symptoms are cognitive features, particularly executive dysfunction and deficits in memory (Bermejo-Pareja, 2011; Vijay Chandran & Pal, 2012; Gasparini et al., 2001). Louis et al. (2010) suggest that these cognitive deficits reflect 'difficulty with initiation and maintenance of information processing strategies', which is similar to deficits seen in patients with cerebellar lesions resulting in impaired cerebellar-thalamo-cortical processing. Additionally, several studies both cross-sectional and longitudinal have demonstrated that ET patients are at a significantly increased risk of developing dementia compared to age-matched otherwise healthy peers (Bermejo-Pareja et al., 2007; Thawani et al., 2009). Another common symptom seen in ET is depression. In a large study done in India, ET patients had significantly higher rates of depression, as measured with the Hamilton Depression Rating Scale, than controls (V. Chandran et al., 2012). This finding was also seen in a cohort in Turkey using the Beck Depression Inventory, and in Korea using the Montgomery-Asberg Depression Rating Scale (S. M. Lee et al., 2015; Sengul et al., 2015). Although depression could be a secondary response to tremor, one study found that baseline self-reported depression was associated with increased risk of incident ET, suggesting that it could be a primary feature of ET (Louis et al., 2007). In addition to depressive symptoms, anxiety is also commonly reported in ET populations. The studies performed in India and Turkey (mentioned above) also assessed anxiety levels and both studies found significantly higher rates of anxiety compared to matched controls (V. Chandran et al., 2012; Sengul et al., 2015).

Understanding whether these neuropsychiatric features are pre-morbid or co-morbid is still unclear, though regardless, they still impact patient well-being and quality of life. New and continued research into non-motor symptoms associated with this disease could help clarify the biological basis of this disease and improve our understanding of the full clinical spectrum of essential tremor.

1.3 IMPULSIVITY

Impulsivity is a broad, multifaceted construct, and in its broadest terms describes poor self-control which is characterized by decision-making without forethought or regard for consequences (Bakhshani, 2014; Jeffrey W. Dalley et al., 2011; J. Evenden, 1999; J. L. Evenden, 1999; Moeller et al., 2001). In the past few decades, impulsivity has been increasingly recognized as playing a central role in several neuropsychiatric disorders (Antonelli et al., 2011; Bornovalova et al., 2005; Housden et al., 2010; Rao et al., 2010; Swann, 2009; Swann et al., 2002; Winstanley et al., 2006). Impulsivity was previously thought of as a unitary construct, but over time has evolved into a multi-factorial construct that comprises varied components of behavior. Because impulsivity is a broad construct, a precise definition is challenging and ways to measure impulsivity vary in experimental studies.

Neural substrates of impulsivity

The classic view of the neural substrates relating to impulsivity come from the extensive research done around addiction behaviors, attention deficit hyperactivity disorder, obsessive compulsive disorder, psychosis, and aggression as impulsivity features as a central feature in all of these (Diaz et al., 2022; J. Evenden, 1999; Figee et al., 2016; Hollander & Rosen, 2000; Hoptman, 2015; J. H. Kim et al., 2013; King et al., 2003; P. Smith et al., 2006). Dopamine (DA), a monoamine neurotransmitter, is central to impulsive behaviors because of its role in motivation, incentive salience, reward processing and valuation, learning, and motor control. Dopamine is produced in two major nuclei in the brain, the ventral tegmental area (VTA) and in the substantia nigra (SN). Projections from these

two brain areas have classically been divided into three (or four, although the tuberoinfundibular pathway will not be described here) networks based on anatomical relationships (Beauchaine et al., 2015). The nigrostriatal pathway consists of dopaminergic projections from the substantia nigra project to the dorsal striatum, made up of the caudate nucleus and putamen and is associated with motor function, reward-related cognition, and associative learning. The other two pathways both have dopamine projections that originate in the ventral tegmental area (VTA). These are the mesolimbic and mesocortical pathways, although in the context of impulsivity have strong interconnections between the pathways and will be referred to as the mesocorticolimbic (MCL) pathway. Dopaminergic projections from the VTA connect to the ventral striatum (which is generally also known as the nucleus accumbens in the human impulsivity literature). Dopamine also projects from the VTA to the prefrontal cortex, amygdala, hippocampus, and cingulate cortex (mesocorticolimbic projections are shown in Figure (1-4). DA has a wide variety of regulatory functions, including neuroendocrine secretion, motor control, emotion and affect, and behavioral responses to rewarding stimuli. Neurotransmission of dopamine is regulated at several points including: DA synthesis, uptake and vesicular transport. Additionally, neurotransmitter receptors in DA neurons can provide feedback, regulate release, and conditionally drive local DA release (D. Sulzer et al., 2017; David Sulzer et al., 2005; Taber & Hurley, 2014). Alterations in dopamine neurotransmission have been implicated, directly or indirectly, in several brain disorders. For example, degeneration of dopamine neurons in the substantia nigra highly contributes to pathogenesis of Parkinson's disease (which is explained in more detail in section 1.3). Additionally, imbalances in dopamine within the MCL system are thought to contribute to other disorders and these regions together have been implicated specifically in impulsive behaviors (Czernecki et al., 2002; Filip et al., 2018; Hammes et al., 2019; Hlavatá et al., 2020; B. Kim et al., 2018; Koh et al., 2020; Rao et al., 2010; Rice et al., 2011).

The prefrontal cortex (PFC) contains distinct regions within it that are crucially involved in cognitive flexibility, planning future actions, modulating attention, abstract rule application, inhibiting impulse action, and decision-making. A direct role for the PFC in regulating impulsive behaviors was shown in 2010, when human subjects were given transcranial magnetic stimulation (TMS), analogous to temporary and reversible lesion, in the dorsolateral PFC (dlPFC; Figner et al., 2010). Results showed that participants who received TMS showed increased preference for immediate rewards over larger delayed rewards, though only while the TMS was active. These findings indicated a critical role in the PFC for self-regulation regarding rewarding choices. Further, rodent models have provided evidence for a causal role of the orbitofrontal cortex (OFC) in impulsive decision making (another distinct region of the PFC) through behavioral measurements on the stop-signal task following a lesion of the OFC (this task is explained in the next section Measuring Impulsivity; (Eagle et al., 2008). Lesions of the OFC resulted in impaired stop-signal task performance in this model (interpreted as increased impulsivity), while lesions of the infralimbic cortex did not.

The orbitofrontal cortex also shares bidirectional connections with the amygdala, a limbic area also considered to play a role in the MCL circuitry. More than fifty years ago, nonhuman primate studies showed that primates with amygdala lesions had impaired

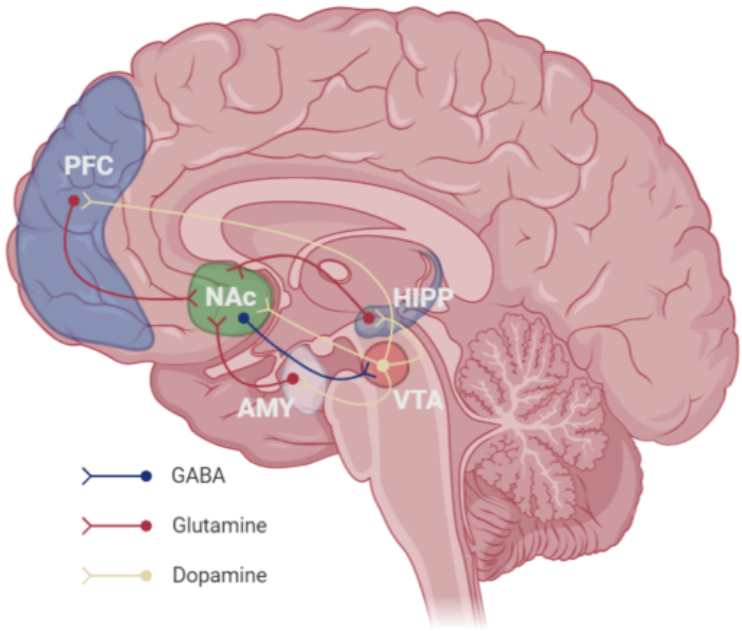


Figure 1-4. Cartoon depicting the mesocorticolimbic dopamine system (simplified). Dopamine neurons (yellow) in the ventral tegmental area (VTA) project to the amygdala (AMY, light purple), hippocampus (HIPP, blue), nucleus accumbens (NAc, green), and prefrontal cortex (PFC, dark blue). Crosstalk between these regions occurs through excitatory glutamate projections (red), and inhibitory GABA projections (dark blue).

ability to link specific objects to food rewards, which provided the basis for considering the role of the amygdala in stimulus-reward association. This research has been expanded upon in more recent years, and Murray and Izquierdo performed an elaborate set of studies to investigate the role of the amygdala and OFC in affective processing (Izquierdo & Murray, 2004; Murray & Izquierdo, 2007). Results showed that both the OFC and amygdala are critically important in linking objects with outcome valuations and that these structures communicate with each other (and presumably other areas of the brain) to guide choices based on value signals. Although reward valuation is not itself impulsivity, impulsive actions and choices are highly related to finding stimuli appetitive or rewarding. Dawe and colleagues proposed a two-component model in 2004 that explains how these constructs are related (Dawe et al., 2004; Dawe & Loxton, 2004). Reward sensitivity is the tendency to approach appetitive stimuli and is the catalyst for setting up the approach response, whereas impulsivity is the resulting engagement of an unplanned and spontaneous behavior in response to a given appetitive stimulus and is usually characterized by the disregard for future consequences or risks of taking action. In addition to the OFC, the amygdala also has a lot of interactions with sensory cortex, and these amygdala-cortico pathways have been suggested to play a role in perceptual processing of environmental stimuli such that the amygdala provides a "top-down" control of emotion on perception, playing an important role in assigning attention to what is decided to be relevant stimuli. Further, new findings have provided increased evidence for a modulatory role of the amygdala (and hippocampus) in motor control in a stop-signal task (Aoki et al., 2019; Ishikawa et al., 2008; Mann et al., 2021), overall suggesting that there is limbic regulation of actional control, which is affected in diseases where the dopamine system is impacted.

Another key component of the mesocorticolimbic system is the nucleus accumbens (NAc). This structure is also frequently referred to in human literature as the ventral striatum (although technically the NAc and olfactory tubercle together make up the ventral striatum). The NAc has a high proportion of dopaminergic receptors and is known to play a role in tracking the value of

subjective stimuli, encoding reward prediction (and error), signaling the presence or expectation of a reward, and dysfunction of this region is associated with impulsive behaviors (Evans et al., 2006; Guo et al., 2020; J. Marín-Lahoz et al., 2020; Petersen et al., 2018; Stark, Smith, Lin, et al., 2018). In fact, the research robustness of dopamine and reward is such that the "dopamine hypothesis of reward" has become a ubiquitous feature of psychopharmacology and behavioral neuroscience (Bromberg-Martin et al., 2010; Koob & Volkow, 2016; Spanagel & Weiss, 1999). Correspondingly, researchers in the last couple of decades have uncovered the labor cost of dopamine, the processes involved in initiating and sustaining actions, including the exertion of effort needed to overcome obstacles. Further, motivation, or willingness to work to obtain a reinforcing stimulus, is an important regulating factor that contributes to effortful actions in order to obtain reward. The ventral striatum has been associated with motivation and effort impairments in a variety of psychopathologies (e.g., addiction) due to the heavy influence that dopamine plays here. The NAc receives substantial dopaminergic innervation from the VTA, and neurons within the NAc express the full variety of dopamine receptors, localized both pre- and post-synaptically in this region, underscoring the important influence of dopamine in this area of the brain (Neve, 2010). It's thought that the NAc integrates information from limbic structures such as the amygdala and hippocampus as well as the prefrontal cortex to help regulate goal-directed (and reward-related) behaviors. In fact, anatomical and electrophysiological studies in rodents provide evidence for afferents projecting from the prefrontal cortex and limbic areas converging onto single NAc neurons, indicating information integration can occur in the NAc at the level of a single neuron (French & Totterdell, 2002; O'Donnell & Grace, 1995). Numerous studies, mostly thanks to animal models that allow for electrophysiological and pharmacological manipulations as well as behavioral assessments, have revealed the NAc to be a central hub for reward-related behaviors and have provided insights in the mechanisms by which information is processed in this structure. The NAc, and dopamine neurotransmission in particular, is critically important in maintaining a balance between limbic and

cortical drive. Dysfunction in this region has been associated with a wide variety of disorders, including Parkinson's disease – especially in impulsive-compulsive behaviors (Caprioli et al., 2013; Stark, Smith, Lin, et al., 2018), Schizophrenia, ADHD, and has been highly studied in the context of drug addiction (Berridge & Robinson, 1998; Chudasama & Robbins, 2006; Ersche et al., 2020; Fotros et al., 2013a; Gifford et al., 2000; André Nieoullon, 2002; Plichta & Scheres, 2014; Tajima-Pozo et al., 2015; Winstanley et al., 2006).

An extensive literature on decision-making processing in both animals and humans provides evidence for the involvement of the mesocorticolimbic areas, namely the prefrontal cortex, ventral striatum (NAc), and amygdala in impulsive choice. New and emerging evidence suggests the cerebellum may also fit into this system, playing a modulatory role in behavioral outcomes. Therefore, alterations to any of these structures may result in dysfunction within the larger network, contributing to impulsive behaviors.

Measuring Impulsivity

Although there are a myriad of ways to measure impulsivity in animal models, this dissertation will focus on impulsivity measures in human subjects. Impulsivity can be measured through behavioral assessments or through self-report. Behavioral paradigms tend to assess the facet of impulsivity that deals with inability to withhold or inhibit responses. For example, one of the most common measures is the Go/No-go Task (also known as the stop-signal reaction time task, or SSRT), in which a subject is tested on their ability to stop (no-go) and predetermined response and the number of errors (go on a no-go trial) is taken as a manifestation of impulsivity (Trommer et al., 1988). A second common measure of impulsivity assesses the value of immediate small rewards versus larger but delayed rewards, with the choice of immediate rewards being an index of impulsivity (Mischel et al., 1989). One of the advantages to using behavioral impulsivity tasks is to obtain neural responses during performance on the task. Several studies have used electroencephalogram (EEG), functional

magnetic resonance imaging (fMRI), anatomical magnetic resonance imaging (MRI), and positron emission tomography (PET) to elucidate some of the neuroanatomical connections to impulsive behaviors in a wide variety of disease states in which impulsivity is a key symptom (Clark et al., 2018; Filip et al., 2018; Koh et al., 2020; Korponay et al., 2017; Korponay & Koenigs, 2021; J.-Y. Lee et al., 2014; Logemann et al., 2010; O'Sullivan et al., 2011; C. T. Smith et al., 2018; Trujillo et al., 2019). Taken together these studies implicate fronto-striatal circuitry in impulsivity, though the specific findings tend to differ depending on the task given. Further, dopamine neurotransmission seems to be highly implicated when assessing impulsivity (C. T. Smith et al., 2018; Stark, Smith, Lin, et al., 2018; Pierre Trifilieff et al., 2017; Weiland et al., 2014).

Self-report measures of impulsivity tend to have four common factors that assess various components of impulsivity (Whiteside & Lynam, 2001). These include a lack of premeditation, a lack of perseverance, sensation seeking, and urgency. One of the first impulsivity scales developed was the Impulsiveness Scale, which was designed to assess the personality traits of impulsivity, venturesomeness, and empathy, all of which were thought to contribute to risk-taking preferences (S. B. Eysenck & Eysenck, 1977). This was used in multiple populations and has since been updated to the Adult Impulsiveness Scale I7 as of 1984 (S. B. G. Eysenck et al., 1985). Ernest S. Barratt, Ph.D. was also a pioneer researcher in attempting to understand and assess impulsivity. He hypothesized that impulsive behavior and anxiety were inversely related to one another, and that impulsivity was not a unidimensional construct, but rather a multi-dimensional construct reflecting multiple sub-domains. The Barratt Impulsivity Scale (BIS), currently in its 11th revision (BIS-11), was then developed after a long series of analyses and is one of the most commonly used self-report measures to this day (Patton et al., 1995; Stanford et al., 2009). This BIS-11 distinguishes three domains of impulsivity into attentional impulsivity, motor impulsivity, and nonplanning impulsivity – for further detail, see description of the BIS-11 and factor structure break down in Chapter 2. Whiteside and Lynam developed a more recent impulsivity scale, created after they conducted a factor analysis of

existing self-report scales to provide a single concise measure that captured differing aspects of impulsivity. This resulted in a 59-item questionnaire called the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation seeking, Positive Urgency, Impulsive Behavior Scale (UPPS), which is also a well-known and validated tool to assess impulsivity (Whiteside & Lynam, 2001). This was then expanded to include a fifth scale of impulsivity, positive urgency, after findings showed that impulsive action under extreme positive emotions (rather than negative emotions) also existed and was not well represented or conceptualized resulting in the expansion of the acronym (UPPS-P) to include this new measure (Cyders et al., 2007).

Interestingly, behavioral measures of impulsivity and self-report measures have been shown to have, at best, modest associations with each other (Meda et al., 2009). This is somewhat unsurprising given the broad dimensionality of impulsivity, these measures are likely capturing different aspects or constructs of this behavior, and therefore are related measures but not necessarily comparable measures. Impulsivity is assessed in healthy subjects and a Parkinson's Disease cohort in Chapter 2 using the BIS-11.

Impulsivity in Parkinson's Disease

Parkinson's Disease (PD) patients, in addition to the cardinal motor symptoms, can present with personality-related changes. Previously, these patients were often described as stoic, serious, rigidly moral, more cautious, risk-averse, and score low on indices of novelty seeking even prior to clinical diagnosis (Menza et al., 1993). The explanation for these behaviors was hypothesized to be a result of damage to the mesolimbic dopamine system as disease pathology progresses through the brain, and results comparing PD to healthy controls supported the idea that novelty seeking was lower in PD subjects and was dopamine dependent (Menza et al., 1993; Robert Cloninger, 2013). In the 35 years or so since these descriptions of the "PD personality" were published, interesting evidence has emerged that contradicts the idea that PD subjects are risk-averse or not interested in novelty. In fact,

more recent studies have shown that more than 25% of idiopathic Parkinson's subjects meet criteria for an impulsive-compulsive disorder, although the percentages vary depending on the study (Antonini et al., 2017, 2011; Aumann et al., 2020; Evans et al., 2019; Garcia-Ruiz et al., 2014a; A. K. W. Lee et al., 2011; Valerie Voon et al., 2007; Weintraub & Claassen, 2017). Patients who experience high levels of impulsive behaviors, especially gambling (one of the most frequently studied behaviors in ICB subjects), can put extra stress on themselves, their caregivers, and their financial situations. One group found that pathological gambling resulted in an average loss of $129,000 (V Voon et al., 2006; Valerie Voon et al., 2007), although other common behaviors such as compulsive shopping and excessive hobbyism can also contribute to emotional and financial burden.

Symptomatic therapy for PD includes dopamine replacement strategies that include L-dopa, a dopamine precursor, or dopamine receptor agonists. Use of dopamine receptor agonists (DAA) has been highly associated with development of impulsive-compulsive behaviors, though, interestingly, not all patients revert to normal behavior once taken off these medications, indicating other factors contribute to development of ICBs. Studies of risk factors for ICBs have suggested that a family history of alcohol abuse may increase the risk for a Parkinson's patient to develop ICBs (Heiden et al., 2017). Other studies in PD show that males more than females, and a younger age at disease onset are associated risks of developing ICBs (Bhattacharjee, 2018a; Kon et al., 2018). Currently, the most useful treatment option remains to reduce or eliminate dopamine agonist treatment while balancing withdrawal syndrome and worsening motor symptoms. No studies to date have shown a benefit to any additional add-on therapy to alleviate ICB symptoms in PD (Weintraub et al., 2006; Demetriades et al., 2011). Further research is needed to provide a full picture of the mechanisms involved in ICBs in PD. In this work, I investigate ICBs in the context of impulsivity (rather than compulsivity) and aim to relate structural and functional changes to impulsivity via imaging tools to expand our knowledge of the networks involved in these dysfunctional behaviors.

1.4 IMAGING TECHNIQUES

Understanding the neural underpinnings of behaviors like impulsivity can be easily investigated in animal models using invasive, but highly effective techniques. Investigating anatomical and functional relationships to behavior in humans can be challenging due to the limited methods considered ethical and safe for humans. Luckily, imaging technology has greatly improved in the last 50 years or so, allowing researchers to explore links between pathology and behavior in new and exciting ways. Two common imaging modalities used in neurological research will be described in this section

Anatomical Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an imaging technique that uses the body's natural magnetic properties to produce highly contrasted images. MRIs employ strong magnetic fields that force protons (hydrogen atoms in our bodies mostly within water) that are normally randomly aligned to align within that magnetic field, called B0. Then a radiofrequency (RF) energy pulse can be applied, which stimulates the protons to spin out of alignment with the magnetic field. When the radiofrequency field is turned off, the protons move back into alignment with the B0 field (Fig. 1-5 shows a simplified cartoon of this process). As the protons relax back into the B0 magnetic field, the energy from the RF pulse is released which is then detected by sensors in the MRI machine. The

protons return to the B0 field through various relaxation processes and emit the energy captured in the RF pulse. That emitted energy is measured through specialized sensors in the MRI machine. A Fourier transformation is used to convert the frequency information from protons in each location within the field to an image, with the information encoded as signal intensity. Varying the sequence of RF pulses allows for different image types to be created. Changing the repetition time (TR) changes the amount of time between successive RF pulses applied to the same slice. Changing the echo time (TE) changes the time between delivery of the RF pulse and the receipt of the echo signal. The contrast in calculated images occurs because the chemical makeup of tissues is different depending on the type of tissue. Tissue can be characterized by two different relaxation times, T1 and T2. The time constant T1 is the time it takes for protons in a given tissue at equilibrium to return to equilibrium following an RF pulse. The transverse relaxation time, T2, is the time constant that describes the amount of time it takes for excited protons aligned orthogonally to B0 to lose their

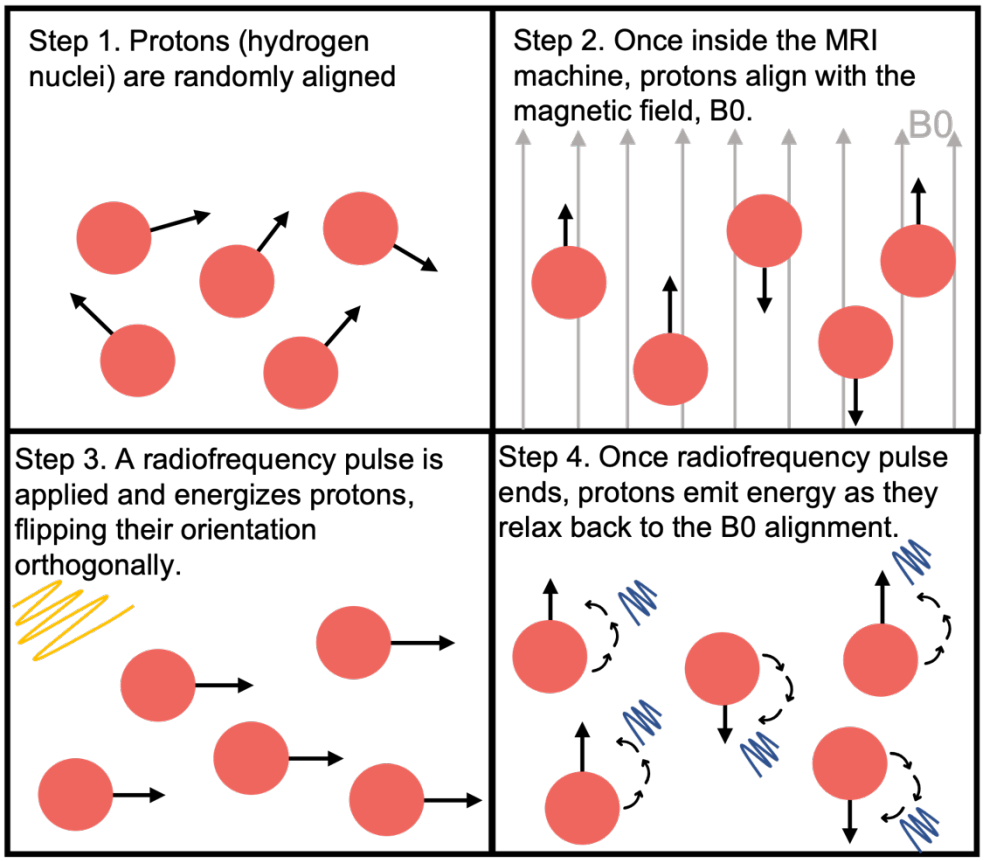


Figure 1-5. Cartoon illustrating proton alignment within an MRI machine before and following a radiofrequency pulse. First, protons (red circles) are in a random orientation. Second, protons align along a magnetic field inside the MRI machine, B0 (grey lines). Third, a radiofrequency pulse is applied (yellow zigzag), and the protons align orthogonally to B0. Fourth, once the radiofrequency pulse ends, the protons relax back into B0 alignment.

phase coherence, or decay. This results in a powerful tool to obtain high resolution anatomical images in a non-invasive way.

Functional MRI

Functional MRI (fMRI) is a type of imaging that allows for measurements in regional, time-varying changes in blood flow in the brain and is used as a proxy for neuronal metabolism. All the processes of neural activity (e.g., propagation of action potentials, vesicle binding, release of neurotransmitters, receptor endo- and exocytosis, etc.) all require energy. The brain, unlike other areas of the body, does not keep large stores of energy available (Mergenthaler et al., 2013). Thus, when neural activity is enhanced, there are concomitant increases in metabolism and blood flow, resulting in a rapid elevation in oxygen consumption in the active area. This process results in what is described as the hemodynamic response (Fig. 1-6). This is an incompletely understood phenomenon in which cerebral blood flow (CBF) rises in response to metabolic demand, delivering increased volumes of oxygenated blood to tissue (Wegener et al., 2007). There is a linear coupling of neuronal activity and oxygen consumption (measured as cerebral metabolic rate of oxygen consumption, or $CMRO_2$) and nonlinear coupling with cerebral blood flow. Local activation of neurons augments cerebral blood flow in excess of $CMRO_2$, leading to an increased oxygen saturation in the venous system and a disproportionate ratio of oxygenated-to-deoxygenated hemoglobin. Oxyhemoglobin has no unpaired electrons, is diamagnetic, and negligibly affects the magnetic resonance (MR) signal, while deoxyhemoglobin has four unpaired electrons, is paramagnetic, and strongly attenuates the MR signal. This excess of oxyhemoglobin results in a lower relative concentration of deoxyhemoglobin. Locally, the T2/T2* shortening effects of deoxyhemoglobin will be attenuated and the BOLD signal in regional active areas will increase. Therefore, the BOLD effect is directly related to the concentration of deoxyhemoglobin, which can vary up to 40% in venous blood (Fox et al., 2005; Pauling & Coryell, 1936).

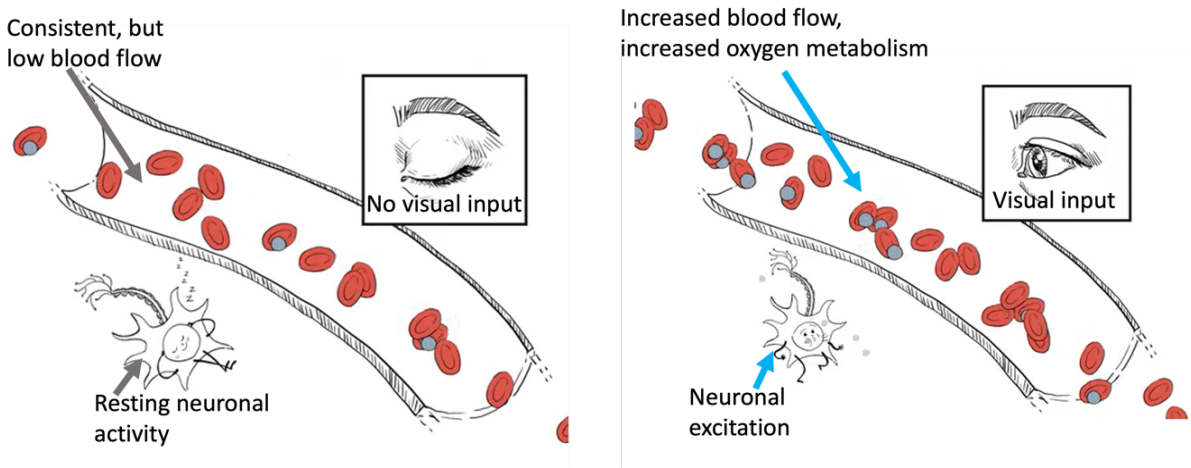


Figure 1-6. The hemodynamic response. The cartoon on the left shows an illustration using brain activity in response to a visual stimulus. When the eyes are closed, there is no visual input, there is a low "resting" neuronal activity for areas associated with visual stimuli in which the blood flow is steady, but the metabolic demand is low. The panel on the right shows incoming visual information, which prompts neuronal excitation and an increase in both blood flow and delivered oxygen. The difference in oxyhemoglobin versus deoxyhemoglobin is measurable and results in the BOLD effect, which is used as a proxy for neuronal activity.

The hemodynamic response can be broken down into three phases. The first consists of a small, transient dip, likely due to the initial increase in available oxygen, which occurs before the compensatory blood flow has made its way to the active area(s). The second phase is a sustained, higher-magnitude increase in fMRI signal due to an overabundance of oxygen-rich arterial blood being delivered to the active area(s). The third, and final phase is a post-stimulus undershoot. The net result of the hemodynamic response is a higher oxygenation level in the draining blood, especially in draining veins localized to the active area(s) (Glover, 2011).

The BOLD contrast

The BOLD contrast is the most commonly used contrast in conventional fMRI methods (Glover, 2011), and will be the contrast used for fMRI assessments in this dissertation work. This contrast results from changes in the magnetic field surrounding red blood cells due to the oxygenated vs. deoxygenated state of hemoglobin. When fully oxygenated, hemoglobin has four paired electrons, is diamagnetic, and is magnetically identical to brain tissue. Conversely, when fully deoxygenated, hemoglobin has four unpaired electrons, is highly paramagnetic, and results in gradients in the

magnetic field that change the T2 and T2* relaxation times of blood (Donahue et al., n.d.; Thulborn, 2012; R M Weisskoff et al., 1994; Robert M Weisskoff, 2012). Using acquisition methods that are sensitive to T2 and T2* results in nicely contrasted images (for further reading on pulse sequences best for acquiring BOLD images, and the various field strength acquisitions, see (Glover, 2011; Huettel et al., 2009; Triantafyllou et al., 2011; Yacoub et al., 2005). Most fMRI studies utilize differences related to a stimulus or task, thereby enabling a more comprehensive understanding of a brain region or network involved in a specific task, emotion, behavior, etc. Additionally, pharmacological challenges can be employed to assess brain regions, temporal windows, and (possible/probable) action mechanisms of the dug applied. Not all BOLD fMRI studies involve observing responses to a stimulus or drug. This paradigm is known as resting state fMRI (rs-fMRI) and application of this technique has produced various resting state networks which demonstrate synchronous activity at rest and can be considered functionally connected (Biswal et al., 1995). Areas of the brain that are functionally connected at rest have been suggested to be an expression of networks subserving complex behaviors or higher levels of cognitive function, partially due to the fact that changes occur on the order of seconds (Rosazza & Minati, 2011).

Advantages and Limitations of BOLD-fMRI

Functional MRI, while a proxy for neuronal activity, has greater spatial and temporal resolution that positron emission tomography (PET) and single-photon emission computerized tomography (SPECT). It is non-invasive and does not require the use of an injected radioactive compound making it more convenient and safer for subjects. Further, the contrast is obtained from manipulating magnetic fields, therefore there is no other external radiation exposure, unlike computerized tomography (CT) or X-rays.

While fMRI strives to measure the neuronal activity in the brain, the BOLD signal is susceptible to bias from other physiological factors. For example, respiratory fluctuations and cardiovascular cycles

affect the BOLD signal being measured in the brain and are controlled for when processing fMRI data (Smitha et al., 2017). Furthermore, because the BOLD signal is reliant on subtle magnetic differences in oxy- vs. deoxyhemoglobin, the signal is susceptible to areas of magnetic inhomogeneity such as the sinuses and other air-tissue interfaces (Oiemann et al., 1997). Additionally, due to the consistent oxygenation of inflowing arterial blood, the venous compartment is overrepresented as a signal source, which can lead to biased mapping of fMRI signal, especially in areas with large draining veins (Krings et al., 1999). Another consideration to bear in mind is that although temporal information can be gathered, it is on the order of seconds, and it's likely that biological processes and communication between brain regions is occurring on much faster time scales. Finally, it is important to remember the relationship between cellular activity and blood oxygenation (even oxygen extraction) is complex and not fully understood, so care must be taken when drawing conclusions from collected data. In fact, given the number of considerations when obtaining this kind of data, many experts have been hesitant to accept findings from BOLD fMRI studies. It has only been recently with further testing and variable controlling that researchers have become confident that the signal being measured is biological, rather than artifact caused by other physiological function (Glover, 2011; Gray et al., 2009; Gretton et al., 2006).

PET imaging

Positron emission tomography (PET) imaging techniques use molecular imaging methods in which competition between endogenously released neurotransmitter and its ligand are exploited. Both the ligand and the neurotransmitter bind to the same receptors competing with one another for occupancy. Thus, if a ligand is injected into a subject, it selectively binds to the receptors in the brain that are unoccupied by neurotransmitter. However, the ligand will be displaced from receptor binding sites if endogenous transmitter is released, as the endogenous transmitter usually has a stronger affinity to the receptor of interest. This technique allows for quantitative measurement of ligand

concentration in different brain areas by radiolabeling it prior to injection and measuring the concentration in relation to an area of the brain without tracer binding (usually called a reference region). Multiple radiotracers have been used in conjunction with PET imaging to detect and measure these types of changes in targets within DA networks in the brain (Gifford et al., 2000; J Mukherjee et al., 1999; Slifstein et al., 2010; Vandehey et al., 2010b). Using popular D_2/D_3 receptor-specific radioligands such as [^{11}C] raclopride, multiple studies have shown that subjects addicted to a wide variety of drugs (cocaine, heroin, alcohol, methamphetamine, and even food resulting in obesity), exhibit significant reductions in D_2 DA receptor availability in the striatum that persist months after protracted detoxification (Pierre Trifilieff et al., 2017). Additionally, striatal dopamine D_2 receptor availability was found to be significantly lower in obese individuals as compared to controls (G. J. Wang et al., 2001). PET measures of receptor availability are the result of measuring radioligand occupancy that can take half an hour or longer (sometimes hours) to achieve, depending on the relative expression of the receptor, as well and the binding affinity of the ligand. Thus, although these methods allow for greater insights into dopamine D_2/D_3 receptor availability, they are still limited in their ability to detect dopamine neurotransmitter release changes that occur at shorter time scales (seconds to minutes).

Among the PET D_2/D_3 antagonist radioligands, there are three that have been utilized in studies with human subjects and that have continued to appear in the recent pharmacological challenge literature (Montgomery et al., 2007; Slifstein et al., 2010; Vandehey et al., 2010a). These are [^{11}C] raclopride, [^{11}C] FLB 457 and [^{18}F] fallypride. [^{11}C] raclopride has fast in vivo kinetics, but because of its relatively low-to-moderate D2/3 receptor affinity, the only brain region in which it can be used to reliably quantify receptor availability is the high $D_{2/3}$ receptor-dense striatum (Slifstein et al., 2010). Both [^{11}C] FLB 457 and [^{18}F] fallypride have higher affinity and signal-to-noise ratios in vivo and can provide reliable quantitative $D_{2/3}$ receptor availability in extrastriatal brain regions where

receptor density is an order of magnitude lower than in striatum (Constantinescu et al., 2011; J Mukherjee et al., 1999). However, both ligands require long acquisition periods to reach a steady, equilibrium state of receptor occupancy in the striatum. The necessary data acquisition time is too long for quantitative imaging within the time constraints imposed by the rapid decay rate of ^{11}C (half-life = 20.3 minutes). The maximal imaging time for obtaining adequate counts with ^{11}C is approximately 2 hours and neither ligand reaches an equilibrium state necessary for quantification in striatum by this time, a necessary condition for accurate quantitative measurement (Laruelle, 2000). Consequently, [^{11}C] FLB 457 can only be used for imaging extrastriatal regions. Because fallypride is labelled with ^{18}F, [^{18}F] fallypride scanning sessions can be extended for a longer duration than for [^{11}C] labelled radioligands, so that it is possible to reliably quantify [^{18}F] fallypride binding in striatum. Thus, [^{18}F] fallypride is unique in that it is the only currently available PET radiotracer than can simultaneously provide quantitative measures of D_2/D_3 receptor binding in the striatum and extrastriatal brain regions in the same scanning session (Slifstein et al., 2010). As most psychiatric disorders involve cortico-striatal circuits, imaging dopamine transmission simultaneously in striatal and extrastriatal regions is a valuable tool. Considering the context of impulsivity, which is highly related to dysfunctional dopaminergic circuitry, the use of PET imaging with [^{18}F] fallypride provides a way to investigate and anatomically pinpoint molecular changes to large scale circuits in human models.

1.5 SUMMARY

Motor movement disorders such as Parkinson's Disease and Essential Tremor are complex neurodegenerative diseases, which have only recently started to have recognized non-motor symptoms known to strongly impact patients and their quality of life. Impulsivity is a multi-faced construct, and there are several ways to interrogate various aspects of impulsivity. Impulsive-compulsive behaviors are well-recognized in Parkinson's Disease, but up to this point have been

investigated using a limited range of behaviors. Impulsivity has been suggested to be a component of other motor movement disorders such as essential tremor, but this has not been thoroughly investigated in a large ET population. Further, it is not well understood if the cerebellum, which is known to have a large role in ET pathology, and a smaller role in PD pathology, contributes to the regulation of impulsive behaviors through connections with the mesocorticolimbic system. In this dissertation, we will assess impulsivity in a PD population using a broader self-report measure of impulsivity, the BIS-11, and how the presence of impulsive behaviors changes mood perception in the presence of a dopamine drug challenge. Additionally, we will investigate behaviors related to mesocorticolimbic systems (apathy, disinhibition, and executive dysfunction) in an essential tremor population to assess their clinical severity, if any, and correlate frontal-like behaviors to cerebellar atrophy to interrogate what areas of the cerebellum may be involved in behavioral regulation. The aim of this work is to expand our knowledge of non-motor symptoms in neurological disorders primarily thought of as motor-movement disorders. Further, we aim to augment our knowledge of the role of the cerebellum in behavioral regulation through investigations into a. dopamine receptor availability, b. relationship of cerebellar atrophy to various behaviors, and c. associated cerebellar atrophy to larger brain networks potentially involved in behavioral regulation.

CHAPTER 2

SELF-REPORTED RATES OF IMPULSIVITY IN PARKINSON'S DISEASE

2.1 PURPOSE

Impulsive decision-making is characterized by actions taken without considering consequences. Patients with Parkinson's disease (PD) who receive dopaminergic treatment, especially dopamine agonists, are at risk of developing impulsive-compulsive behaviors (ICBs). Unfortunately, many studies rely on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) to assess impulsivity, which limits impulsive behaviors to a select few - gambling, sexual, buying, and eating behaviors, as well as compulsive medication use, punding, hobbyism, and walkabout behaviors. While this is a reliable and valid measure, impulsivity remains a heuristic construct that encompasses a wide range of acts that reflect broadly on lack of cognitive control. Given the array of behaviors that could manifest, we assessed impulse-related changes across a large heterogeneous PD population using a broader measure of impulsivity, the Barratt impulsivity scale (BIS-11) by evaluating BIS-11 first- and second-order factors in both PD patients and age- and sex-matched peers.

2.2 SUMMARY

Patients with Parkinson's disease (PD) who receive dopaminergic treatment, especially dopamine agonists, are at risk of developing impulsive–compulsive behaviors (ICBs), which results in often unplanned behavioral actions that are performed without thought for consequence or impact. These impulsive behaviors can have a negative impact on patient quality of life and are important symptoms to assess clinically. Here we assessed a total of 204 subjects: 93 healthy controls (HCs), and 68 ICB– and 43 ICB + PD patients who completed the Barratt impulsivity scale (BIS-11). Using a general

linear model and a least absolute shrinkage and selection operation regression, we compared BIS-11 scores between the HC, ICB– PD, and ICB + PD groups. We found that patients with PD (both ICB+ and ICB-) rated themselves as more impulsive than HCs in the BIS-11 total score, second-order attention domain, and first-order attention and self- control domains. ICB + patients recorded higher total scores as well as higher scores in the second-order non-planning domain and in self-control and cognitive complexity than ICB– patients. These results indicate that the patients with PD show particular problems with attentional control, whereas ICB + patients show a distinct problem in cognitive control and complexity. Additionally, it appears that all patients with PD are more impulsive than their age- and sex-matched healthy peers. Increased impulsivity may be a result of the disease course, or attributed to dopaminergic medication use, but these results expand our knowledge of the kind of impulsive behaviors experienced in these patients, and emphasize the importance of the cognitive components of impulsivity in patients with PD.

2.3 INTRODUCTION

Impulsivity is a multi-faceted construct, involving several factors including quick action, lack of focus on tasks, and lack of planning (Patton et al., 1995), and can be expressed behaviorally, via actions in daily life, and/or through performance on cognitive assessments (Bloxham et al., 1987; Getz & Levin, 2017; Smulders et al., 2014). Impulsivity is generally thought to include a lack of behavioral inhibition and/or premature decision making, and when it becomes a behavioral problem, e.g. impulse control disorders, can manifest through engagement of spontaneous, unplanned, or reckless activities regardless of potential negative consequences (Grall-Bronnec et al., 2018; Sharma et al., 2013) Maladaptive impulsivity is a feature of several neuropsychopathologies, including attention-deficit/hyperactivity disorder, borderline personality disorder, and substance abuse (Allen et al., 1998).

Poor proficiency of impulse control is common in patients with Parkinson's Disease (PD), in which dopamine therapy is the standard of care in treating the motor movement disruptions resulting from progressive degeneration of dopamine neurons in the substantia nigra pars compacta. However, PD is a complex disease, impacting cognitive, behavioral, and emotional symptoms, all of which need to be considered when determining personalized treatment plans (Bhattacharjee, 2018b; Meda et al., 2009; Nombela et al., 2014). Impulsive-Compulsive Behaviors (ICBs) have gained recent attention in the literature with estimates above 25% (Bhattacharjee, 2018b; Erga et al., 2017) of PD patients that are treated with dopamine agonists (DAA). PD patients that take DAA, such as pramipexole and ropinirole, show marked improvements in their motor symptom severity (Piercey, 1998). However, a subset of PD patients taking these agonists have been reported to develop maladaptive ICBs such as pathological gambling, shopping, binge eating, hypersexuality, as well as heightened novelty seeking (Claassen et al., 2011; Valerie Voon et al., 2011; Weintraub & Claassen, 2017; Weintraub et al., 2010). Impulsive shifts that occur in PD may be underappreciated by patients who are experiencing a multitude of changes in their lives as part of their disease. Assessing their subjective experiences of behavioral and cognitive control can give caregivers and treatment providers insight into some of the earlier changes that may precede development and expression of an ICB.

Although the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) is used often as an instrument for assessing impulsive behaviors in PD, it lacks broader cognitive constructs such as attention and planning, which are known to be altered in PD patients (Getz & Levin, 2017; Goris et al., 2007; Kehagia et al., 2010; Lezak, 1982; Maidan et al., 2019). Furthermore, the scope of ICBs in PD encompasses a broader range of compulsive appetitive behaviors such as hypersexuality, compulsive shopping, gambling, and medication use (Grall-Bronnec et al., 2018;

Weiss & Marsh, 2012b). While these are troublesome problems, the QUIP does not capture impulsive behavioral changes that may occur outside of the conventionally defined features of ICB.

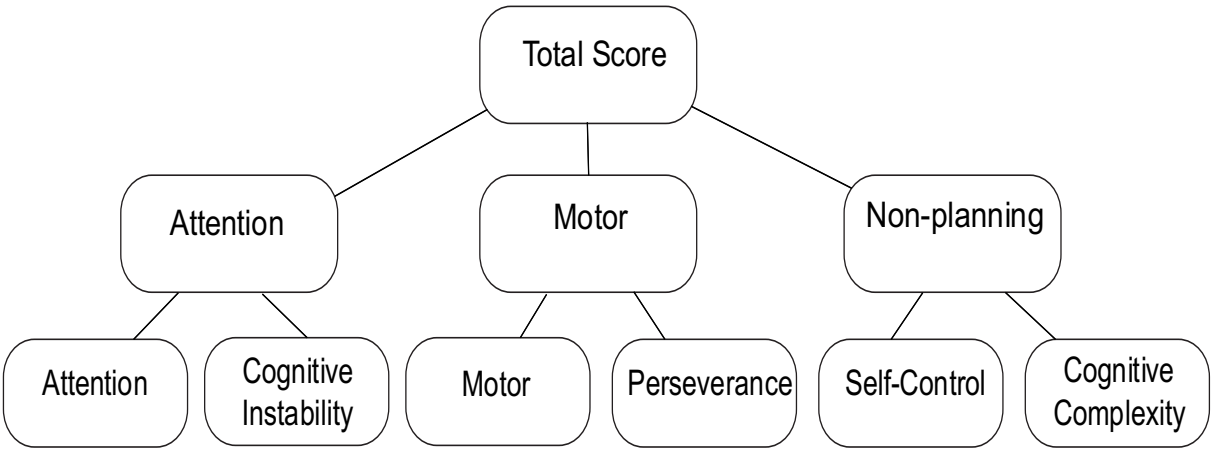


Figure 2-1. BIS-11 hierarchy structure. The 6 first order factors shown on the bottom row each contribute 2 factors to the boarder second-order factors of attention, motor, and non-planning shown in the middle row. Each of the 3 second-order factors contributes to the total score.

The Barratt Impulsivity Scale (BIS-11) (Patton et al., 1995) is a common self-report instrument used to assess impulsivity, and has been used in a variety of populations (Rodriguez-Jimenez et al., 2006; P. Smith et al., 2006; Swann et al., 2002, 2004; Valerie Voon & Fox, 2007). It is designed to assess the behavioral construct of impulsivity through 30 items that describe cognitive and behavioral preferences. The BIS-11 provides information about overall impulsivity through a total score but can also provide information on the more specific facets of impulsivity through the first- and second-factor subscales. There are 6 first-order components (attention, cognitive instability, motor, perseverance, self-control, and cognitive complexity) and 3 second-order factors (attention, motor, non-planning), with 2 first-order factors loading on each second-order component. For instance, attention and cognitive instability load onto the second-order attention domain, motor and perseverance together make up the second-order motor domain, and self-control and cognitive complexity form the non-planning second-order factor (Fig. 2-1). Although many studies of PD report total BIS-11 scores, some of which report second-order scores (Ruitenberg et al., 2018; Sauvaget et al., 2017; Sharma et al., 2013; Stark, Smith, Petersen, et al., 2018; Valerie Voon et al.,

2011), none to our knowledge investigate first-order factors. While these studies do tend to find differences in total and second-order level BIS scores, there are inconsistencies of how second-order factors differ between PD and healthy participants. These may be due to poor statistical power, given frequent sample sizes less than 100. A larger cohort of PD patients would allow for an in-depth look at both the first- and second-order subscales, elucidating both the primary traits expressed in PD patients, as well as those who meet criteria for ICB. Assessing first-order factor data could impart a more detailed understanding of impulsive changes within a PD population (Sauvaget et al., 2017). For instance, while the first-orders of attention and cognitive instability both contribute to the second-order factor of attention, they are comprised of different elements, with first-order attention reflecting a failure to maintain cognitive attention, while cognitive instability is characterized by the presence of racing or extraneous thoughts. By analyzing distinct components of impulsiveness, we hope to understand the nature of self-reported ratings of impulsivity in PD, and especially in patients with ICBs. In this study, we applied the BIS-11 to a large number of PD and non-PD participants. We assessed the relative contribution of the total, first-order, and second-order factors, as well as the contribution of individual questions from the BIS-11. We also assess the precise relationships of self-reported impulsivity in PD ICB+ and, PD ICB- patients.

2.4 METHODS

Subjects

A total of 204 participants completed the BIS-11 and a clinical interview (Table 2-1). All healthy participants were recruited from the Nashville, TN area and patients with PD were recruited from the Vanderbilt University Movement Disorders Clinic. PD recruitment efforts were not biased toward a single subcategory of behaviors. All participants provided informed, written consent approved by the Vanderbilt University Institutional Review Board. The diagnosis of PD was based on United Kingdom Brain Bank criteria, (S. E. Daniel & Lees, 1993; Tolosa et al., 2006) and PD patients

meeting this criterion were prescribed levodopa/carbidopa and/or DA agonist for relief of motor symptoms. Patients were excluded if they had implanted deep brain stimulator, received antipsychotic treatments, suffered from co-morbid neuropsychiatric, cerebrovascular, or cardiovascular disease (as determined through medical history, and clinical interview). Healthy control subjects did not have a history of psychiatric illness, head trauma, substance abuse, or co-morbid vascular disease. The Unified Parkinson's Disease Rating Scale (UPDRS) exam was performed on all participants to rate symptom severity in PD population, and a neurologic assessment confirmed an absence of parkinsonian features in HC subjects (Martínez-Martín et al., 1994).

The presence of ICB was determined by a clinician and defined as clinically problematic behavior(s) following DA agonist treatment according to the Diagnostic and Statistical Manual of Mental

Table 2-1. Demographic information based on the population groups (HC, PD ICB-, and PD ICB+).

Variable	HC	PD ICB-	PD ICB+	Statistic*	p-value	Tukey post-hoc
N	93	68	43	---	---	
Gender (male/female)	50/43	53/15	25/18	10.31[1]	0.01	
Age (years)	57.96 (7.98)	64.97 (8.22)	60.98 (6.97)	15.22[2]	<0.01	0.001[A]
Disease Duration (years)	---	5.01 (3.72)	4.07 (2.62)	2.02[2]	0.16	
MoCA score	---	25.38 (2.69)	26.67 (2.36)	6.31[3]	0.01	
UPDRS						
II	---	20.59 (9.27)	21.06 (8.11)	0.06[3]	0.81	
III	---	27.58 (12.35)	25.88 (13.06)	0.39[3]	0.54	
Dopamine Replacement Therapy						
Total LEDD (mg/day)	---	740.95 (410.6)	642.59 (397)	1.27[3]	0.26	

Gender is shown as the ratio of males to females. Scores for age, disease duration, MoCA, UPDRS II, UPDRS III, and total LEDD are shown as averages with standard deviations in parenthesis.
**Different statistical tests were performed for the data where the superscript number indicates the test used*
[1]indicates the chi-squared test
[2]indicates the F-value for t-tests
[3]indicates the F-statistic for an ANOVA.
The superscript A indicates a significant difference between the HC And ICB- groups

Disorders (DSM-V) (American Psychiatric Association, 2013).

Experimental Task and Procedures

PD patients completed part II of the UPDRS (questionnaire of patient-rated motor experiences of daily living), and part III (a clinical assessment of motor function in PD) in an OFF-medication condition after overnight washout of dopamine medications (Ebersbach et al., 2006a; Werner Poewe & Mahlknecht, 2009b). HC were deemed free of motor deficits through medical history and neurological examination by a physician.

All participants completed the self-report Barratt Impulsiveness Scale (BIS-11) questionnaire (Harris et al., 2019, 2009) (ON-medication for PD subjects), which uses a 4-point Likert-type scale: rarely/never, occasionally, often, and almost always/always for which we determined total score, as well as separate scores for the six first-order factors, and the three second-order factors. The Montreal Cognitive Assessment (MoCA) was administered to assess PD patients' global cognitive abilities, and to exclude individuals that were severely impaired (Hoops et al., 2009; Nazem et al., 2009). MoCA scores range from 0-30, with higher scores indicating better cognitive function. Considering the age range of the sample for this study, we excluded patients with a score of 22 or below on the MoCA examination (Ciesielska et al., 2016; Damian et al., 2011a; Luis et al., 2009; Malek-Ahmadi et al., 2015). HCs were initially recruited for the purposes of a separate study and therefore did not complete a MoCA but were deemed cognitively intact without evidence of cognitive impairment or neuropsychiatric disorder through a battery of neuropsychological assessments (e.g. (David Watson et al., 1988) Stroop task (MacLeod, 1991), Wechsler Adult Intelligence Scale (Dumont et al., 2014) and Structured Clinical Interview for the DSM (First, 2015).

Data Analysis

Differences in group demographics were determined by a t-test or ANOVA if comparing all 3 groups. Sex differences between groups were tested using the chi-square test. For demographic information,

p-values were considered significant if $p < 0.05$ (Table 2-1). A General Linear Model (GLM) controlling for age and gender followed by a False Discovery Rate (FDR) correction, was used to analyze group mean differences for HCs and PD participants with and without ICB (ICB+/ICB-) with threshold for significance set at $p = 0.05$ using R statistical software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). For each GLM, the t-statistic for the variable of interest only was reported and P-value was computed accordingly. The FDR correction was performed on the computed P-values as described in the original FDR paper (Benjamini & Hochberg, 1995) . FDR corrections were performed on multiple applications of GLM, not after each GLM. All BIS-11 p-values shown were corrected for FDR at 0.1.

The BIS-11 presents interpretational challenges due to concerns about the fit of factor solutions, redundancy of some questions and low correlations between others (Reise et al., 2013). To address impulsivity in our cohort without the constraints of *a priori* first- and second-order scales, we applied a Least Absolute Shrinkage and Selection Operation (LASSO) regression to observe group responses to individual questions of the BIS-11 with 500 bootstraps, controlling for age, gender, and disease duration in PD participants (Tibshirani, 1996). This approach simultaneously performs regularization and variable selection, which allows for a higher prediction accuracy and specificity of interpretation. The variable with ≥80% chosen is deemed a significant variable in relation to either PD/HC or ICB+/- status (Friedman et al., 2010; Petersen et al., 2018). LASSO regression was performed using the glmnet package and bootstrapped in R statistical software (R Development Core Team, 2018).

2.5 RESULTS

Demographics

Both our PD ICB- and PD ICB+ groups had significantly more males than females ($t = 10.31$, $p = 0.01$). Our HC group was significantly younger than both our PD ICB- and PD ICB+ group ($t =$

15.22, p < 0.01). Among our PD participants, there was no significant difference in the overall disease duration between the ICB- and ICB+ groups (t = 2.02, p = 0.128). There were no significant differences in average UPDRS II or III scores between ICB- and ICB+ subjects (t = 0.06, p = 0.39 and t = 0.39, p = 0.27, respectively). There was a significant decrease in MoCA scores in the ICB- patient group compared to ICB+ patients (t = 6.31, p = 0.01).

BIS-11

Total Score – The BIS-11 total scores increased in a step-wise fashion (Figure 2-2), in which HC scored the lowest, PD ICB- scored significantly higher than HC (t = 2.49, p_{corr} = 0.045), and PD ICB+ group had significantly higher scores than PD ICB- groups (t = 2.40, p_{corr} = 0.045) and significantly higher than HC (t = 5.63, p_{corr} <0.001) (Figure 2-2A).

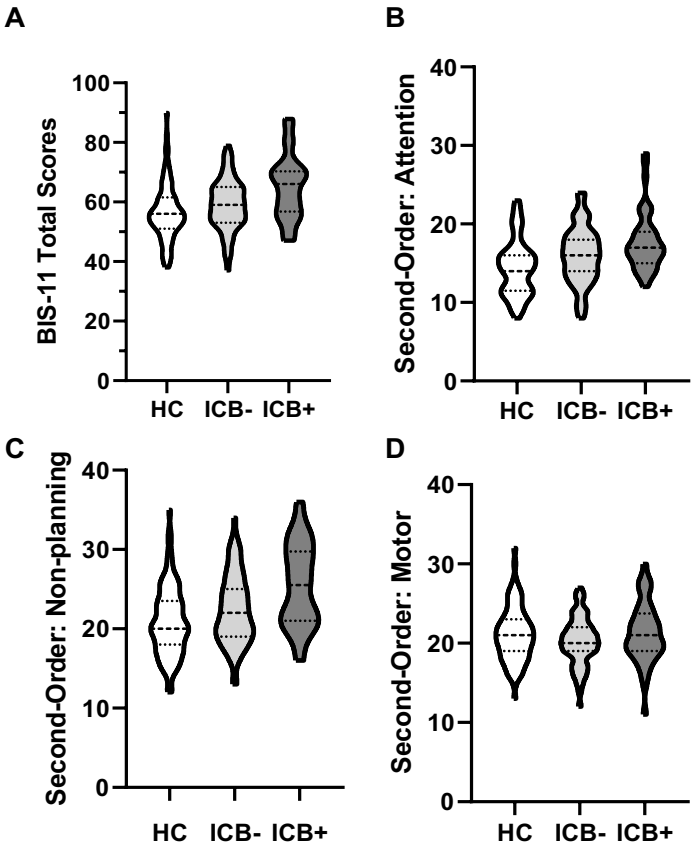


Figure 2-2. Violin plots showing the group responses for the BIS-11 total score (A), and second-order factors: attention, motor, and non-planning (B-D). The thickest dashed line in the middle of each violin plot indicates the median score.

Second-Order Factors - PD ICB- and PD ICB+ groups scored significantly higher than HC in the attention domain (t = 2.52, p_{corr} = 0.045, and t = 3.33, p_{corr} = 0.008, respectively; Figure 2-2B). Additionally, both PD ICB- and PD ICB+ groups scored significantly higher on average than HC in the non-planning domain (t = 2.75, p = 0.007; t = 3.65, p_{corr} = 0.0003, respectively; Figure 2-2C). There were no significant differences in the motor domain (Figure 2-2D).

First-Order Factors - The PD ICB+ group scored significantly higher than HCs in the attention (t = 4.07, p_{corr} < 0.001), self-control (t = 3.78, p_{corr} < 0.001), and cognitive complexity (t = 3.42, p_{corr} = 0.003) domains (Fig. 2-3A, 2-3E, and 2-3F, respectively). The PD ICB- group also showed significantly higher scores than HCs in the attention (t = 2.52, p_{corr} < 0.001) and self-control (t = 2.35, p_{corr} = 0.048) domains, such that a step-wise pattern emerges in which both average attention and self-control scores increase from HC to PD ICB- to PD ICB+ (Fig. 2-3A & 2-3E). The cognitive instability, motor, and perseverance domains showed no significant differences between any groups. When we run the GLM model controlling for MoCA scores, the first-order factor of attention is no longer significant between ICB- and ICB+ subjects (for further detail see supplementary Table 2 in Aumann et al., 2020).

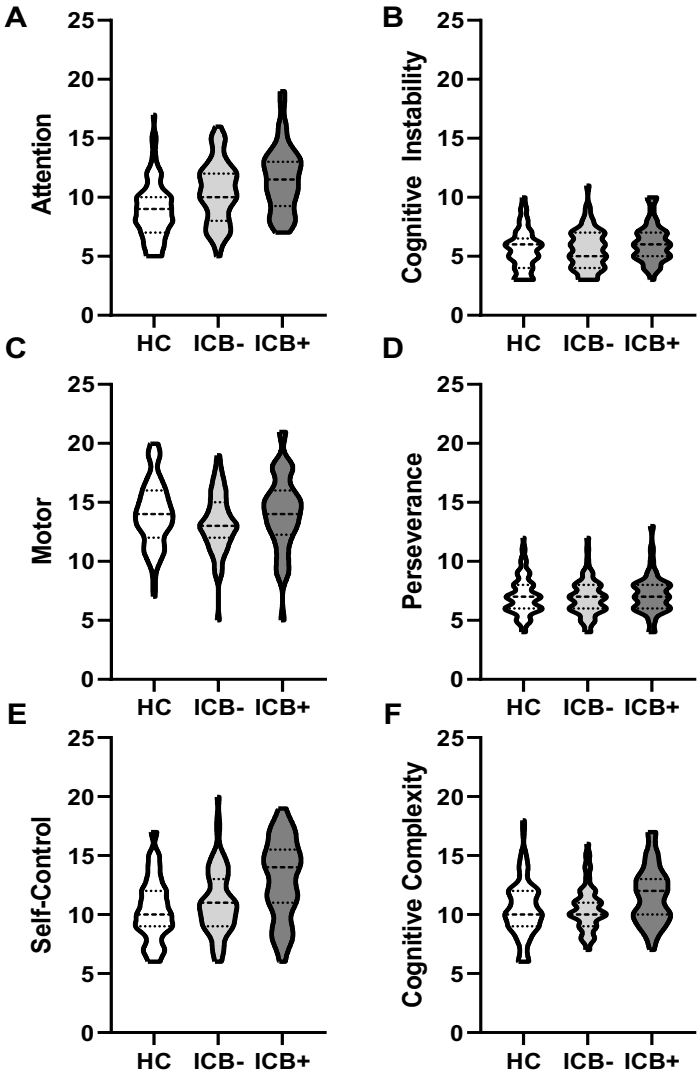


Figure 2-3. Violin plots showing group results for each of the first-order factors: attention(A), cognitive instability (B), motor (C), perseverance (D), self-control (E), and cognitive complexity (F). The thick dashed line in each plot indicates the median.

LASSO Regression

A LASSO regression shows how responses to individual questions contribute to outcomes, in this case, disease status (HC, IBC-, ICB+). The LASSO analysis identified 13 individual questions from the BIS-11 that were chosen with a frequency of ≥ 80% as important questions for distinguishing between HC and PD state. PD subjects were more likely to respond with "Almost Always," unless the question is starred, in which case PD subjects were more likely to report "Rarely/Never" (Fig. 4A). Additionally, when looking at questions that distinguish between ICB status (ICB+/-), question 8, "I am self-controlled" is more likely to distinguish ICB+ subjects, who more reported "Almost Always" with a frequency of ≥ 80% (Fig. 2-4B). It may be worth noting that if you extend the threshold to a choice of ≥ 60%, two more questions emerge as important distinguishers between ICB states ("I save regularly" and "I am a steady thinker").

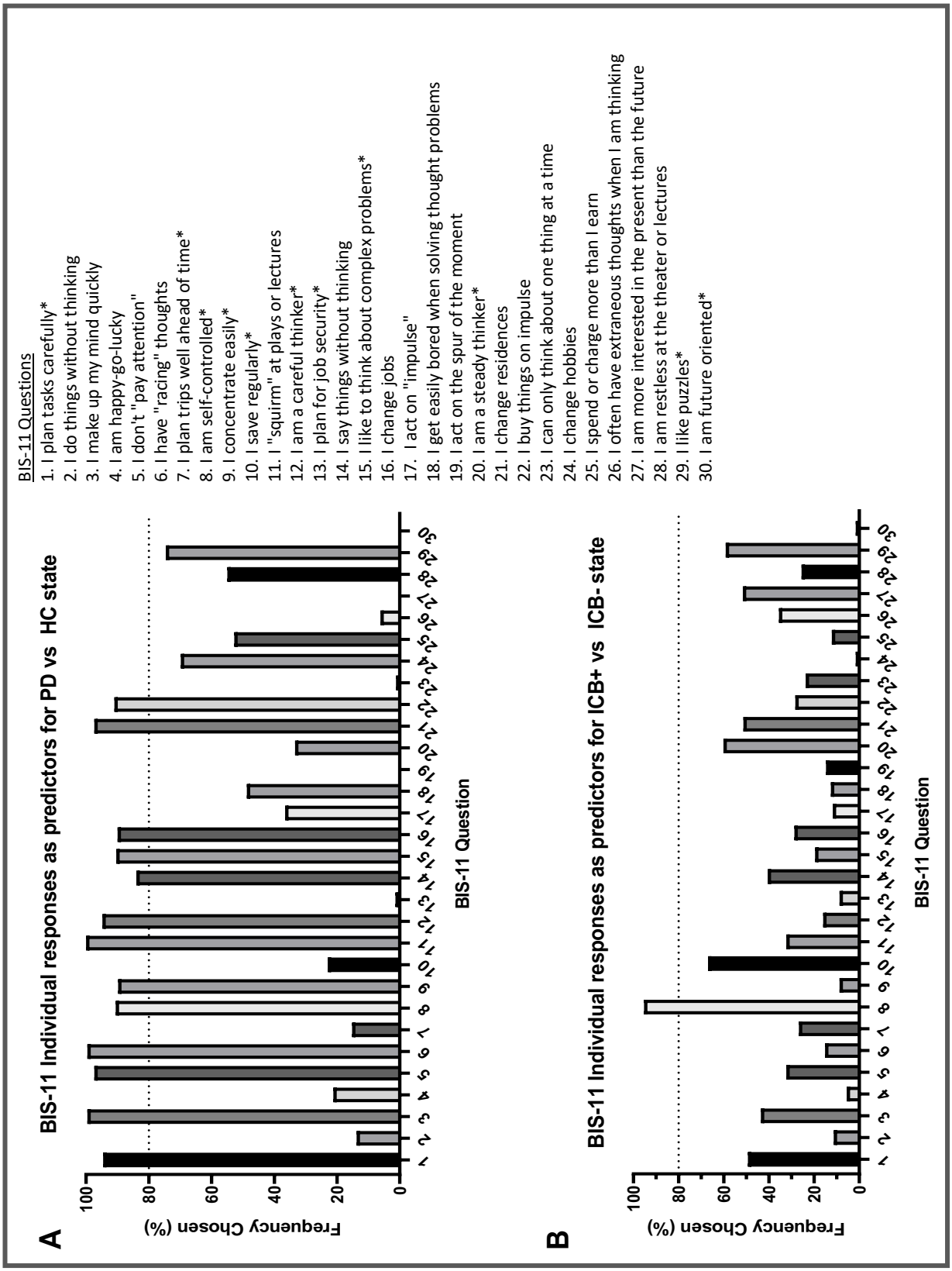


*Figure 2-4. LASSO graphs showing the frequency with which the BIS-11 question was marked as "always/almost always" (unless reversed scored as indicated by a * symbol) for PD vs HC (A), or for PD ICB+ vs PD ICB- (B).*

2.6 DISCUSSION

Cognitive and behavioral changes that impact motivation and attention are common features in PD patients, especially as the disease progresses (Aarsland et al., 2017; Bronnick et al., 2007; Claassen & Wylie, 2012; Czernecki et al., 2002; Petersen et al., 2018; Pillon et al., 2003). In a large PD cohort, we have demonstrated that patients report behavioral symptoms linked to elevated impulsivity. This increase is independent of a diagnosis of ICB, with symptoms primarily in the attention and non-planning domains and occurring at elevated rates in both PD patient groups. Patients with clinically diagnosed ICBs report even greater BIS-11 scores, as well as in these same domains. A question-based regression analysis highlights that ICB patients experience a perceived lack of self-control. Importantly, study results emphasize that PD patients are subjectively aware of changes to self-regulation of behavior and thinking, and that the nature of these deficits are heightened in patients with ICB.

These results extend past assessments of impulsive behaviors in PD, which have found higher ratings on the BIS-11 in ICB+ patients in both the BIS-11 total score across the attention and non-planning domains (Ruitenberg et al., 2018; Sauvaget et al., 2017; Sharma et al., 2013; V Voon et al., 2006; Valerie Voon et al., 2011), but had not evaluated first order factors. Interestingly, we observe significant differences between the ICB+ and ICB- group in only one attentional first-order factor (attention), and in both non-planning first-order factors of self-control and cognitive complexity. The attention domain reflects an inability to focus or concentrate on a specific task, while the non-planning domain reflects an inability to defer gratification, where patients note difficulty in either staying focused enough to complete a task, or struggle with strategic decisions that require delayed gratification. These results are consistent with previous studies assessing delayed discounting and reward-strategies (Filip et al., 2018; Kehagia et al., 2014; Swann et al., 2002), although this effect was not apparent in a smaller cohort (Bentivoglio et al., 2013), nor a cohort that did not compare scores to a group of HCs (Juan Marín-Lahoz et al., 2018). Furthermore, while previous studies focus

on PD patients with and without ICB, we included analyses that self-assess behavioral symptoms in a healthy cohort. Findings regarding motor impulsivity are less consistent, with some studies showing increased motor impulsivity in ICB patients (Bentivoglio et al., 2013; Valerie Voon et al., 2011), although we do not see greater motor impulsivity scores in ICB patients, a finding consistent with previous studies that show intact behavioral motor inhibitory control in ICB patients (Trujillo et al., 2019; van Wouwe et al., 2014; Wylie et al., 2018) and lower self-reported ratings of motor impulsivity in PD patients with addictions (Sauvaget et al., 2017).

Our results emphasize that impulsive behavioral changes occur in PD, regardless of ICB status. Indeed, the LASSO analysis reveals most questions distinguishing PD from HCs that align with the changes to attention or inhibitory control, as demonstrated by high ratings on questions such as: "I don't 'pay attention'," "I (don't) plan tasks carefully," "I am (not) self-controlled," and "I buy things on impulse." Although the Urgency-Premeditation-Perseverance-Sensation seeking Impulsive Behavior Scale (UPPS) measures different dimensions of impulsivity than the BIS-11, our findings align well with overall findings from a study that found that PD subjects had lower premeditation and greater risk taking than HCs (Bayard et al., 2016). While difficult to compare to BIS-11 findings, we believe that the changes in self-control and cognitive complexity agree with this finding. Of note, a few questions did not appear to align well with the cohort demographics, such as "I change jobs" and "I change residences." Conceivably these questions may not be relevant to an older cohort and could be modified or excluded in future studies in an older population.

Previous attempts to describe the pattern of cognitive changes that evolve over the course of PD suggest a progression from anterior (attention and executive function) to posterior (visuospatial and memory) dysfunction (Claassen & Wylie, 2012; Cosgrove et al., 2015; Fengler et al., 2017b; O'Callaghan & Lewis, 2017a; Weintraub & Mamikonyan, 2019). Cognitive deficits are present at various stages of disease, including in the prodromal stage, and early in the disease course (Goldman & Postuma, 2014). Impairments to attention and planning are likely a result of alterations to fronto-

striatal circuitry, where the anterior cingulate cortex (ACC), (i.e. response initiation, intention, and inhibition) (D. J. Brooks & Piccini, 2006; Kubera et al., 2019; Petersen et al., 2018; Stark & Claassen, 2017), orbitofrontal cortex (OFC) (decision making and encoding values of expected reward outcomes) (Izquierdo & Murray, 2004; Kubera et al., 2019; Petersen et al., 2018) and the dorso-lateral prefrontal cortex (dlPFC), (complex problem-solving, organizational planning strategies, concept-formation, and working memory) (D. Zgaljardic et al., 2006) are functionally linked to basal ganglia structures altered in PD. Our findings agree with previously described changes to frontal-striatal networks, where behavioral impulsive actions, reflected in items such as "I (don't) plan tasks carefully," "I say things without thinking," and "I buy things on impulse," reflect challenges with exerting behavioral self-control. Interestingly, when we re-run our model additionally controlling for MoCA scores between the ICB- and ICB+ groups, both the first-order factors of self-control and cognitive complexity remain significant, but the first-order attention factor is no longer significant between these groups. These findings suggest that increased impulsivity may be a direct consequence of deteriorating cognitive function. It may be noted, we excluded patients with MOCA score of less than 22. While this excluded patients with dementia, in the absence of formal neuropsychological testing, it is possible that some patients may have met criteria for mild cognitive impairment. A previous study found that there was no difference in BIS-11 scores and domain scores between PD and PD-MCI patients (Bayard et al., 2016). We hypothesize that self-reported problems with attention in this PD population may reflect early dysexecutive symptoms, of which the MoCA screening is heavily weighted. Behavioral changes linked to attentional and executive dysfunction should be formally explored in future studies assessing cognitive decline and behavioral impulsivity in PD. Our findings emphasize that impairments to self-regulation are a key deficiency in the ICB population. While self-report measures of impulsivity often have only modest to moderate associations with task-based measures of cognitive functioning and impulsivity (Bentivoglio et al.,

2013; Imperiale et al., 2018; Sharma et al., 2013), many PD patients are indeed aware of alterations in cognitive functioning and behavior changes (Mack et al., 2013).

Use of the first-order factors provided specific information on domains most affected in ICB patients, which may be of use when clinically evaluating a PD patient for an ICB, and when considering future therapeutic interventions. It is useful to note that the BIS-11 captures broad behavioral constructs, which is different than other assessments such as the QUIP, which is more limited to explicit behaviors that are commonly encountered in the clinical setting (e.g. eating, sexual activity, gambling etc.). Here we show that patients with ICBs were significantly more impulsive, particularly in the attentional and non-planning domains of self-control and cognitive complexity. Due to the cross-sectional nature of this study, it remains unclear if increases in impulsivity are due to alterations from PD pathophysiology, secondary effects of chronic dopaminergic treatments, or both. Future studies investigating the relationship between ICBs in PD in a DAA naïve group may help elucidate the role DAA play in development of ICBs. This study also reinforces the relevance of non-motor symptoms in PD, as these findings emphasize the cognitive changes that may prove valuable in assessing the efficacy of a therapeutic intervention.

2.7 CONCLUSIONS

Here we provide evidence for increased subjective rates of impulsivity in Parkinson's patients and demonstrate distinctions in patients without and without impulse-compulsive behaviors. Study results emphasize that PD subjects are aware of changes to behavioral regulation and cognition, particularly in the domains of attention and non-planning. These findings expand on previous work and our understanding of impulsive changes in Parkinson's Disease by highlighting changes that are not protypic of ICB behavior. This finding will encourage future studies investigating the clinical relevance and biological mechanism of PD-related changes to decision-making proficiency.

CHAPTER 3

BEHAVIORAL EFFECTS OF STIMULATED DOPAMINE RELEASE AND D2-LIKE RECEPTOR DISPLACEMENT IN PARKINSON'S PATIENTS WITH IMPULSE CONTROL DISORDER

3.1 PURPOSE

Affecting more than one million Americans, Parkinson's disease (PD) has been long treated with dopamine (DA) replacing therapies that mainly target motor symptoms. However, studies assessing the etiology of this disease and its symptoms estimate that between 15 and 40% of patients on long-standing DA agonist (DAA) therapy will develop impulsive and compulsive behaviors (ICBs) as an unintended side effect. Widely thought to result from aberrant DA-ergic neurotransmission in structures such as the striatum, ICBs are a substantial source of morbidity in an already vulnerable population.

Besides motor effects, several studies have explored the role of DAA in modulating affect among PD patients, who often experience mood changes including apathy, depression, and anxiety. However, we lack an understanding of the neuroanatomical correlates of these on-drug mood changes, as well as an appreciation for how the presence of ICBs influence the mood effects of DAA therapies. These questions motivated the current study, in which we investigate the associations between dopamine D2 receptor availability, mood, and impulsivity. Here, we applied a dextro-amphetamine (dAMPH) challenge to simulate acute DA release in a population of PD patients who completed a variety of mood assessments and quantified D2-like receptor availability using positron emission tomography (PET) imaging with the high affinity D2/3 receptor ligand [^{18}F]-fallypride.

3.2 SUMMARY

Dysregulated dopamine (DA) release in the mesocorticolimbic circuit is noted in Parkinson's disease (PD) patients with impulsive and compulsive behaviors (ICBs). However, the effect of acute DA release on mood, localization of this process, and phenotypic differences in patients with ICB remains unknown. In this study, we applied a placebo-controlled dextro-amphetamine (dAMPH) challenge in 20 PD patients, 10 with ICBs (PD-ICB) and 10 without (PD-C). Subjective mood experiences were measured with well-described self-reported measures including the Positive and Negative Affect Scale (PANAS), Drug Effects Questionnaire (DEQ), and Amphetamine Interview Rating Scale (AIRS). D2-like receptor availability was measured as non-displaceable binding potential (BP_{ND}) using PET imaging with the high-affinity D2/3 receptor ligand [^{18}F]-fallypride. Among all subjects, dAMPH increased PANAS positive, DEQ feel, DEQ high, and AIRS total scores. Increases in PANAS positive and AIRS total scores were greater in the PD-ICB cohort. Results from a mixed effects model correlated these questionnaire changes with dAMPH-induced reductions in BP_{ND} in ventral striatum (VS), caudate, amygdala, and caudo-medial orbitofrontal cortex. Further, baseline caudate, VS, and amygdala BP_{ND} positively correlated with lower on-dAMPH PANAS positive scores. Taken together, we find that elevated mood symptoms of acute dAMPH administration in PD are linked to DA release in mesocorticolimbic regions. Distinctions in behavioral effects seen among PD-ICB subjects emphasize that dysregulated striatal and extra-striatal DA-ergic networks alter mood responses to stimulated DA release and may also contribute to behavioral changes resulting from DA-targeting therapies in PD.

3.3 Introduction

Patients with Parkinson's disease (PD) experience a variety of non-motor symptoms that include psychiatric and behavioral changes, among which apathy, anxiety, and depression are the most common (Ahearn et al., 2012a; Wen et al., 2016). While necessary for symptomatic control of

motor dysfunction, treatments that target dopamine (DA) can also modify behavioral affect, where D2 and D3 receptor agonists have evidence of improving depressive symptoms (Menza et al., 1990). However, DA agonist (DAA) usage is the strongest risk factor for development of impulsive and compulsive behaviors (ICBs), which arise in about one-third of treated PD patients (Ambermoon et al., 2011; Garcia-Ruiz et al., 2014b; Park & Stacy, 2011; Weiss & Marsh, 2012a). Defined as pathologic failures to resist urges to perform acts regardless of their negative consequences (Mestre et al., 2013; Zhang et al., 2014), ICBs have been linked to altered ventral striatal D2-like receptor (D2-R) expression and dysregulated mesocorticolimbic DA release, emphasizing the influence of the DA-ergic system in regulating mood in PD (Buckholtz et al., 2010; Probst & van Eimeren, 2013; Song et al., 2021; Stark, Smith, Lin, et al., 2018).

The dorsal and ventral DA networks are differentially impacted in PD. Motor symptoms such as tremor and bradykinesia clearly respond to DAA therapies which modulate dorsally-located structures such as the substantia nigra and dorsal striatum. The relative preservation of ventral DA networks, especially early in the course of PD, may predispose PD patients to ICBs as a result of DAA increasing DA neurotransmission in the ventral striatum (VS), putamen, and caudate head (Evans et al., 2006; C. T. Smith et al., 2018; Song et al., 2021; Steeves et al., 2009; Pierre Trifilieff & Martinez, 2014; Valerie Voon et al., 2014). DA dysregulation that contributes to ICBs may also occur extra-striatally, particularly in the amygdala, caudo-medial orbitofrontal cortex (cmOFC), insula, and anterior cingulate cortex (Carriere et al., 2015; Cilia et al., 2008; Cilia & van Eimeren, 2011; McHugh et al., 2013; C. T. Smith et al., 2016; Song et al., 2021).

Pharmacologic challenge studies can provide important insights that link neurotransmitter changes to neuroanatomical circuits and behavioral responses. Amphetamine is commonly used to study DA neurotransmission since it robustly causes DA release through its combined ability to increase pre-synaptic DA release from stored vesicles, impair DA reuptake by inhibiting DA transporters (DAT), and promote DAT-mediated reverse transport of DA into the synaptic cleft

(Fleckenstein et al., 2007). Many behavioral studies have utilized dextro-amphetamine (dAMPH) to understand how acute DA release influences mood, affect, and physical sensations. Indeed, amphetamine has been consistently associated with increased feelings of vigor, elation, friendliness, and overall positive mood enhancement (Johanson & Uhlenhuth, 1981; B. C. Kelly et al., 2006). Although these mood effects have been associated with increased levels of DA (Ashby et al., 1999), there are inconsistent reports of what areas of the brain are related to mood changes, with one study reporting that males but not females show positive mood-associated DA release in the left substantia nigra (Riccardi et al., 2011), while another study failing to find any significant brain regions associated with amphetamine-induced positive affect (Riccardi et al., 2006).

In this study we performed a single-blinded, placebo-controlled dAMPH intervention, with concomitant D2-like receptor imaging, in a cohort of PD patients with and without ICB. Our goals were to 1) assess dAMPH-mediated effects on mood in PD, 2) localize dAMPH-induced DA release, and 3) determine the relationship between baseline D2-R availability and dAMPH-induced effects on mood. D2-R were quantified using positron emission tomography (PET) with [^{18}F]-fallypride (Riccardi et al., 2006), a ligand that provides both striatal and extra-striatal assessments of D2-like receptor non-displaceable binding potential (BP_{ND}). Acute effects on mood were assessed using the Positive and Negative Affect Schedule (PANAS) (Sacheli et al., 2019; S.-M. Wang & Tickle-Degnen, 2018; D Watson et al., 1988), which assesses emotional affect in a two-dimensional model of mood; the Drug Effects Questionnaire (DEQ) (Fischman & Foltin, 1991; Morean et al., 2013), which assesses the acute subjective effects of addictive substances; and the Amphetamine Interview Rating Scale (AIRS) (Schneier et al., 2009; Van Kammen & Murphy, 1975), which assesses the effects of amphetamine on mood and physical sensations. By examining the relationship between D2-R availability and subjective mood ratings in PD patients with and without ICB, our study provides insight into the neuroanatomical substrates of DA-ergic regulation of mood in PD.

3.4 METHODS

Population

Participants were recruited from the Vanderbilt University Medical Center Department of Neurology, and all completed written informed consent approved by the Vanderbilt University Institutional Review Board. Exclusion criteria included DAA therapy for >8 years; patient age <45 or >80 years; concomitant use of GABA-altering medications; comorbid neurological disease (e.g. stroke, dementia, etc.); diagnosis of an untreated mood disorder from the Diagnostic and Statistical Manual of Mental Disorders (5th ed.) (American Psychiatric Association, 2013); prior history of deep-brain stimulation surgical implant; and any other condition precluding MRI imaging.

Table 3-1. Demographic and clinical evaluation of PD participants

Variables	**All PD**	**ICB+ (PD-ICB)**	**ICB- (PD-C)**	**Test statistic, p (PD-ICB vs. PD-C)**
N	20	10	10	-
Sex (M/F)	12/8	7/3	5/5	0.833, 0.361
Age (yrs)	64.1 ± 5.78	65.8 ± 6.60	62.4 ± 4.53	2.12, 0.198
Disease duration (yrs)	6.43 ± 3.07	6.10 ± 2.28	6.75 ± 3.81	2.13, 0.650
MDS-UPDRS-III (off-dAMPH)	28.7 ± 13.1	27.6 ± 12.4	29.7 ± 14.3	2.10, 0.730
Total LEDD (mg/day)	671 ± 302	671 ± 314	672 ± 306	2.10, 0.994
QUIP-RS	26.0 ± 13.9	30.0 ± 12.0	19.9 ± 12.1	**1.88, 0.038**

Data are shown as mean ± standard deviation. Statistical tests: chi-squared test (sex); non-parametric t-test (age, disease duration, MDS-UPDRS-III, Total LEDD, QUIP-RS). Significant comparisons ($p < 0.05$) are shown in bold.
Abbreviations: MDS-UPDRS = Movement Disorders Society-United Parkinson's Disease Rating Scale, LEDD = Levodopa Equivalent Daily Dose; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale.

20 participants diagnosed with idiopathic PD completed the study. Based on diagnostic interview, 10 met criteria for ICB disorder (PD-ICB) and 10 did not (PD-C). All participants completed the Montreal Cognitive Assessment (MoCA) to assess global cognitive functioning (with average scores equalling 26.0), the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (UPDRS) (Ebersbach et al., 2006b; Goetz et al., 2007; Werner Poewe & Mahlknecht, 2009a) parts II and III to assess symptom severity, and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) to assess and quantify impulsive behaviors (Weintraub et al., 2009a, 2012). The groups were evenly matched for sex, age, disease duration, UPDRS-III score, and levodopa equivalent daily dose (Table 3-1). The PD-ICB cohort had significantly higher QUIP-RS ($p = 0.038$) scores than the PD-C cohort (Table 3-1).

Trait impulsivity, subjective measures

Patients completed four questionnaires: QUIP-RS, PANAS, DEQ, and AIRS. Subscale scores were calculated including the 2 sub-domains of PANAS, 5 sub-domains of DEQ, and 6 sub-domains of AIRS; the QUIP-RS had no sub-domains. Percent-change in scores was defined as (score off-dAMPH – score on-dAMPH) / maximum subscale score, which accounted for baseline scale scores rated as zero. Scores in PANAS positive and PANAS negative both ranged from 10 to 50. Scores in DEQ feel, DEQ high, DEQ dislike, DEQ like, and DEQ want ranged from 0 to 100 each. Scores in AIRS activation and AIRS depression both ranged from 0 to 120; AIRS physical from 0 to 180; AIRS euphoria from 0 to 80; AIRS dysphoria from 0 to 140; and AIRS sleepiness from 0 to 40.

MRI acquisition

Magnetic resonance imaging (MRI) scans were acquired to provide high-resolution structural delineation for quantification of [^{18}F]-fallypride non-displaceable binding potential (BP_{ND}). All scans were completed with a 3.0 T Philips scanner using body coil transmission and 32-channel SENSE

array reception. Structural images were acquired using a T_1-weighted high-resolution anatomical scan (MPRAGE; spatial resolution = 1 x 1 x 1 mm^3; TR/TE = 8.9/4.6 ms). MRI scans were obtained prior to PET scans on each patient's first visit day.

PET imaging, data processing

[^{18}F]-fallypride was produced by the Vanderbilt Radiochemistry Core laboratory using synthesis and quality control procedures described in U.S. Food and Drug Administration IND 12,035. PET scans were completed on a Philips Vereos PET-CT scanner with a 3D emission acquisition and a transmission attenuation correction. Images had an axial resolution of 4 mm and in-plane resolution of 4.0 mm with a 5.8 mm FWHM. Following a bolus injection of 5.0 mCi [^{18}F]-fallypride, serial scans were obtained for approximately 3.5 hours. Subjects received two scans, one in the on-dAMPH state and another in the off-dAMPH state. PET image corrections and registration were performed as previously described (Mann et al., 2021; Song et al., 2021). [^{18}F]-fallypride BP_{ND} was quantified using the simplified reference tissue (SRTM) model in the Pixel-wise Modeling Tool from PMOD, version 4.2. The cerebellum served as a reference region due to its limited $D_{2/3}$-R expression. For subject-level analyses, parametric BP_{ND} images from both sessions were co-registered to each participant's MRI image as previously described (Mann et al., 2021; Song et al., 2021).

Regions-of-interest (ROI) were obtained in ventral striatum (VS), caudate head, putamen, globus pallidus (GP), substantia nigra (SN), amygdala, caudo-medial orbitofrontal cortex (cmOFC), hypothalamus, insula, and anterior cingulate cortex (ACC). Bilateral subcortical ROIs of VS, caudate head, putamen, SN, amygdala, and cerebellum were manually defined on the T_1 MRI image according to established anatomical criteria. The hypothalamus was manually defined using a previously described method (Klomp et al., 2012). The cmOFC was manually defined using landmarks previously described definitions (Ongür & Price, 2000) including Brodmann areas 14c

and the posterior medial aspect of area 13; this definition was also used in (Song et al., 2021). The GP was defined using segmentation provided by FSL (version 6.0, FMRIB Software Library).

Experimental design

Each subject underwent a baseline general physical exam, electrocardiogram, complete blood count with basic metabolic panel, assessment of PD severity utilizing the MDS-UPDRS parts II and III (Ebersbach et al., 2006b; Werner Poewe & Mahlknecht, 2009a), assessment of impulsivity with a semi-structured interview, and completion of the QUIP-RS. We used a two-scan protocol to evaluate the effects of dAMPH on DA-R availability estimated with BP_{ND} and percent-change BP_{ND} relative to baseline, defined as (BP off-dAMPH – BP on-dAMPH) / BP off-dAMPH. Following 72-hour DAA medication withdrawal, patients received placebo on the first experimental day and 0.43 mg/kg dAMPH on the day of the second scan, although patients were informed that the order of placebo and drug would be randomized. The order of scans was arranged to minimize any potential of dAMPH-induced changes to D2-R. 3 hours after single-blinded administration of treatment, patients completed the PANAS, DEQ, and AIRS. PET and MRI images were also obtained as described above. Following a 48-hour washout, patients received the opposite treatment using the same protocol as described above. All patients were consistently monitored for possible adverse events throughout the experiment.

Statistics

Analyses were computed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests assumed non-normal distributions of data and considered the covariates of sex and a principal component (PC1) for age and UPDRS-III score, which assesses severity of PD motor symptoms. Wilcoxon signed-rank test assessed change in behavioral subscale scores in off- vs. on-dAMPH states; this assessment was performed for all subjects, ICB+ subjects (PD-ICB), and ICB-

subjects (PD-C). A mixed effects model (BP_{ND} on/off ~ behavioral subscale score on/off + sex + PC1) assessed the relationship between behavioral subscale scores and BP_{ND} within each ROI, with treatment (off- vs. on-dAMPH) as the repeated measures variable. A Spearman correlation assessed the relationship between QUIP-RS scores and percent-change in behavioral subscale scores. Finally, a Spearman correlation assessed the relationship between off-dAMPH (i.e., baseline) BP_{ND} within each ROI and percent-change in behavioral subscale scores. Results were controlled at a False Discovery Rate (FDR) of 0.05 to correct for multiple comparisons as used previously (Stark, Smith, Petersen, et al., 2018) and reported as p_{CORR} unless otherwise specified. Effect sizes for the Wilcoxon analysis were calculated by Cohen's d.

3.5 RESULTS

dAMPH effects on mood

We evaluated the effect of dAMPH on behavioral outcomes as measured by three complimentary scales that assess stimulant effects on mood. Scores reported in the placebo state are denoted as OFF, and those reported in the dAMPH state are ON. dAMPH administration increased PANAS positive scores across all PD subjects (Cohen's d = 0.612; p_{CORR} = 0.002) (Fig. 3-1). When separated by ICB status, we found that this relationship is more prominent in the PD-ICB group, which showed significant changes

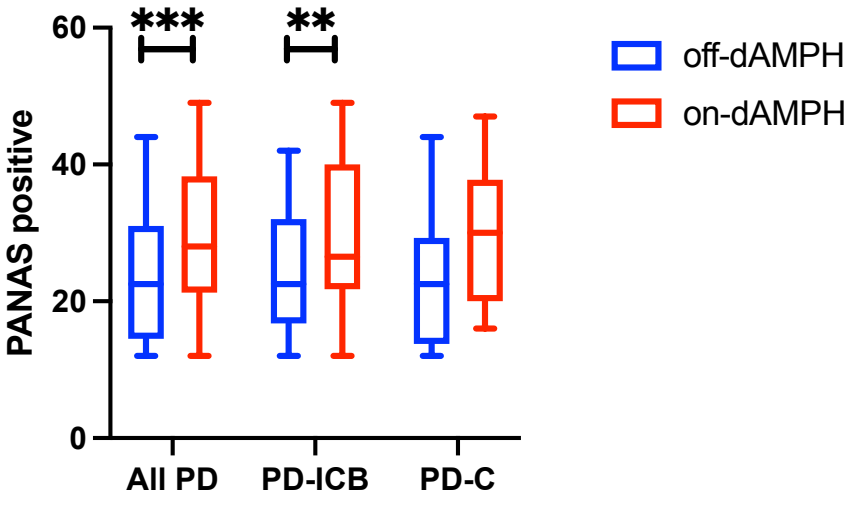


*Figure 3-1. Box and whisker plots showing mean and standard error for PANAS positive scores in all PD subjects (left) and split into PD-ICB (middle) and PD-C cohorts (right), in both off-dAMPH (blue) and on-dAMPH (red) conditions. ** indicates statistically significant results after multiple comparisons correction at p < 0.05, and *** at p < 0.01.*

when assessing the ON-OFF state (d = 0.660; p_{CORR} = 0. 025) compared to the PD-C group, whose ON-OFF differences were noticeable but did not survive multiple comparisons correction (d = 0.533; p = 0.026; p_{CORR} = 0.338) (Fig. 3-1). QUIP-RS ratings did not correlate with the PANAS positive response (data not shown). No effect of dAMPH was observed for the PANAS negative subscale.

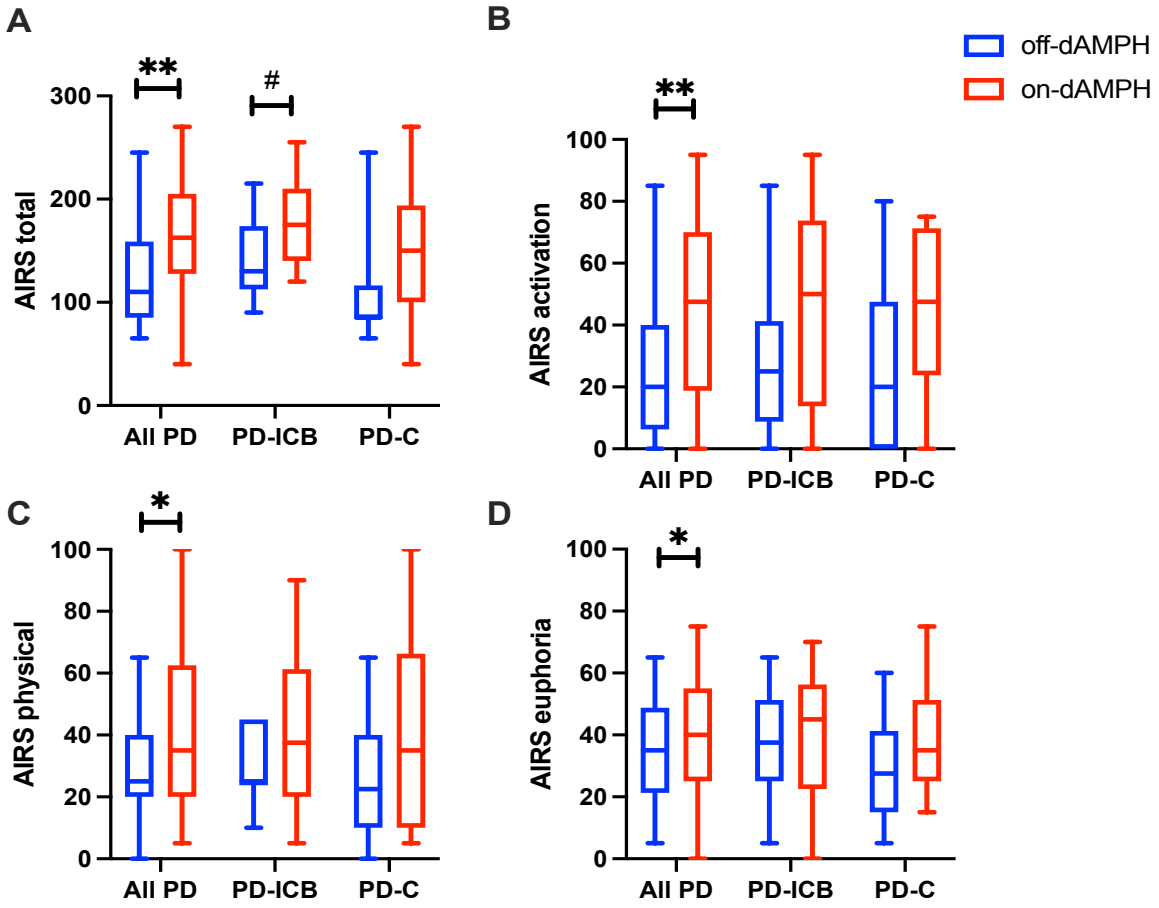


*Figure 3-2. Box and whisker plots showing mean and standard error scores for all PD subjects (left) and split into PD-ICB (middle) and PD-C cohorts (right) in both off-dAMPH (blue) and on-dAMPH (red) conditions for AIRS total (A), AIRS activation (B), AIRS physical (C), and AIRS euphoria (D) scores. * indicates statistically significant results after multiple comparisons correction at p < 0.1 and ** at p < 0.05. # indicates results significant (p < 0.05) before multiple comparisons correction.*

When considering dAMPH-related changes in AIRS, total scores increased significantly from placebo across all participants (d = 0.829; p_{CORR} = 0.012) (Fig. 3-2A). Within AIRS, across all PD subjects, dAMPH significantly increased scores in the activation (d = 0.645; p_{CORR} = 0.029), physical (d = 0.561; p_{CORR} = 0.061), and euphoria (d = 0.329; p_{CORR} = 0.088) subscales (Fig. 3-2B, 3-2C, 3-2D respectively). For these subscales, it did not appear that either PD-ICB or PD-C cohort responded

differently to dAMPH (Fig. 3-2B, 3-2C, 3-2D). Interestingly, while AIRS sleepiness scores did not change across all participants (d = -2.75; p_{CORR} = 0.39), the PD-ICB cohort showed significant reductions in AIRS sleepiness (d = -0.628; p_{CORR} = 0.025; data not shown in figure) which was not seen in the PD-C group. No effect of dAMPH was observed for the AIRS depression and dysphoria subscales. QUIP-RS scores negatively correlated with dAMPH-induced change in the AIRS depression (R^2 = 0.19; p_{CORR} = 0.054) subscale only, indicating greater subjective feelings of depression (Fig. 3-3) while on dAMPH.

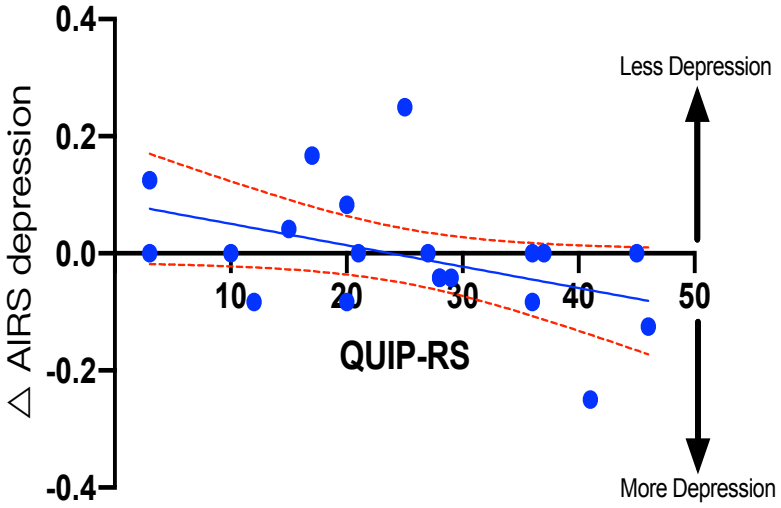


Figure 3-3. Spearman correlation indicating the relationship between change in AIRS depression scores, defined as (off-dAMPH – on-dAMPH) / off-dAMPH, related to QUIP-RS across all PD subjects. Blue dots indicate individual subjects; solid blue line indicates regression line; red dotted lines indicate 95% confidence interval.

Finally, when assessing dAMPH-induced changes in the DEQ subscales, we noted significant increases across all PD subjects in DEQ feel (d = 0.793; p_{CORR} = 0.063) (Fig. 3-4A) and DEQ high scores (d = 0.777; p_{CORR} = 0.086) (Fig. 3-4B). However, neither PD-ICB nor PD-C cohort responded differently to dAMPH (Fig. 3-4A and 3-4B) in either subscale. QUIP-RS ratings did not correlate with the DEQ feel or high response (data not shown). No effect of dAMPH was observed for the DEQ dislike, like, or want subscales.

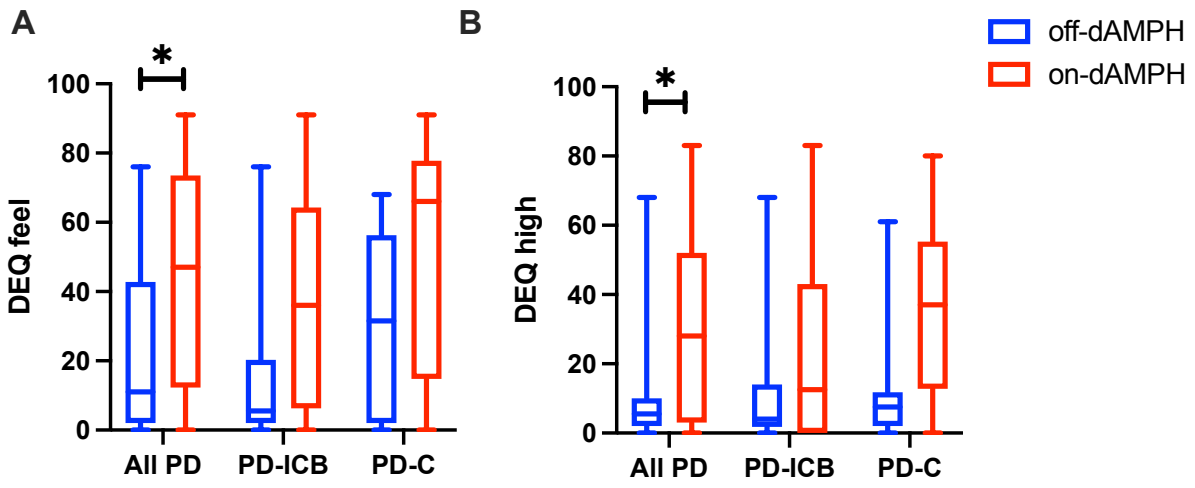


*Figure 3-4. Box and whisker plots showing mean and standard error scores for all PD subjects (left) and split into PD-ICB (middle) and PD-C cohorts (right) in both off-dAMPH (blue) and on-dAMPH (red) conditions for DEQ feel (A) and DEQ high (B) scores. * indicates statistically significant results after multiple comparisons correction at $p < 0.1$.*

Localization of DA release associations with subjective experiences

The effect of dAMPH on non-displaceable binding potential (BP_{ND}) and behavioral responses was assessed using a linear mixed effects model; for quantification of dAMPH-induced displacement, see Table 2 in (Song et al., 2021). This analysis focused on the questionnaire subscales where significant dAMPH-induced effects were noted among all participants. Subscale score relationships with regional BP_{ND} changes can all be found in Table 3-2. Total AIRS scores significantly correlated with dAMPH-induced reductions in VS BP_{ND} ($b = -0.011$; $p_{CORR} = 0.027$), amygdala BP_{ND} ($b = -0.001$; $p_{CORR} = 0.080$), and cmOFC BP_{ND} ($b = -0.006$; $p_{CORR} = 0.070$). Among the subscales assessed, a significant correlation between AIRS activation scores and VS BP_{ND} was noted ($b = -0.022$; $p_{CORR} = 0.059$).

Although the following relationships did not survive multiple comparisons correction, we find these results noteworthy since similar ROIs appeared in multiple statistical analyses. PANAS positive scores correlated with dAMPH-induced reductions in VS BP_{ND} ($b = -0.055$; $p = 0.034$). DEQ feel scores correlated with dAMPH-induced reductions in caudate head BP_{ND} ($b = -0.009$; $p = 0.020$) and VS BP_{ND} ($b = -0.012$; $p = 0.031$). DEQ high scores correlated with dAMPH-induced reductions

in caudate head BP_{ND} (b = -0.008; p = 0.050). AIRS activation scores correlated with caudate BP_{ND} (b = -0.011; p = 0.046) and hypothalamus BP_{ND} (b = -0.003; p = 0.041; data not shown in table). AIRS physical sub-scale scores correlated with caudate head BP_{ND} (b = -0.014; p = 0.039), VS BP_{ND} (b = -0.022; p = 0.019), cmOFC BP_{ND} (b = -0.011; p = 0.050), and insula BP_{ND} (b = -0.004; p = 0.036; data not shown in table). There were no significant correlations between AIRS euphoria scores and BP_{ND} in any ROI.

There were no significant correlations between any of the questionnaire scores and BP_{ND} in putamen, GP, SN, and ACC. All regression coefficients from significant comparisons were negative, indicating that a reduction in D2-R availability corresponded with a higher questionnaire score.

Table 3-2. Results of mixed effects model correlating questionnaire scores with regional BP_{ND}

	BP_{ND} (regression coefficient, p-value uncorrected, p-value corrected)			
Questionnaire	Caudate head	Ventral striatum	Amygdala	cmOFC
PANAS positive	-0.019, 0.32, 0.48	-0.055, 0.034*, 0.28	-0.004, 0.33, 0.48	-0.027, 0.11, 0.28
Total AIRS	-0.005, 0.062, 0.16	**-0.011, 0.0027, 0.027**	**-0.001, 0.024, 0.080**	**-0.006, 0.014, 0.070**
AIRS activation	-0.011, 0.046*, 0.15	**-0.022, 0.0059, 0.059**	-0.001, 0.29, 0.48	-0.006, 0.22, 0.44
AIRS physical	-0.014, 0.039*, 0.13	-0.022, 0.019*, 0.13	-0.003, 0.087, 0.15	-0.012, 0.050*, 0.13
AIRS euphoria	-0.005, 0.71, 0.71	-0.020, 0.23, 0.50		-0.006, 0.60, 0.71
DEQ feel	-0.009, 0.020*, 0.16	-0.012, 0.031*, 0.16	-0.003, 0.23, 0.50	-0.006, 0.070, 0.23
DEQ high	-0.008, 0.050*, 0.47	-0.010, 0.11, 0.47	-0.001, 0.27, 0.41	-0.004, 0.28, 0.47
			-0.001, 0.24, 0.47	

Only ROIs with significant findings are shown in table. Significant comparisons ($p_{CORR} < 0.1$) are shown in bold. Comparisons significant ($p < 0.05$) before multiple comparisons correction are shown with an asterisk (*). Abbreviations: cmOFC = caudo-medial orbitofrontal cortex

Baseline D2-R availability as a predictor of amphetamine effects

Finally, we assessed baseline (off-dAMPH) D2-R availability as a predictor of dAMPH-induced changes in subjective mood. We found significant positive associations between changes in PANAS

positive scores and baseline BP_{ND} in amygdala ($R^2 = 0.36$; $p_{CORR} = 0.091$) (Fig. 3-5A), caudate head ($R^2 = 0.33$; $p_{CORR} = 0.091$) (Fig. 5B), and VS ($R^2 = 0.37$; $p_{CORR} = 0.091$) (Fig. 3-5C) were observed. This relationship indicates that a higher BP_{ND} corresponded to a greater reduction in PANAS positive following dAMPH administration. We did not find associations involving DEQ feel, DEQ high, total AIRS, or any AIRS subscale scores and baseline BP_{ND} that survived multiple comparisons correction for this analysis. In addition, no significant associations involving any ROI other than amygdala, caudate head and VS were noted.

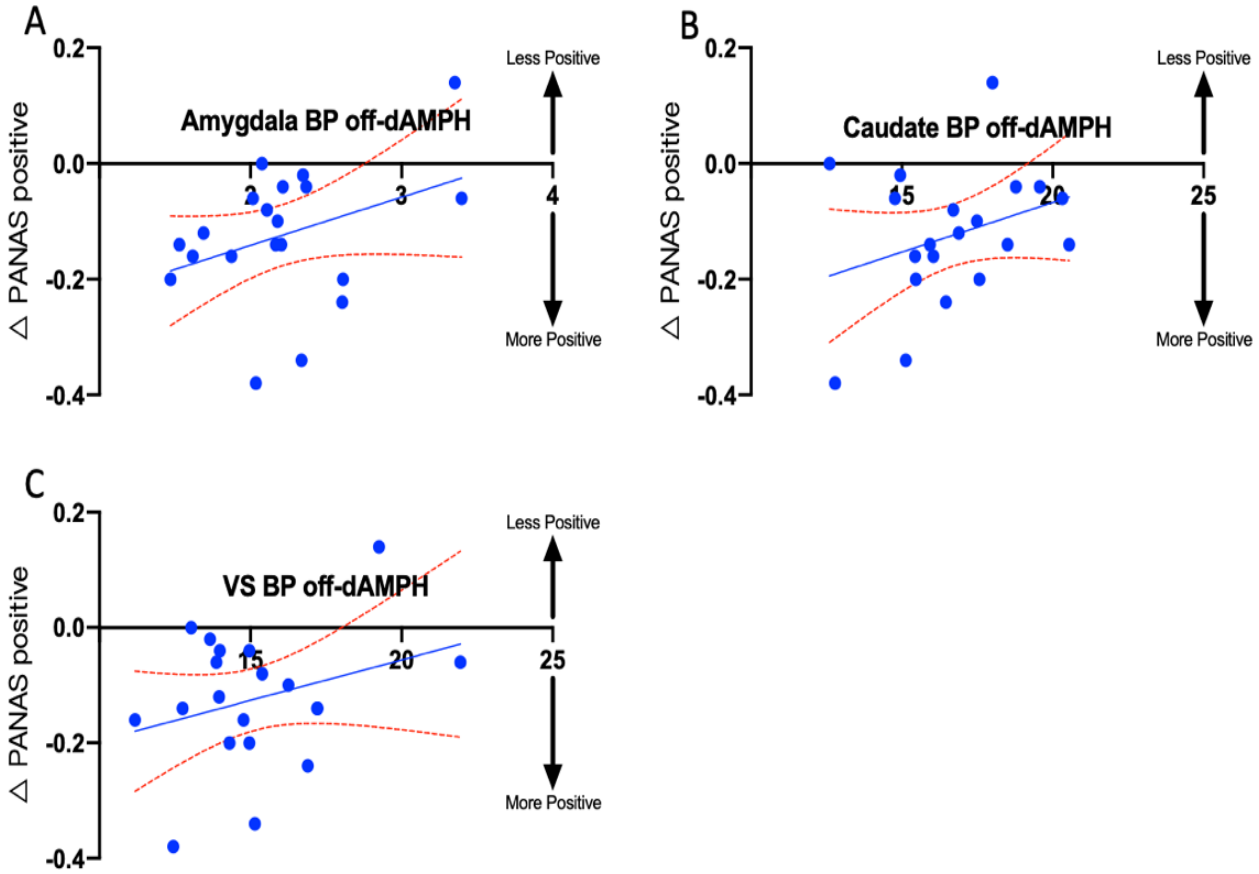


Figure 3-5. Spearman correlation indicating the relationship between change in PANAS positive scores, defined as (off-dAMPH – on-dAMPH) / off-dAMPH, related to baseline (off-dAMPH) [^{18}F]-fallypride non-displaceable binding potential (BP) in amygdala (A), caudate head (B), and VS (C) across all PD subjects. Blue dots indicate individual subjects; solid blue line indicates regression line; red dotted lines indicate 95% confidence interval.

3.6 DISCUSSION

In patients with PD, acute dAMPH administration induced positive mood effects that localized to mesocorticolimbic structures, most significantly in ventral striatum (VS), but also in caudate head and the extra-striatal regions of amygdala and cmOFC. While previous studies have implicated the VS and caudate in positive mood and affect (Yoo et al., 2019) in PD, we are the first to report contributions from amygdala and cmOFC in this capacity. In PD patients, impulsivity correlated positively with dAMPH-induced depression, suggesting that dysregulated DA neurotransmission in mesocorticolimbic structures may result in abnormal mood and behavioral symptoms. Finally, baseline D2-R availability in the mesocorticolimbic structures of VS, caudate head, and amygdala inversely correlated with dAMPH-induced changes in positive mood responses; we interpret greater D2-R availability as more preserved DA-ergic networks.

To date, short-term dAMPH effects have been investigated only in healthy subjects; physical symptoms include increased heart rate and blood pressure, while affective changes include euphoria, feelings of drug effect, and positive mood (Harro, 2015; Wardle & De Wit, 2012; Wardle et al., 2012). Of note, (Kirkpatrick et al., 2016) reports that among healthy adults, dAMPH induced significant changes in 'positive' mood domains (e.g. 'arousal' and 'drug high') but no net effect on 'negative' domains, a finding noted in our cohort of PD patients which reported an overall net positive effect of dAMPH on mood. Furthermore, an [^{18}F]-fallypride study in healthy adults related dAMPH-induced DA receptor displacement in VS to attention and cognitive processing, but not affect (Riccardi et al., 2006). This study extends previous [^{18}F]-fallypride-based investigations of dAMPH effects by involving patients with known neuroanatomical defects (e.g., PD) and linking dAMPH-induced mood and behavioral effects to changes in D2-R availability in both striatal and extra-striatal regions. Here we discuss these findings and the implications for future therapeutic interventions in PD.

Localization of dAMPH effects

The focus on the effects of acute dAMPH administration in a PD population allows us to investigate DA release in the mesocorticolimbic network, as dorsal DA networks are essentially lesioned in PD. Since early motor manifestations of PD involves progressive loss of dorsally-located DA-ergic neurons most notably in midbrain (i.e. substantia nigra) and dorsal striatum, we did not expect significant DA release to occur in this network. This was corroborated by our mixed effects model which showed positive mood effects localizing chiefly to VS, with similar trends in the caudate head, amygdala, and cmOFC. Our results reinforce findings from preclinical studies indicating a role for mesocortical structures in affective and behavioral regulation (Everitt et al., 1999; Haber & Knutson, 2010). Moreover, given the VS and caudate's known roles in reward and habit formation (R. Daniel & Pollmann, 2014; Yin & Knowlton, 2006; Zald et al., 2004), we accurately hypothesized that the acute mood effects of an addictive substance such as amphetamine would correlate with DA release in VS and caudate.

Besides the striatum, our study found extra-striatal contributions to positive mood regulation among PD patients. The OFC sends dense projections to amygdala, and they both share bidirectional inputs to hypothalamus. These three structures play complimentary roles; the amygdala encodes information about emotional value, the hypothalamus coordinates peripheral emotional responses, and the OFC helps adapt behavior in relation to emotional cues (O'Doherty, 2004; Rempel-Clower, 2007). These structures are likely involved in broad emotional valence rather than one specific mood state, consistent with recent findings indicating that the amygdala and OFC are sensitive to positive emotion intensity (Bonnet et al., 2015). Interestingly, previous literature has investigated these structures' roles in aggression (Gouveia et al., 2019; Kunwar et al., 2015); although our study did not investigate aggressive behaviors, we found that increased DA neurotransmission in the aforementioned structures is involved in positive emotional effects. Finally, while (Fotros et al., 2013b) and (C. T. Smith et al., 2016) have examined the role of amygdala and cmOFC respectively

among healthy subjects' responses to dAMPH, we are the first to explore how these structures contribute to mood regulation in PD. Overall, our results are consistent with a relatively intact mesocorticolimbic circuit in early-to-mid stages of PD.

Interestingly, PANAS and DEQ dAMPH-related score changes were associated with DA release from caudate head and VS, whereas AIRS changes correlated both in striatum (caudate and VS), and extra-striatally in amygdala and cmOFC. These differences could be explained by the AIRS assessment, which interrogates more physical symptoms (e.g., alertness, dizziness, etc.) rather than PANAS or DEQ. Indeed, in our cohort, AIRS subscale scores were highest in the activation and physical responses, indicating that under the influence of dAMPH, PD patients feel not merely positive mood effects but increased levels of overall arousal. Both amygdala and OFC have been shown to play a role in arousal, and primate data supports the importance of the OFC in directing attention and modulating arousal in relation to emotional and social cues (Goursaud & Bachevalier, 2020).

Together, our data suggest a striatal-fronto-cortical network of mood regulation in the presence of dAMPH, and the mesocorticolimbic circuit as a viable target for mood symptoms in PD. Moreover, findings in the amygdala and cmOFC emphasize the use of [^{18}F]-fallypride as an assay for D2-R availability both within and outside the striatum, and underscores how affective regulation occurs extra-striatally.

Impulsivity and mood in PD

ICBs among PD patients are thought to emerge from DAA-induced increases in phasic DA release in structures such as VS (Song et al., 2021). In otherwise healthy subjects, other studies have linked impulsivity to increased tonic levels of synaptic DA in the striatum (Cools et al., 2011; Evans et al., 2006; P Trifilieff et al., 2013). Among ICB patients, an altered neurobiology of striatal DA networks may predispose patients to unwanted non-motor side effects from typical DA-modifying

therapies. Predictably, we observed differing mood responses to dAMPH based on ICB status. Specifically, ICB+ patients (PD-ICB cohort) showed greater dAMPH-induced elevations in positive mood compared to their ICB- counterparts (PD-C cohort), as well as greater increases in AIRS total scores, indicating an overall elevation in multiple symptom domains to include physical perceptions in addition to affective changes. Our data implies that increased tonic synaptic DA in striatum may augment the pleiotropic effects of phasic DA release. Clinically, acute modification of DA tone in mesocorticolimbic structures results in differing emotional and physical perceptions between ICB+ and ICB- PD populations.

The net positive effect of dAMPH on mood remained consistent in both PD-ICB and PD-C cohorts. However, when taken as a continuous variable (e.g., QUIP-RS score), impulsivity was found to positively correlate with greater feelings of depression following acute dAMPH administration. Notably, we are not the first to observe a relationship between impulsivity and depression in PD; Scott et al (2020) observed that among PD patients, depression was most common alongside both apathy and ICB, and cited a lack of motivational control as a potential unifier between negative mood and dysregulated behavior. Our study suggests that although acute dAMPH administration is related to overall positive mood across the entire cohort, patients with sufficiently severe ICB may experience the opposite effect. These results echo prior reports of an inverted U-shaped relationship between baseline DA-R availability and mood responses to DAA therapy (Cools & D'Esposito, 2011) as well as sensation-seeking personality (Gjedde et al., 2010). Mechanistically, since ICBs are associated with stronger striatal and extra-striatal phasic DA release (Song et al., 2021), increased DA neurotransmission in mesocortical areas involved in motivation and reward could paradoxically result in more depressive feelings – consistent with the 'dopamine overdose hypothesis' of mood. Finally, the fact that PD patients exhibit higher levels of impulsivity compared to healthy controls (Aumann et al., 2020) highlights the importance of considering baseline D2-R availability in the general PD population, not merely those patients with diagnosed ICBs.

Baseline BP_{ND} as predictors of mood effects

We found an interesting relationship between BP_{ND} in the off-drug state and the PANAS positive subscale. All PD subjects experienced greater dAMPH-induced increases in positive mood, with decreased baseline D2-R availability in VS, caudate head, and amygdala. Our results could be explained by D2-R downregulation and neuronal death, both pathologic processes that worsen as PD progresses (Hisahara & Shimohama, 2011); fewer receptors would increase competition for binding spots, resulting in a lower BP_{ND}. Additionally, because these processes tend to progress in a caudo-rostral fashion, it is likely that DA receptors in more rostral parts of the brain such as VS are more preserved. Notably, Stark et al (2018) found that compared to age- and sex-matched controls, PD patients exhibit significantly lower BP_{ND} in caudate and amygdala, but not VS. It is noteworthy that when assessing positive mood effects in relation to baseline D2-R availability, the structures of VS, caudate, and amygdala were again implicated to subserve mood effects of dAMPH – mirroring our mixed effects model. These results further underscore the role of DA in mood regulation and provide support for the mesocorticolimbic circuit in modulating affective responses to DA-ergic changes.

Our study had several limitations, most notably a sample size of 20. However, such a cohort size is not uncommon for PET studies given the rigorous nature of these investigations. To mitigate, we employed a study design so that every participant received both placebo and dAMPH, and consistently used the covariates of age, sex, and UPDRS-III score in all statistical analyses, with age and UPDRS-III scores combined into a principal component in our general linear models to reduce the number of covariates. Notably, the ROIs of VS, caudate, amygdala were found to significantly correlate with mood effects in two different statistical analyses, underscoring the consistency of our results. Another limitation was that self-reported questionnaires relied on patient insight into changes in mood and behavior; however, responses were obtained in both off- and on-drug conditions so that

each subject had a baseline score to serve as an internal control. Finally, D2-R availability is heterogenous in this population and relates to other factors besides mood such as patient age, disease severity, and disease duration (Hisahara & Shimohama, 2011). To mitigate these effects, we accounted for these factors in our statistical analyses, and our mixed effects model used both off- and on-drug BP_{ND} to account for each subject's D2-R availability at baseline.

3.7 CONCLUSIONS

In this study, we found that in PD, dAMPH exerts a net positive effect on mood that is mediated by DA neurotransmission in key mesocorticolimbic structures: ventral striatum (VS), caudate head, amygdala, and cmOFC. Impulsivity alters how PD patients perceive dAMPH mood effects and correlates with dAMPH-induced depression. Finally, baseline D2-R occupancy in VS, caudate, and amygdala can predict dAMPH-induced improvements in mood. These results emphasize that modification of DA-ergic tone in the mesocorticolimbic circuit overall improves mood in PD, but these effects can also be influenced by pre-existing derangements in reward neurocircuitry associated with ICBs. The role that these striatal and extra-striatal structures play in overall affect warrants further investigation, especially given the prevalence of apathy and depression among PD patients (Ahearn et al., 2012a; Wen et al., 2016). Lastly, our study investigated the acute mood effects of DA release, although future studies are needed to explore how DAA therapies influence mood with chronic administration.

CHAPTER 4
AMPHETAMINE-INDUCED DOPAMINE RELEASE IN THE CEREBELLUM IN PARKINSON'S PATIENTS

4.1 PURPOSE

Long thought to be solely involved in motor control and coordination, the cerebellum has recently been investigated for its potential roles in behavioral and executive control. Recent evidence has emerged indicating the presence of dopamine receptors in areas of the cerebellum thought to be involved in behavioral regulation. Studying dopamine receptor availability in this region of the brain in humans is challenging due to most positron emission tomography studies using this a reference (receptor-poor) region, so data regarding localization of dopamine receptors *in vivo* in human subjects remains low. This study aims to assess cerebellar dopamine displacement in response to an amphetamine challenge in a human Parkinson's disease model using a translatable model of time activity curve measurements and a classical non-displaceable binding potential model.

4.2 SUMMARY

In this study we investigated the hypothesis that the posterior cerebellum, particularly Crus I and Crus II has sufficient D2 receptors that dopamine displacement could be quantified under pharmacological challenge with amphetamine as measured with positron emission tomography (PET) imaging. We found that, in a group of 20 Parkinson's patients, dextroamphetamine (dAMPH) has a significant decrease on [^{18}F] fallypride binding potential in both the ROIs consisting of the Crus I-II areas and the ROI consisting of cerebellar lobules VIIIa, VIIIb, and IX, when using the middle cerebellar peduncle as a reference region, and a statistically significant decrease in the area under the curve when assessing the kinetics in the time activity curve. These results provide evidence that there are sufficient dopamine receptors in the cerebellum to measure displacement using a pharmacological

challenge and connects recent findings in the animal literature to a human population. Additionally, these results provide further evidence that the cerebellum plays a modulatory role in larger known dopamine systems, such as the mesocorticolimbic and/or nigrostriatal systems.

4.3 INTRODUCTION

Classically, the cerebellum has been considered a brain area that is solely responsible for motor movement coordination and control (Anderson, 1993; V. B. Brooks, 1975; Bruggencate, 1975; J D Schmahmann & Sherman, 1998; Jeremy D. Schmahmann, 1991). However, in the last decade or two there has been increasing evidence that the cerebellum also plays a role in cognition, emotion, and even social abilities (Baillieux et al., 2008; Carta et al., 2019; Cutando et al., 2022; Locke et al., 2020, 2018; Strick et al., 2009; Turner et al., 2007). Several studies have published on the location and role of serotonin (5-HT) and noradrenaline (NA) in modulation of cerebellar activity, however there remains a relative paucity of data regarding potential mechanisms and distribution of the monoamine dopamine in the cerebellum (Kitzman & Bishop, 1994; Moises et al., 1983; Sievers et al., 1981; Strahlendorf et al., 1984; Woodward et al., 1991 are early work, but full literature nicely reviewed in Flace et al., 2021) .

However, anatomical connections between the cerebellum and dopamine-related structures have been established. Although indirect pathways had been established from the cerebellum to VTA (Mittleman et al., 2008; Rogers et al., 2011, 2013), recent findings in a mouse model revealed direct projections from deep cerebellar nuclei to the ventral tegmental area (VTA), and stimulation of these projections was rewarding and resulted in increased sociability (Carta et al., 2019). Further, VTA connections are the major pathways by which the brain controls reward, motivation, salience, and other related behaviors. The VTA sends projections to prefrontal cortex, amygdala, and nucleus accumbens, all part of the mesocorticolimbic system, and potential targets for cerebellar-mediated VTA activity (Fudge et al., 2017; Han et al., 2017; Ikemoto, 2007; Mikhailova et al., 2016). In fact,

modulation of cerebellar activity has been shown to change dopamine efflux in the prefrontal cortex (Mittleman et al., 2008). The cerebellum has been implicated in multiple dopamine-related neurological and neuropsychiatric disorders including, but not limited to, Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD), schizophrenia, autism spectrum disorders (ASD), and addiction (Andreasen & Pierson, 2008; Bruchhage et al., 2018; Glaser et al., 2006; Mittleman et al., 2008; Moers-Hornikx et al., 2009; Palmen et al., 2004; J D Schmahmann & Sherman, 1998; Stoodley, 2016).

A recently published paper used a mouse model with a fluorescent reporter to visualize and quantify dopamine D2 receptors throughout the cerebellum (Cutando et al., 2022). They found widespread D2 receptors in the Purkinje cell layer of the cerebellar vermis and hemispheres, but particular abundance located in Crus I-II. Further, they found that ablation of dopamine receptors in Crus I-II resulted in mice that spent less time with a novel mouse than a familiar mouse, indicating a role for cerebellar dopaminergic influence over social novelty (Cutando et al., 2022). These results closely resemble results found in a study done in 1997 that found a high density of TH immunoreactive fibers distributed in posterior cerebellar vermal areas, and in lobules VI, Crus, I and Crus II in a cat model (Nelson et al., 1997).

Evidence provided by multiple animal models has provided sufficient evidence to conclude that dopamine receptors (both D1-like and D-2 like) are present in the cerebellum, most prominently in the posterior cerebellum localized to lobules VI, Crus I, and Crus II. Importantly, as mentioned above, both direct and indirect projections from deep cerebellar nuclei to the VTA have been established as a way for the cerebellum to modulate brain activity across the mesocorticolimbic system (Carta et al., 2019; Mittleman et al., 2008; Rogers et al., 2011, 2013; Snider et al., 1976a, 1976b). Furthermore, these connections and their relationship to dysexecutive function have been investigated non-invasively using diffusion and tractography magnetic resonance imaging (MRI)

techniques. Recent imaging studies in both non-human primates and humans revealed strong functional connectivity between the cerebellum and prefrontal cortical areas (Krienen & Buckner, 2009). Cognitive and emotional impairments such as deficits in associative learning, verbal ability, planning, and working memory have been observed clinically in patients with cerebellar lesions and cerebellar atrophy, which further implicates the cerebellum in these processes (Botez-Marquard & Botez, 1993; Bracke-Tolkmitt et al., 1989; Kumar et al., 2010; Rapoport et al., 2000; Rogers et al., 2011; J D Schmahmann & Sherman, 1998).

Assessing cerebellar dopamine with PET provides a challenge, as the cerebellum is generally used as a reference region when assessing D2 receptor availability in other brain regions, although at least three studies using another high affinity D2 receptor ligand [^{11}C] FLB 457 have found significant amounts of binding in the cerebellum (Asselin et al., 2007; Delforge et al., 1999; Olsson et al., 2004). Interestingly, a study comparing the non-displaceable binding potential of [^{11}C] FLB 457 and [^{18}F] fallypride found significant specific binding in the cerebellum with [^{11}C] FLB 457 but not with [^{18}F] fallypride (Vandehey et al., 2010a), though they were interested in the difference between the two tracers and did not use an alternative reference region. Here, we aim to investigate if D2 receptors in two ROIs in the posterior cerebellum can be measured in human subjects using a white matter region of the cerebellum as a reference region.

4.4 MATERIALS AND METHODS

Subjects

Twenty subjects were recruited from the Movement Disorders Clinic at Vanderbilt University Medical Center (Nashville, TN, USA). The inclusion criteria for the study included a diagnosis of idiopathic PD as defined by the standard of the UK Brain Bank criteria, aged between 45-80 years, a Montreal Cognitive Assessment (MoCA) score greater than 22, current dopamine agonist use (defined as contiguous use for at least 30 days), and the ability to give informed consent (Damian et

al., 2011b; Hoops et al., 2009; Nazem et al., 2009). Levodopa and dopamine agonist dosages were converted to levodopa-equivalent daily dose (LEDD). Exclusion criteria consisted of use of GABAergic medications, previous exposure to dAMPH or stimulant use, comorbid neuropsychiatric symptoms such as untreated depression, mania, psychosis, or schizophrenia, and/or a medical condition that affects metabolic, neurologic, or cardiac systems. Finally, because this study involved the use of a radiolabeled ligand, subjects were excluded if they had received radiation in the past year, had regular exposure to radiation, or contraindications to either magnetic resonance imaging (MRI) or positron emission tomography (PET) imaging (e.g., excessive tremor, claustrophobia, presence of deep brain stimulator, etc.). This study was approved by the Vanderbilt Institutional Review Board, and all participants provided written and informed consent.

As part of the standard screening process, all potential subjects underwent a review of medical history, blood work including a complete blood count and metabolic panel, urine drug screen, and electrocardiogram (EKG) to ensure patient safety and eligibility. To determine if impulsive-compulsive behaviors (ICBs) were present, all participants completed the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) and underwent a semi-structured interview with a board-certified neurologist (D.O.C). The QUIP is a well-validated assessment tool that covers a range of highly reported ICBs and includes compulsive gambling, buying, sexual behavior, and eating as well as related behaviors: hobbyism, punding, and dopamine dysregulation syndrome (Evans et al., 2019; Weintraub et al., 2009b). ICB symptoms were required to be clinically problematic and were defined using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000). 10 out of the 20 participants that were eligible met criteria for an ICB diagnosis.

Study visit

Participants completed two [^{18}F] fallypride PET sessions within a two-week period and were blinded to administration of an oral dose of either placebo or dAMPH (0.43mg/kg), with the dose rounded up to the nearest 2.5 mg by institutional investigational drug service pharmacy. Although all participants were blinded to the order of administration, each participant received placebo on the first visit and dAMPH on the second visit with the intention of avoiding possible receptor expression in response to dAMPH.

Table 4-1. Demographic and clinical evaluation of participants

Variable	PD
N	20
Age, years	64.1 ± 5.8
Sex, M/F	12M/8F
Disease Duration, years	4.9 ± 2.9
CES-D	13.9 ± 9.8
MDS-UPDRS Part III	
placebo	28.7 ± 12.7
dAMPH	26.0 ± 12.8
Hoehn & Yahr Scale	2
Total LEDD (mg/day)	671.0 ± 294.1
QUIP-RS Total Score	25.0 ± 12.5

Data for age, disease duration, CES-D, MDS-UPDRS, LEDD, and QUIP-RS are shown as the average ± the standard deviation.
CES-D = Center for Epidemiologic Studies Depression Scale
MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale
LEDD = Levodopa equivalent daily dose
QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale

All participants completed part III of the Movement Disorders Society – Unified Parkinson's disease Rating Scale (UPDRS-III) to assess motor function during each visit. Participants underwent a 48-hour withdrawal from dopamine agonists, entacapone, and amantadine; and a 16-hour withdrawal from carbidopa-levodopa prior to each study visit. A brief neurologic exam was performed by the study physician (D.O.C) at the beginning of the study visit, and physiological measures (blood pressure, respiration, pulse, and temperature) were monitored through the duration of the study to

ensure patient safety as required by regulatory guidance. Clinical characteristics and demographics are described in Table 4-1.

Imaging Protocol

All MRI scans were acquired in order to provide high-resolution anatomical delineation for quantification of [^{18}F] fallypride non-displaceable binding potential (BP_{ND}). MRIs were completed with a 3.0T Philips (Philips Intera Achieva, Philips Healthcare, Best, The Netherlands) MRI scanner using body coil transmission and 32-channel SENSE array reception. All structural images were acquired using a T1-weighted high-resolution anatomical scan (MPRAGE; spatial resolution 1x1x1 mm3; TR/TE = 8.9/4.6 ms).

All PET scans were acquired on a Philips Vereos PET/CT scanner with a three-dimensional emission acquisition and a transmission attenuation correction. [^{18}F] fallypride was synthesized and imaged by a previously described method (reference). In summary, serial scan acquisition began with a simultaneous 5.0 mCi slow bolus injection of [^{18}F] fallypride over a 30-second period. Additionally, CT scans were acquired prior to each of three emission scans for attenuation correction. Total scan time was approximately 3.5 h with two breaks of 15 minutes between emission scans (at approximately 70 min and 135 min post-injection) to best ensure participant comfort.

Image processing

Following attenuation correction and decay correction, serial PET scans were co-registered to a mean reference frame (frame 20), using Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK, https://www.fil.ion.ucl.ac.uk/spm/software/) to correct for motion across emission scans. A mean parametric PET image was then co-registered to the high-resolution T1 MR image using FSL's FLIRT with 6 degrees of freedom and a mutual info cost function (FSL v6.0, FMRIB, Oxford, UK).

[^{18}F] fallypride non-displaceable binding potential was quantified using the simplified reference tissue model (SRTM) in the PXMOD module of PMOD (PMOD technologies, Zurick, Switzerland; Lammertsma AA & Hume SP, 1996). Because this study was interested in assessing binding potential changes in cerebellar lobules, which most studies use/include as part of the larger cerebellum reference region, the middle cerebellar peduncle was used a reference region for its likely lower D2/3 receptor expression than posterior cerebellar lobules of interest. Our main area of interest was an ROI that consisted of Crus I and Crus II, and a secondary cerebellar ROI, which consisted of lobues VIIIa, VIIIb, and IX. The two lobule-based ROIs were made using bilateral labels from the SUIT atlas, available in the FSL library (Diedrichsen, 2006; Diedrichsen et al., 2009). The reference region ROI was created using the labels for the middle cerebellar peduncle from the JHU atlas, also available in the FSL library (Hua et al., 2008; Wakana et al., 2007). The middle cerebellar peduncle was used as a reference region as it was far enough away to not have any overlapping regions with the other cerebellar ROIs, and it was assumed to have lower D2/3 receptor binding compared to the two cerebellar grey matter-based ROIs.

Time activity curves were also generated from the SRTM model in the PXMOD module of PMOD for both placebo and dAMPH scans, with binding data collected at 31 time points: 15s, 30s, 45s, 60s, 75s, 90s, 105s, 120s, 150s, 180s, 210s, 240s, 270s, 300s, 360s, 420s, 480s, 540s, 600s, 660s, 810s, 1110s, 1410s, 1710s, 2310s, 2910s, 3510s, 4110s, 6037s, 6787s, 7535s.

Statistical Methods

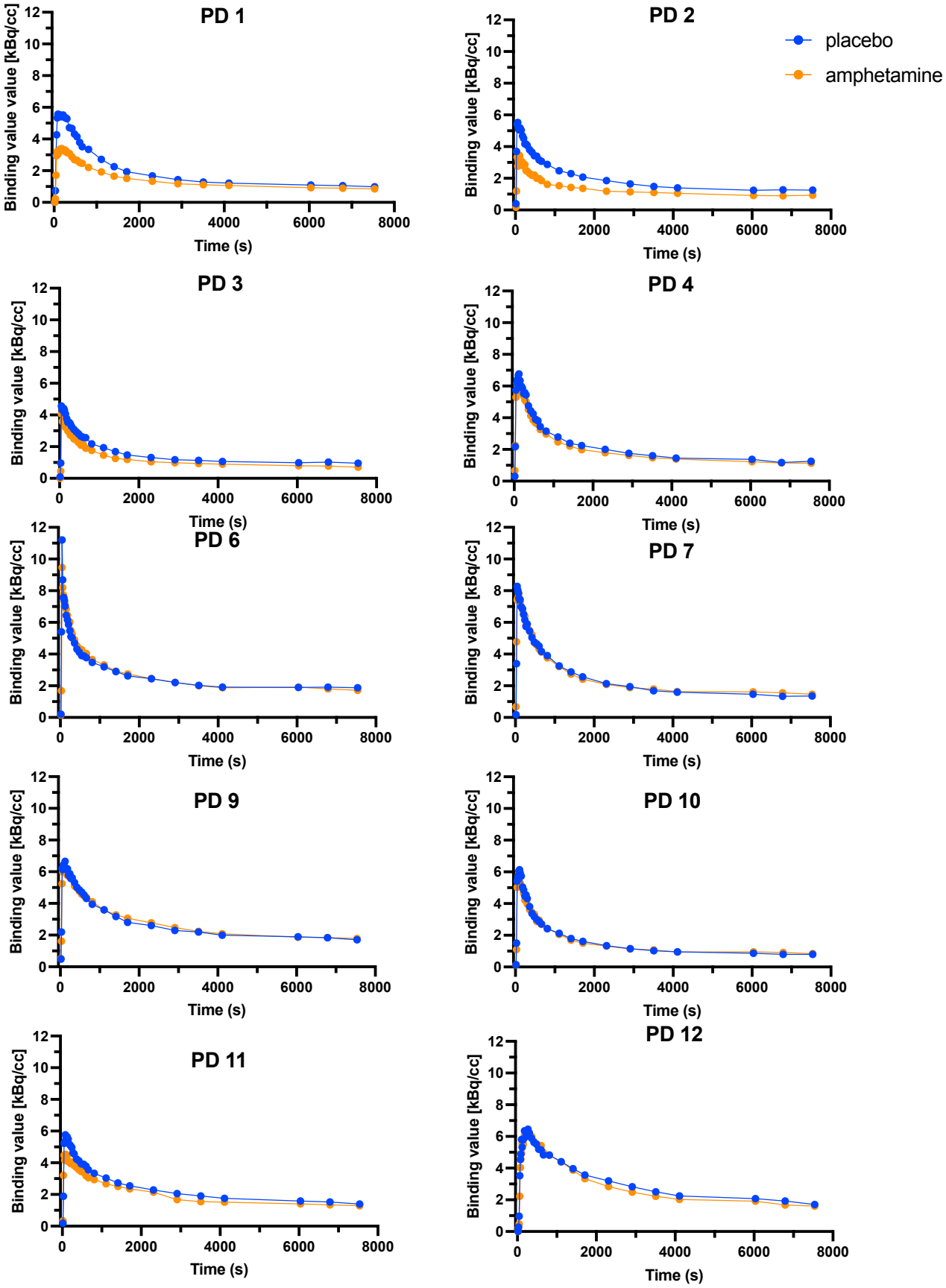
To determine if changes could be seen in the off (placebo) vs. on (dAMPH) drug state, we calculated the area under the curve (AUC) and the rate of decay for each subject from the time activity curve modeling results in PMOD. We then performed a Wilcoxon signed-rank test to compare the AUC in the off vs. on drug states using R statistical software (version 4.1.1). To test the difference in BP_{ND} in the posterior cerebellum between drug states, we used a Mann-Whiteney test. Next, we calculated

percent change in the off vs. on state ((Off BP_{ND} – ON BP_{ND})/OFF BP_{ND}). Additionally, we used a general linear model to assess the relationship between baseline BP_{ND} and patient demographic information including, UPDRS-III scores, age, disease duration, and QUIP scores. Finally, we investigated the possible relationship of cerebellar [^{18}F] fallypride displacement with midbrain [^{18}F] fallypride displacement using a Spearman correlation.

4.5 RESULTS

Effects of d-amphetamine on time activity curves of [^{18}F] fallypride

Effects of amphetamine were evaluated by assessing the area under the curve and the maximum value difference between the placebo and amphetamine scans for each patient individually (Fig. 4-1 shows all the time activity curves). Wilcoxon-signed rank test results show that placebo scans had a significantly larger area under the curve than amphetamine scans ($p = 0.0012$) across our PD subjects. Although this was true on the whole, there were a few cases in which the amphetamine scans had equivalent or slightly larger AUC than the placebo (see subjects PD6, PD7, PD9, PD16, PD25 in Fig. 4-1). Upon further examination, these patients do not appear to be statistically or demographically distinct in any way from the larger group (although four out of the five do not meet criteria for an impulsive-compulsive disorder; data not shown). Additionally, there are patients that do not have expected "normal" amphetamine responses in that are described in the literature, the relationship for why these subjects do not respond remain unclear (Frankle et al., 2018). It is possible this sample may be slightly enriched for non-responsers, or noise in these patients is higher, resulting in a bais in the TACs.


PD 1
PD 2
PD 3
PD 4
PD 6
PD 7
PD 9
PD 10
PD 11
PD 12
placebo
amphetamine
Binding value value [kBq/cc]
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0
2
4
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8
10
12
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2000
4000
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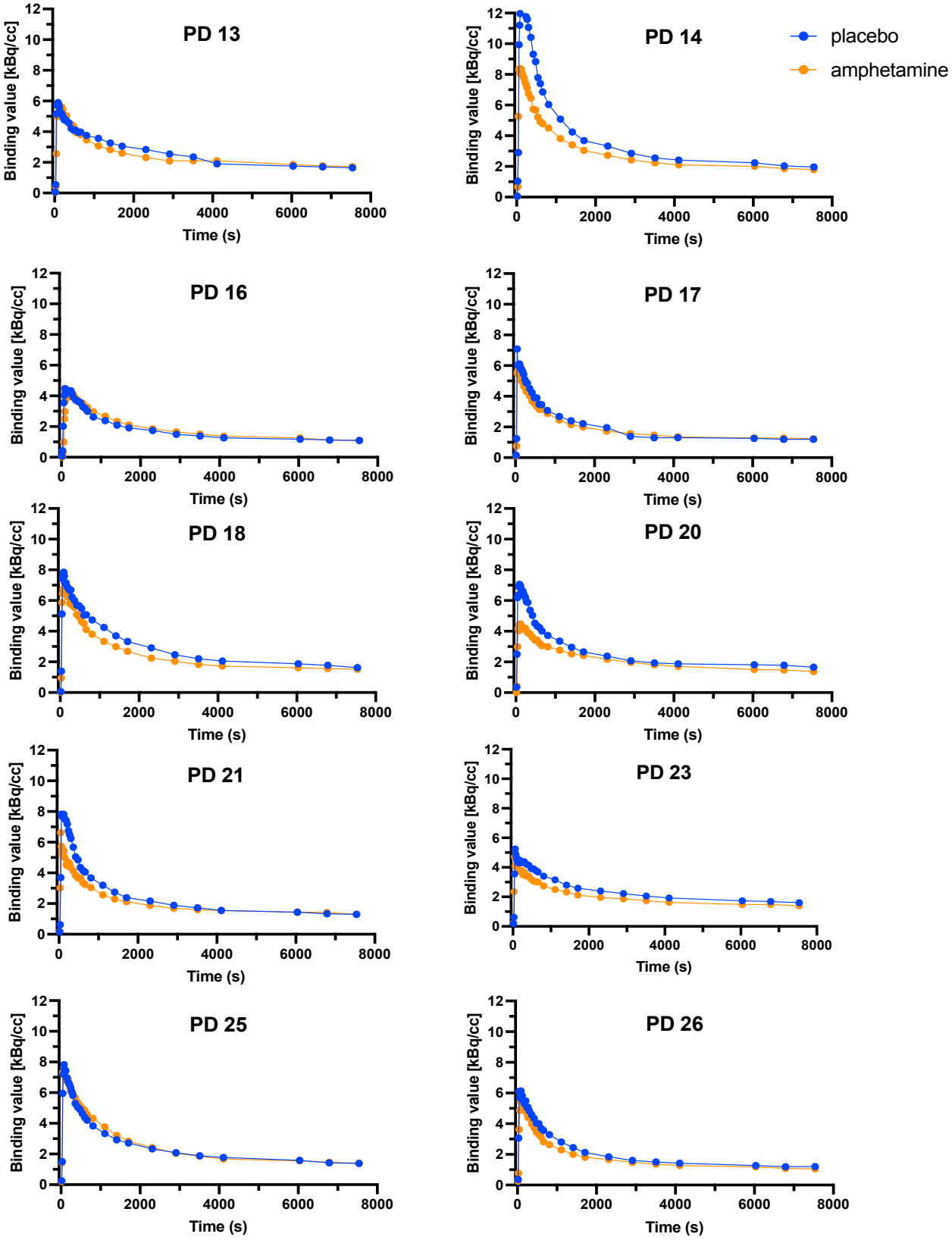

Figure 4-1. Time activity curves in the Crus I-II region of the cerebellum in each PD subject (PD 1, PD 2, PD 3, etc.) following administration of [^{18}F] fallypride. Placebo scan time activity curves are shown in blue, and amphetamine (dAMPH) are shown in orange.

Effects of d-amphetamine on posterior cerebellar [^{18}F] fallypride binding potential

Mean BP_{ND} from placebo and dAMPH conditions, as well as percent displacement for both ROIs are presented in Table 4-2. Mann-Whitney tests show significant reductions in BP_{ND} in both the ROI containing Crus I-II ($t = 4.3$, $p = 0.002$) and the ROI containg lobules VIIIa, VIIIb, and IX ($t = 4.6$, $p = 0.003$) following dAMPH administration. Further, the Crus I-II ROI showed significantly higher baseline BP_{ND} than the posterior cerebellar ROI ($t = 4.8$, $p < 0.001$).

Table 4-2. dAMPH-induced displacement in binding potentials

	Crus I-II			Lobules VIIIa, VIIIb, IX		
Subject	**Placebo BP_{ND}**	**dAMPH BP_{ND}**	**Percent displacement**	**Placebo BP_{ND}**	**dAMPH BP_{ND}**	**Percent displacement**
1	0.1136	0.0681	40%	0.0555	0.0120	78%
2	0.2673	0.1854	31%	0.1339	0.0173	87%
3	0.1235	0.0906	27%	0.0243	0.0232	5%
4	0.4516	0.2862	37%	0.1934	0.0477	75%
5	0.3299	0.2135	35%	0.1069	0.0221	79%
6	0.3243	0.1850	43%	0.1259	0.0839	33%
7	0.2669	0.2460	8%	0.1473	0.0434	71%
8	0.1451	0.1153	21%	0.1251	0.0083	93%
9	0.4099	0.2813	31%	0.2242	0.1951	13%
10	0.1859	0.1263	32%	0.0616	0.0317	49%
11	0.1703	0.1295	24%	0.1019	0.0879	14%
12	0.1661	0.1350	19%	0.0336	0.0310	8%
13	0.1746	0.1318	24%	0.0299	0.0087	71%
14	0.1667	0.1134	32%	0.0722	0.0429	41%
15	0.2277	0.1510	34%	0.1892	0.1155	39%
16	0.1380	0.0858	38%	0.0860	0.0516	40%
17	0.1624	0.1208	26%	0.0417	0.0220	47%
18	0.0959	0.0624	35%	0.0410	0.0251	39%
19	0.1399	0.0920	34%	0.0667	0.0166	75%
20	0.1849	0.1386	25%	0.1127	0.0863	23%
	0.211 ± 0.100	**0.1360 ± 0.062**	**30%**	**0.099 ± 0.058**	**0.049 ± 0.046**	**49%**

Bolded values in the bottom row show the average ± the standard deviation for each column.

Relationships between binding potential and demographic characteristics

A general linear model was used to assess the relationship between baseline BP_{ND} in Crus I-II and patient, age, disease duration, UPDRS-III scores and QUIP scores. There was no significant relationship between baseline BP_{ND} and age ($p = 0.86$), disease duration ($p = 0.24$) or UPDRS-III scores ($p = 0.17$), not shown. Interestingly, we do see a significantly positive relationship between baseline BP_{ND} in Crus I-II and QUIP scores ($p = 0.002$; Fig. 2).

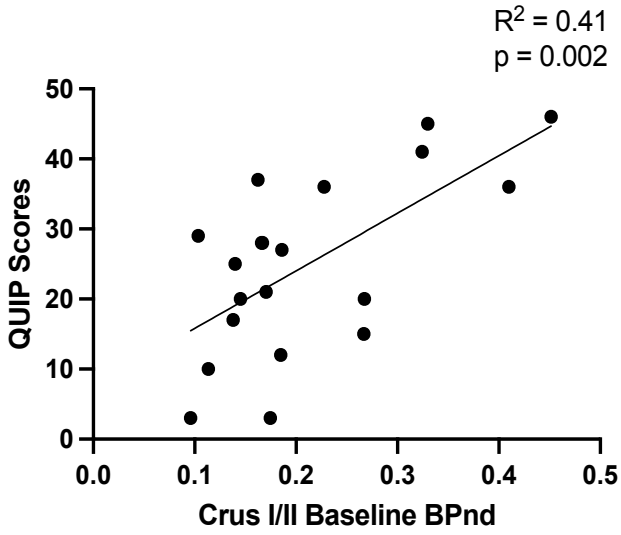

Figure 4-2. Scatterplot showing relationship of the baseline BP_{ND} in Crus I-II with QUIP scores for each subject including the regression line from the general linear model results.

Relationships between cerebellar displacement and midbrain displacement

Because of established connections from deep cerebellar nuclei to the VTA (a midbrain structure), we investigated the correlation between [^{18}F] fallypride displacement in Crus I-II and midbrain (midbrain data obtained for the purposes of a separate study). We do not see any

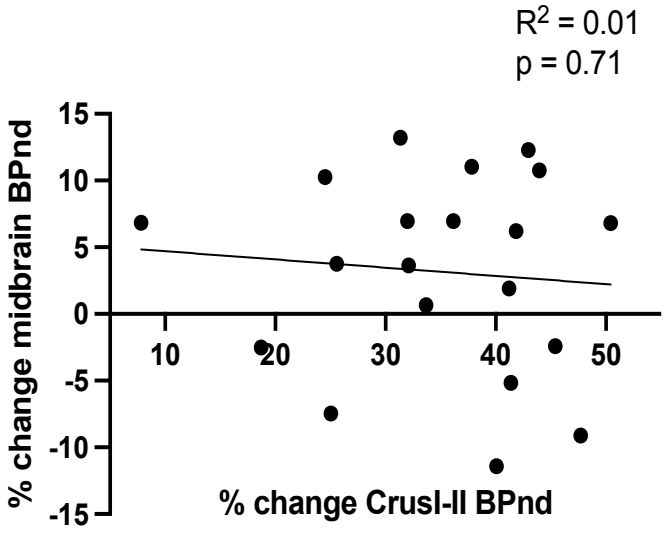

Figure 4-3. Scatterplot showing the relationship between the percent change in BPND in Crus I-II and the percent change in BP_{ND} in the midbrain with the regression line included from the general linear model.

significant correlation between percent change in BP_{ND} in the cerebellar Crus I-II and midbrain ($p = 0.71$).

4.6 DISCUSSION

Here, we aimed to investigate whether dopamine receptor availability could be quantified using positron emission tomography (PET), and if receptor availability related to motor or behavior characteristics in a Parkinson's disease cohort. We found that dAMPH-induced dopamine release in the cerebellum resulted in significant decreases in available D2 receptors in both cerebellar ROIs. Despite baseline D2 receptor availability being significantly higher in the ROI containing Crus I-II compared to the ROI contianing lobules VIII and IX, the effect sizes for the changle in BP_{ND} following amphetamine in the two regions were similar ($t = 4.3$ and $t= 4.6$, respectively). We did not see any significant associations with demographics such as age, disease duration, or UPDRS-III scores, but we did find a significantly positive relationship between baseline BP_{ND} in Crus I-II and QUIP scores.

BP_{ND} values in the cerebellum, while expected to be low, are consistently less than even low level cortical areas (Buchsbaum et al., 2006; Olsson et al., 2004; Stark, Smith, Lin, et al., 2018; N. D. Woodward et al., 2009) This is unsurprising, given that the cerebellum has consistently been used as a reference (receptor-poor) region for dopamine receptor readioligands for decades. However, in this study, we show that D2 receptor availability is high enough in these two regions of the cerebellum that it can be a. quantified in reference to the white matter region of the middle cerebellar peduncle, and b. quantified under drug challenge of dAMPH. These results set the precedent for future dopamine receptor studies in the cerebellum using a cerebellar white matter reference region. It's possible that some of the values calculated are biased by intrisic noise associated with PET imaging, though we tried to mitigate that by using a within-subject design so that on and off-dAMPH measures were done in the same person, and therefore subjected to the same background noise (though there

are slight variations in dose delivered and time following radiotracer synthesis). In addition to reliance on BP_{ND} values obtained using the SRTM modeling methods, we showed that the area under the time activity curves significantly differ between drug states, which lends support to the assumption that we are capturing low level dopamine receptor occupancy changes in response to dAMPH administration. Time activity curve chacteristics have been used before to assess differences in [^{11}C] methionine for diagnosing brain tumors in humans, and in assessing uptake differences across the brain in non-human primates (Jogeshwar Mukherjee et al., 2005; Nomura et al., 2018). To our knowledge, this is the first study to use TACs to assess changes in binding kinetics in an on- and off-drug paradigm. Here, we see that the time activity curves for this novel reference region are similar across subjects with good fit, providing evidence that binding values in this region are not due to noise. Further, findings from these assessments align well with observed differences in regional BP_{ND}, indicating that this assessment could be another useful marker of change in PET imaging. Time activity curves can be useful tools to improve our understanding of tracer kinetics in various areas of the brain as they allow for a view of when maximum values occur and and overall look at washout of the tracer under varying drug conditions, which is not possible with just an overall binding potential value.

One of the caveats to consider when evaluating time activity curves is that not every person will receive the exact same amount of [^{18}F] fallypride, and the time from synthesis to injection is slightly variable, so these curves may be subject to small, but variable amounts in radiotracer amount and decay. Here, we assessed the doseage differences from day 1 to day 2 and did not find significant differences in dose amount (difference between the means = 0.042 mCi with the standard error of the mean = 0.08, data not shown). Interestingly there were 25% of subjects (N = 5) that showed a lower BP_{ND} following dAMPH administration compared to placebo, but had an equivalent or slightly larger AUC when assessing differences in their time activity curve. These subjects do not vary in their demographic characteristics, and are not in the bottom 25% of Crus I-II BP_{ND} at baseline (with the

exception of subject PD25), so it's unlikely that an "extra-low" level of dopamine receptors is contributing to these results. Other than the aforemention possibility of varying injection dose and decay upon injection, it's possible that the relatively low amount of dopamine receptors in these regions lends itself to a small and limited time activity curve, in which the kinectics of tracer binding would be less variable following a drug challenge as they would in a dopamine receptor rich area such as the putamen.

We expected challenges such as these to arise when assessing the most commonly used reference region however, we see consistent and statistically significant changes in the BPnd in both the ROI made up of Crus I-II and in the ROI made up of lobules VIIIa, VIIIb, and IX of the cerebellum. These regions have been shown in multiple animal modules to have the highest percentage of dopamine receptors, which has led us to believe these are biologically relevant measures of dopamine in this area of the cerebellum. Further, studies using the high affinity D2/3 receptor ligand [^{11}C] FLB 457 have suggested not to use the cerebellum as a reference region if employing a high affinity radioligand due to true occupancy in cerebellar regions resulting in underestimations in cerebral regions (Asselin et al., 2007).

Our results demonstrate that dAMPH administration results in a significant decrease in dopamine receptor availability in the cerebellum, which provides further evidence for a role of the cerebellum in larger dopaminergic networks. Further, baseline D2 receptor availability is strongly positively correlated with impulsivity in this population. A recent study found that patients with cerebellar ataxia showed significantly higher rates of self-reported impulsivity than age- and sex-matched peers, which provides support for the idea that cerebellum dysfunction may result in not just dopaminergic, but impulsive-specific behavioral dysfunction (Chen et al., 2022). Further, recent data demonstrated projections from the cerebellum to VTA robust enough to module reward-driven beahvior (Carta et al., 2019) Given the hypotheses described by Miquel et al., (2019), it's possible that cerebellar cortical D2 receptors are activating deep cerebellar nuclei, which leads to increased

signals from VTA to mesocorticolimbic structures, resulting in increased impulsive behaviors, though this is purely speculative. Assuming that hypothesis is correct, we may only see relationships with cerebellar D2 receptor expression and impulsivity in a population where D2 receptors are more abundant in ventral striatal and cortical regions (rather than basal ganglia) due to disease pathology. Future studies, especially in younger and disease-free cohorts, are needed to further elucidate the relationship between cerebellar D2 receptors and impulsivity.

4.7 CONCLUSIONS

Overall, findings here indicate a dopamine system robust enough to measure changes following a drug challenge, which could open the possibility of the cerebellum as a target for innovative non-invasive treatments, such as magnetic or electrical stimulations for neurological and psychiatric disorders related to cerebellar and dopamine dysfunction such as Parkinson's disease, ADHD, and schizophrenia. We implicate cerebellar D2 receptor availability in impulsive behaviors, though more research is needed to clarify this relationship. Future studies should confirm dopamine receptor availability in other populations, especially in an otherwise healthy cohort. Additional receptor occupancy studies could also be performed with radioligands more sensitive to areas with lower receptor density than the striatum (e.g. [^{11}C] FLB 457).

CHAPTER 5

CEREBELLAR NETWORKS OF FRONTAL BEHAVIORS IN ESSENTIAL TREMOR

5.1 PURPOSE

Essential tremor (ET) has traditionally been considered a progressive movement disorder that manifests with tremor that occurs when performing tasks, such as reaching for a pen or drinking from a glass. However, in the last few decades cognitive and behavioral problems in this population have gained attention. Although the symptom presentation can be heterogeneous in nature, there have been consistent reports of cognitive changes associated with a 'frontosubcortical' profile (Janicki et al., 2013). Furthermore, the underlying mechanisms remain uncertain given the evidence for a cerebellar etiology. It's possible that cognitive and behavioral changes are a result of the progressive cerebellar dysfunction of ET itself; alternately, they may be a feature of concomitant neurodegenerative diseases that have been associated with essential tremor, including both cerebellar diseases such as progressive supranuclear palsy, and non-cerebellar related diseases such as Alzheimer's and Parkinson's disease. This study aims to investigate the presence of frontal behaviors in a large ET population and relate those behaviors to specific areas of the cerebellum. Further, we aim to elucidate what larger networks are involved in cerebellar regulation of these frontal behaviors.

5.2 SUMMARY

Patients with essential tremor (ET) often present with non-motor symptoms including dysexecutive behaviors. While cerebellar pathology is noted in ET, cerebellar contributions to behavioral symptoms and cortico-cerebellar connectivity has not been previously investigated in this population. Structural MRI and behavioral assessments were obtained in 105 ET patients. The Frontal Systems

Behavioral Scale (FrSBe) was used to assess overall dysexecutive behaviors and subscales of Apathy, Disinhibition, and Executive Dysfunction. The relationship between behavioral scores and cerebellar atrophy was investigated using voxel-based morphometry (VBM). To ascertain cortico-cerebellar network connectivity, VBM results were used as seed regions in a functional connectivity analysis using a separate connectome derived from resting state fMRI in 1,000 healthy subjects. All four FrSBe scores were significantly elevated. Overall behavioral symptoms correlated with cerebellar atrophy in Crus I, Crus II, and lobule IX. Apathy networks correlated positively with the midbrain, thalamus, and striatum, and anticorrelated with the parietal cortex. Disinhibition networks were evident in the occipital cortex, with anticorrelations in temporal and frontal cortices. Executive dysfunction networks related to anterior cerebellum, midbrain, thalamus, and occipital cortex, with anticorrelations seen diffusely across temporal and frontal cortices. These results are the first to associate clinically elevated dysexecutive behaviors in ET to localized grey matter atrophy in the cerebellum, and the first to relate those areas in the cerebellum to larger cerebral networks.

5.3 INTRODUCTION

Essential tremor (ET) is one of the most common motor movement disorders, with an estimated prevalence of ~3.2 cases per 1,000 individuals that increases to 28.7 cases per 1,000 in those aged 80+ years (Barbosa et al., 2013; Julian Benito-León et al., 2005; Haerer et al., 1982; Elan D Louis et al., 1995) . Although tremor is the defining feature of ET, emerging evidence indicates a spectrum of non-motor symptoms including cognitive and psychiatric symptoms (Chatterjee et al., 2004; Gasparini et al., 2001; Hughes et al., 2019; Elan D. Louis, 2010; Thenganatt & Louis, 2012). Elevated levels of apathy and executive dysfunction have been described in several cohorts(Bermejo-Pareja, 2011; Musacchio et al., 2016). While the etiology of ET is likely heterogeneous, an expanding body of literature implies that cerebellar dysfunction plays an important role in the pathophysiologic process (Julián Benito-León & Louis, 2006; Helmich et al., 2013; Holtbernd & Shah, 2021). A meta-

analysis of abnormalities in ET shows diffuse alterations across the cerebellum, including motor areas (in lobules I-IV) and cognitive areas (including lobules VI-IX, and Crus I and II), emphasizing the heterogeneity of cerebellar-related ET neurodegenerative processes (Cerasa & Quattrone, 2016).

Transdiagnostically, impairments to posterior cerebellar function are linked to alterations in emotion and cognition. Specifically, lobules VI, IX, and Crus I and II, are associated with cognitive executive dysfunction and impaired affect (J D Schmahmann & Sherman, 1998; Stoodley & Schmahmann, 2010; Tavano et al., 2007). These findings have been extended to a broad range of populations, including autism spectrum disorder, Friedreich ataxia, and schizophrenia. Linking behavioral symptoms and the posterior cerebellum (particularly lobules VI, IX, Crus I and II) is an important step in clarifying the localization of behavioral symptoms to the cerebellum in ET. Already, recent studies in ataxic disorder suggest an elevated rate of impulsivity, reward-based behaviors, and disinhibition (Aumann et al., 2020; Chen et al., 2022). While elevated rates of apathy and cognitive executive dysfunction are reported in ET, there are few studies that address behavioral disinhibition (Miquel et al., 2019).

The present study aims to evaluate dysexecutive behaviors in ET and their relationship to cerebellar atrophy, as well as related functional networks. We tested the hypothesis that in a large ET cohort, atrophy in the posterior cerebellum would be associated with overall dysexecutive behavior including apathy, behavioral disinhibition, and cognitive executive dysfunction. Furthermore, posterior cerebellar atrophy in these patients would be functionally related to the ventral striatum and frontal cortex.

5.4 METHODS

Participants

In this retrospective study, 105 patients with ET were seen at the Vanderbilt University Medical Center (VUMC) Department of Neurology (Nashville, TN) as part of a screening assessment for

candidacy for deep brain stimulation surgical treatment and completed written and informed consents as approved by the Vanderbilt Institutional Review Board. The diagnosis of ET was made by a movement disorders neurologist according to established criteria (Bhatia et al., 2018). Demographic data are described in Table 5-1.

Dysexecutive Behaviors

Patients' caregivers completed the Frontal Systems Behavioral exam (FrSBE), which is a 46-item questionnaire that measures behaviors associated with dysfunction of frontal systems (Grace & Malloy, 2001b). We used the total score and three subscale scores for "Apathy" (14 items), (behavioral) "Disinhibition" (15 items), and (cognitive) "Executive Dysfunction" (17 items) describing current behaviors. FrSBe raw scores were converted to standardized T-scores (mean = 50, standard deviation = 10), norm-referenced for age, sex, and education (Grace & Malloy, 2001b; Stout et al., 2003). Per manual recommendations, average T scores range from 40 to 60, elevated scores of 61 to 64 indicate borderline dysfunction, and scores ≥65 indicate clinically significant neurobehavioral abnormalities (Grace & Malloy, 2001b). The FrSBE has been shown to have high internal consistency and validity (Carvalho et al., 2013; Grace & Malloy, 2001b; Malloy & Grace, 2005). It can be completed by either the patient or a caregiver, the latter of which can prove particularly useful, as patients do not always have insight into behavioral symptoms.

Image Acquisition

Brain imaging was performed using a 3.0T MRI scanner (Achieva, Philips Healthcare, the Netherlands) using phased-array SENSE 8-channel reception and body coil transmission. Scanning included a 3D structural T_1-weighted whole brain image, (MPRAGE, TR/TE=8.9/4.6 ms; turbo gradient echo factor=131; spatial resolution=1x1x1 mm^3). General anesthesia was administered for the duration of the MR imaging as part of the standard-of-care protocol for Deep Brain Stimulation

surgical planning. The functional imaging data (fMRI) were acquired in a separate publicly available population of 1,000 healthy adult subjects (Buckner et al., 2014). fMRI data were acquired on a 3T MRI scanner (Siemens, Germany) with a 12-channel phased-array head coil using a gradient-echo echo-planar imaging (EPI) sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (TR/TE= 3,000ms/30 ms; flip angle = 85°, FOV = 216mm, spatial resolution = 3x3x3 mm^3).

Voxel Based Morphometry Analyses

Each subject's T_1-weighted scan was first corrected for inhomogeneity bias field using the N4 method (Tustison et al., 2010). We then generated probability tissue maps (gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the Atropos method (Avants, Tustison, Wu, et al., 2011). Spatial normalizations were conducted using a deformable model on the Parkinson's Disease temple from the Montreal Neurological Institute (ICBM-MNI PD25) (Xiao et al., 2015) and the symmetric normalization method provided by the ANTs toolbox (Avants, Tustison, Song, et al., 2011). Spatially normalized GM maps were then modulated using the Jacobian determinant to preserve the amount of gray matter volume from the original image. Finally, spatial smoothing was performed with a Gaussian kernel with FWHM equal to 8mm. Data were then processed using Statistical Parametric Mapping 12 software (http://www.fil.ion.ucl.ac.uk/spm/) to evaluate structural properties and associations with FrSBe scores. To evaluate differences in GM volume in relation to disinhibition subscale scores, we performed a general linear model within the GM volumes of the entire cerebellum controlling for age and sex. To adjust for multiple comparisons, we used a false discovery rate-corrected p-value (p_{corr}) threshold of 0.05. Cluster location is based on the SUIT Atlas available in the FSL library (Diedrichsen, 2006; Diedrichsen et al., 2009).

Atrophy Network Mapping

We quantitatively tested whether dysexecutive behavior-related cerebellar atrophy was functionally connected to cerebral regions previously described to be involved in frontal behaviors, particularly those related to the FrSBe (Baillieux et al., 2008; Bhalsing et al., 2014; Cummings, 1993; R. M. Kelly & Strick, 2003; Lansdall et al., 2017; Middleton & Srrick, 1997; Middleton & Strick, 2000; Pierce & Péron, 2020; J. D. Schmahmann, 2001; Jeremy D. Schmahmann & Caplan, 2006; Timmann & Daum, 2007). Specifically, we used a method called atrophy network mapping to compute the temporal correlation between spontaneous brain activity recorded from the p-corrected significant grey matter region-of-interest from our VBM results and all other parts of the brain(Tetreault, Phan, Orlando, et al., 2020; Tetreault, Phan, Petersen, et al., 2020). First, VBM atrophy results in PD25-MNI space were registered to MNI152 space using FSL FLIRT and FNIRT (FSL v6.0; FMRIB). Using a publicly available normative functional connectivity dataset of 1,000 healthy volunteers from the Brain Genomics Superstruct Project (GSP), we measured average blood oxygenation level-dependent (BOLD) time-courses within the seed region and correlated these values with the BOLD time course at every other brain voxel. Resulting *r*-values were converted to a normal distribution using Fischer's *r-to-z* transform and were used to compute a single-group, voxel-wise t-test across the 1,000 subjects in the normative dataset to generate network t-maps. To visualize these maps, we thresholded and binarized each map at $t > 20$, corresponding to a voxel-wise Bonferroni corrected p-value < 0.05.

5.5 RESULTS

Sample Characteristics

Table 5-1 reports demographics and clinical characteristics of the 105 ET cohort, including FrSBe T-scores. Participants were, on average, 67 years of age, had 14 years of education, and an 18-year disease duration. The severity of tremor was rated moderate-to-high, as indicated by their

Washington Heights–Inwood Genetic Study (WHIGET) and Fahn-Tolosa-Marin (FTM) scores (Fahn S et al., 1988; Elan D. Louis et al., 1997). Mean FrSBe T-scores were all significantly elevated (i.e., T-score ≥ 65; Grace & Malloy, 2001a): total score was 73.70 ± 15.55 and subscale score means were 74.53 ± 13.95 for Apathy, 70.94 ± 17.83 for Disinhibition, and 66.55 ± 14.19 for Executive Dysfunction (Table 5-1).

Table 5-1. Demographics and clinical characteristics

	Essential Tremor
Total n	105
Sex (M/F)	65/40
Age	67.16 ± 9.17
Years of Education	14.11 ± 2.77
Disease Duration	18.15 ± 13.61
Tremor Score*	
WHIGET total score (n = 38)	28.61 ± 10.53
FTM scale score (n = 61)	50.58 ± 17.08
FrSBe Total Score	73.70 ± 15.55
Apathy	74.53 ± 13.95
Disinhibition	70.94 ± 17.83
Executive Dysfunction	66.55 ± 14.19
Medications*	
Primidone	52.4%
Beta-blockers	42.9%
Gabapentin	28.6%
Topiramate	13.3%
Benzodiapines	15.2%
Dopamine replacement therapy	9.5%

Data are shown as the average ± the standard deviation.
WHIGET = Washington Heights-Inwood Genetic Study
FTM = Fahn-Tolosa-Marin scale
FrSBe = Frontal Systems Behavior Scale

FrSBe Apathy Subscale and imaging correlates

After applying this VBM approach, we found significant atrophy in the posterior cerebellum, with the largest clusters of atrophy located bilaterally in lobule IX ($p_{corr} < 0.001$) and smaller clusters located in left Crus II ($p_{corr} < 0.001$), and in the right Crus I area ($p_{corr} = 0.02$) (Fig. 5-1). There were no significant positive associations with grey matter density and apathy scores. After application of our VBM results as a seed region, we found significant BOLD connectivity correlation within a large portion of the cerebellum (overlapping the seed in Crus I and Crus II, but not in lobule IX), particularly along the antero-medial cerebellum including lobules I-VI, VIIa, VIIb, and IX (Figure 5-2). Additionally, we see areas of correlated connectivity in the pons, in the midbrain including substantia nigra, and

ascending into thalamus and putamen (Fig. 5-2). We do not see any positive BOLD associated activity in the cortical areas of the cerebrum. Next, when we assessed anticorrelated BOLD activity associated with the VBM-based seed region, we found significant anticorrelations bilaterally in the temporal cortex (Brodmann's area 21), in the left somatosensory cortex (Brodmann's area 7), midline precuneus, and a smaller cluster in the left motor cortex (Brodmann's area 4) (Fig. 5-2). We did not find any significant anticorrelated activity in subcortical structures or within the cerebellum.

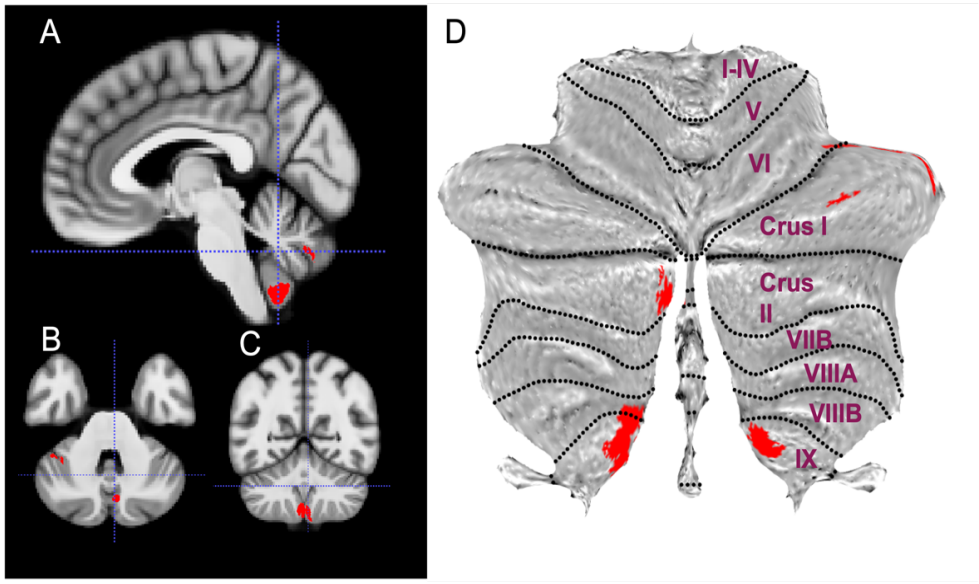

Figure 5-1. Apathy-related atrophy voxel-based morphometry (VBM) clusters (red) shown in sagittal (A), axial (B), and coronal (C) views. VBM results displayed using the SUIT flatmap (D) of the cerebellum with lobule labels for better visualization.

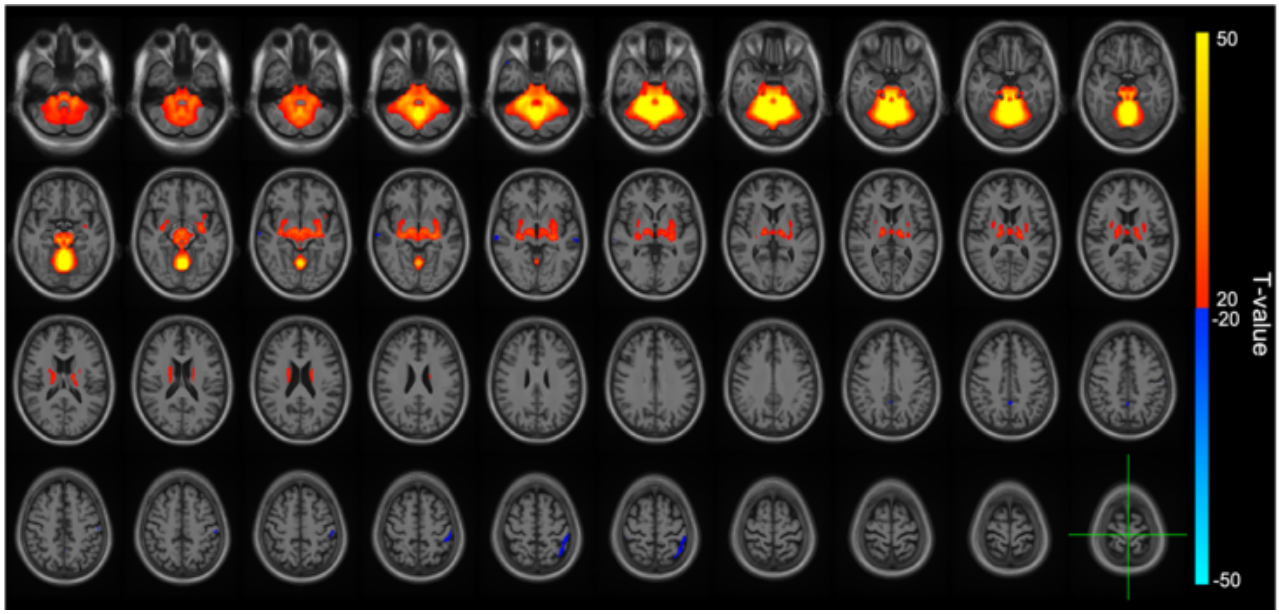

Figure 5-2. Ascending axial slices of BOLD connectivity related to Apathy VBM seed region with positive correlations shown in red-hot colors and anticorrelations shown in blue-cool colors.

3.3 FrSBe Disinhibition Subscale and imaging correlates

After applying the VBM method correlating grey matter density with disinhibition subscale scores, we find significant clusters of atrophy bilaterally in Crus I ($p_{corr} = 0.012$) (Fig. 5-3). There were no significant positive correlations between grey matter density and disinhibition scores. Using our VBM results as a seed region to assess functional connectivity related differences, we find significant positive BOLD correlated activity bilaterally in

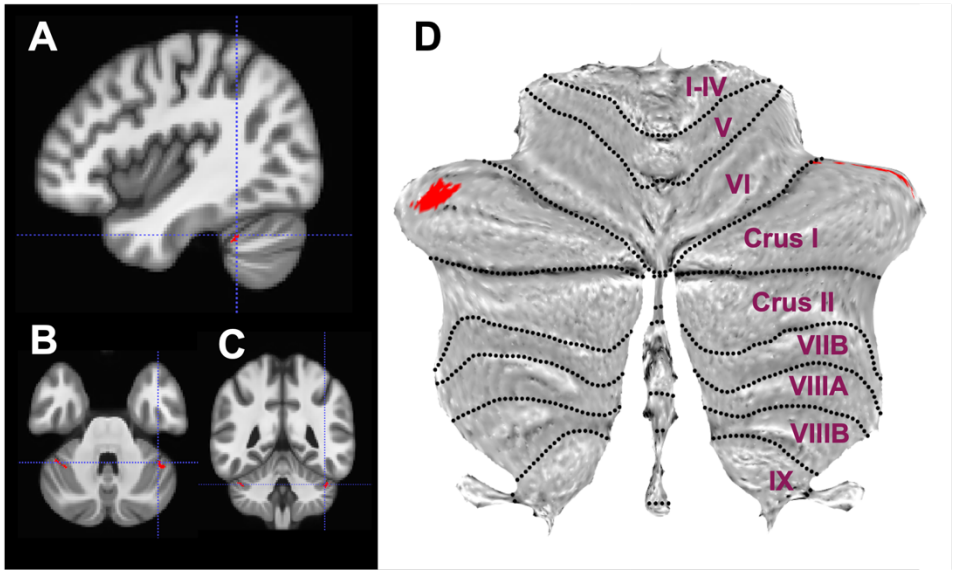

Figure 5-4. Disinhibition-related atrophy voxel-based morphometry (VBM) clusters (red) shown in sagittal (A), axial (B), and coronal (C) views. VBM results displayed on flatmap (D) (SUIT atlas) of the cerebellum for better visualization.

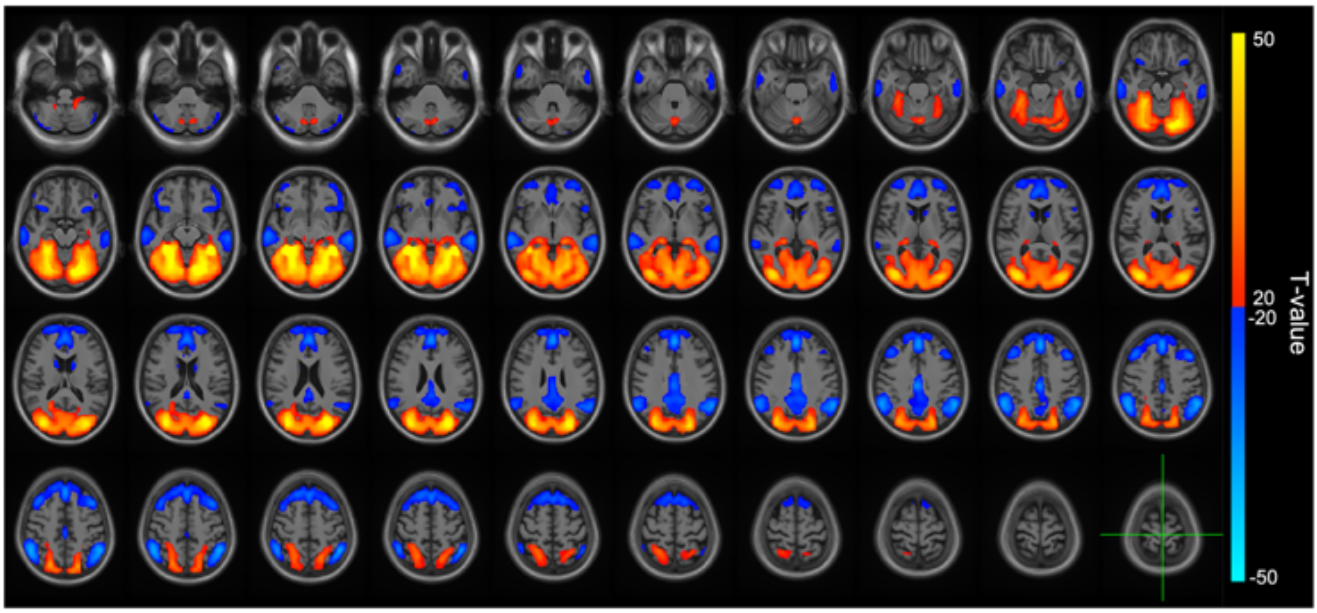

Figure 5-3. Ascending axial slices of BOLD connectivity related to Disinhibition VBM seed region with positive correlations shown in red-hot colors and anticorrelations shown in blue-cool colors.

the cerebellum in lobules VIIb, VIIIb, lobule IX, and along vermis V, VI, and VIIb, with no overlap in the seed region.

Positive correlations in the greater cerebrum are seen in the occipital lobe, and more anteriorly in the superior cerebellar peduncles, posterior thalamus, and tail of the caudate (Fig. 5-4). Additionally, we find significant anticorrelated BOLD connectivity in the cerebellum along the lateral edge of Crus I and Crus II, with no overlapping connectivity to seed region (Fig. 5-4). In the cerebrum, we find significant anticorrelated BOLD connectivity bilaterally in the somatosensory cortex (Brodmann's area 7), precuneus and posterior cingulate cortex (Brodmann's areas 21 and 23), caudate, temporal cortex (Brodmann's area 21 and 20), and anteriorly in medial prefrontal cortex (Brodmann's Areas 9, 10, 32), anterior cingulate cortex, dorso-medial prefrontal cortex (Brodmann's Areas 6, 8, and 9), and lateral orbito-frontal cortex (Brodmann's Area 11). (Fig. 5-4).

FrSBe Executive Dysfunction Subscale and imaging correlates

After applying the VBM method correlating grey matter density with Executive Dysfunction subscale scores, we find the largest clusters of atrophy localized bilaterally in lobule IX ($p_{corr} < 0.001$), and a second cluster along the Right VI-Crus I border ($p_{corr} = 0.003$) (Fig. 5-5). There were no significant positive correlations between grey matter density and

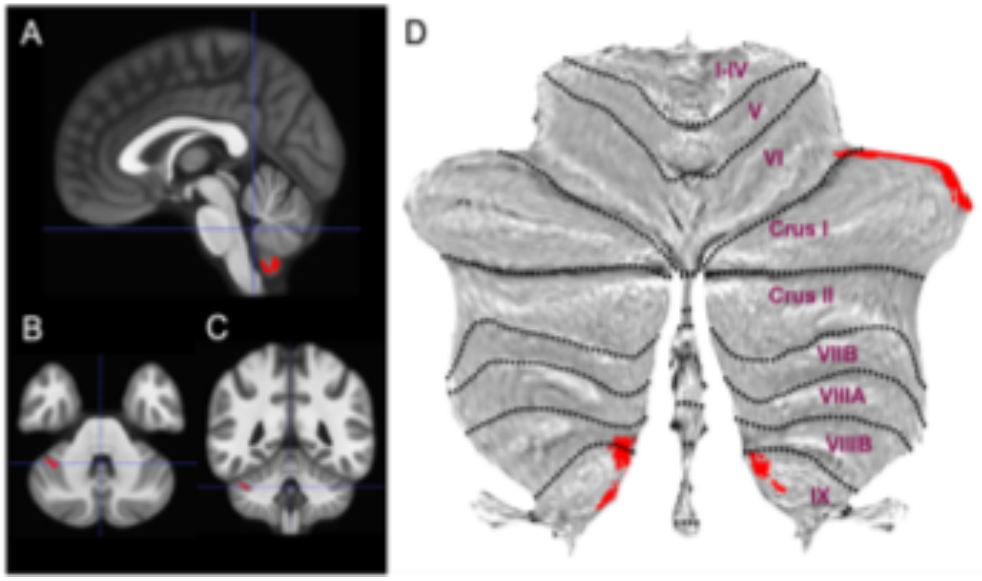

Figure 5-5. Executive Dysfunction-related atrophy voxel-based morphometry (VBM) clusters (red) shown in sagittal (A), axial (B), and coronal (C) views. VBM results displayed on flatmap (D) (SUIT atlas) of the cerebellum for better visualization.

Executive Dysfunction scores. Using these significant clusters as seed regions for BOLD connectivity analyses, we found significant positively correlated BOLD connectivity in antero-medial portion of the cerebellum covering most of the lobules with the exception of Crus I, Crus II, and lobule IX (Fig. 5-6). Positive correlations are also seen in the pons, substantia nigra, thalamus, occipital cortex, and sensory-motor cortex (Fig. 5-6). Additionally, we find significant anticorrelated BOLD connectivity bilaterally in the somatosensory cortex (Brodmann's area 7) and prefrontal

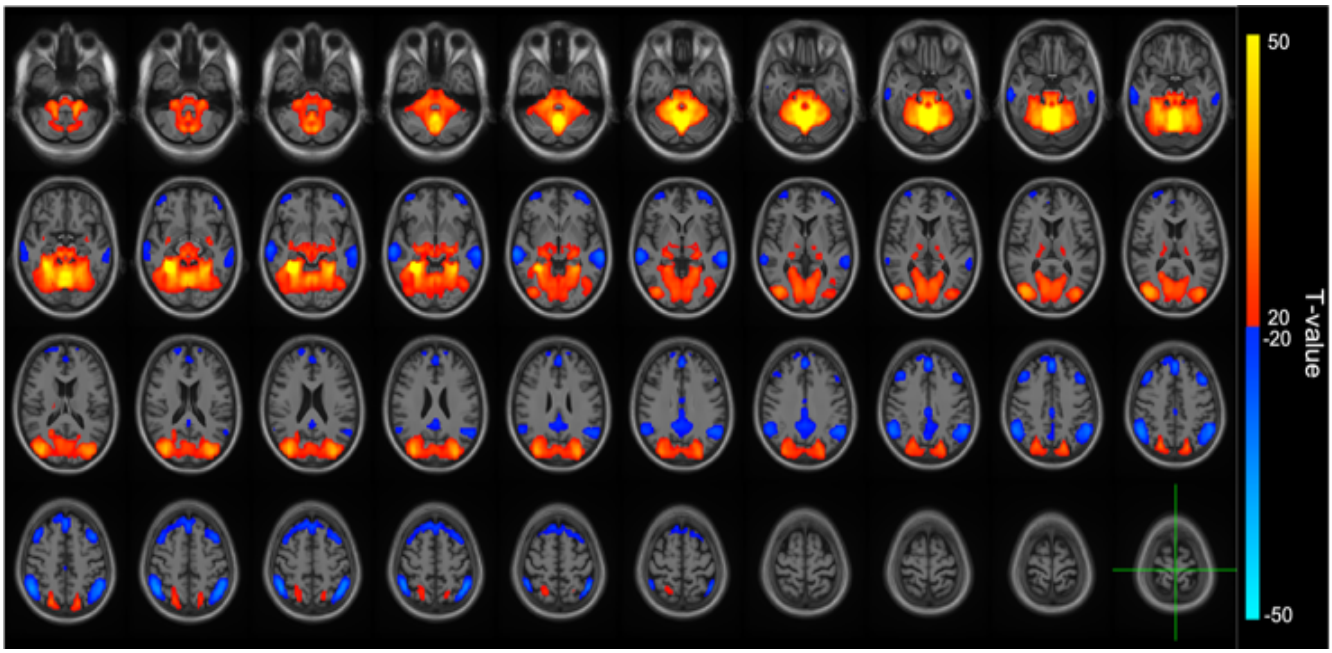

Figure 5-6. Axial view of BOLD connectivity related to Executive Dysfunction VBM seed region with positive correlations shown in red-hot colors and anticorrelations shown in blue-cool colors.

cortex (Brodmann's areas 6, 8, and 10) (Fig. 5- 6). We do not see any significant anticorrelated BOLD connectivity in the cerebellum.

Collectively, these VBM results cluster primarily in the Crus I and lobule IX areas in the cerebellum and are in line with previously reported findings of non-motor functions in the cerebellum having multiple areas of representation, particularly located in lobules VI-Crus I, lobules Crus II-VIIb, and lobules IX-X (Likova et al., 2021), further crediting the idea of reciprocal roles of function within the cerebellum.

5.6 DISCUSSION

In this study we observe significantly elevated dysexecutive behaviors in a large ET cohort, where apathy and behavioral disinhibition relate to atrophy in Crus I/II and lobule IX. Apathy and executive dysfunction are noted in previous studies of patients with ET (Bermejo-Pareja, 2011; Elan D. Louis et al., 2012; Musacchio et al., 2016), but these results extend these findings in linking cerebellar atrophy in the Crus I/II area, and lobule IX to clinically elevated behavioral symptoms. Our results support previous findings of cerebellar involvement in ET, where cerebellar atrophy in the vermis, Crus I, and lobule IX, were noted (Hett et al., 2021). Also, the cerebellar atrophy patterns conform to the proposed 'triple representation' of non-motor function: area VI/Crus I, Crus II and lobule VIIB, and lobules IX/X (Guell et al., 2018). Taken together, this study emphasizes the role of the cerebellum in behavioral control, further localizing the Crus I/II and lobule IX to 'frontal' behaviors.

Apathy-related symptoms have been noted in ET populations previously (Elan D. Louis, 2010, 2016; Elan D. Louis et al., 2012; Thenganatt & Louis, 2012). There is a paucity of data describing disinhibited behaviors in ET, with a single finding of pronounced disinhibition in social interactions or inhibition accompanied by blunted affect (Lombardi et al., 2001). To our knowledge, this is the first study to show elevated disinhibition in ET. The relationship between apathy and impulsivity has been investigated previously, and was postulated to be at the opposing spectrum of dopamine-related behaviors(Sierra et al., 2015), despite positively correlated measures of apathy and impulsivity(Petitet et al., 2021). Ahearn and colleagues showed that in PD, those with apathy report greater attentional-impulsivity, and persons with impulsive-compulsive behaviors (ICBs) have elevated apathy scores, particularly related to social indifference (Ahearn et al., 2012b). If one considers these behaviors in the context of behavioral motivation, a diminished internal ability to motivate actions and an increase in automatic responsiveness for highly salient stimuli could manifest with both apathy and disinhibition. Our results lend credit to these behaviors existing along parallel

behavioral presentation and being related components of larger frontal network dysfunction. Here, we show that these symptoms map to the crus I/II area, which suggests that the cerebellum is important for regulating multi-dimensional behavioral symptoms like apathy and impulsivity and may play an integral role in sustained goal-directed behavior.

Investigating putative cerebellar networks revealed regionally distinct anticorrelated and correlated networks. Anticorrelated posterior cerebellum networks include the frontal cortex (medial PFC), lateral orbitofrontal cortex, and parietal lobes. Correlated networks involve the striatum, midbrain, occipital lobe, and cerebellum. We integrate these results by inferring a model of putative network changes in ET, and how these results inform cerebellum function and behavior. Anticorrelated BOLD connectivity patterns may suggest an inhibitory direction from the posterior cerebellum to frontal cortex, particularly along the medial PFC. This network is necessary for sustained attention, inhibitory control, decision making, and working memory (synthesized in Jobson et al., 2021). Disinhibition-related BOLD patterns also show an anticorrelated activity in the lateral orbitofrontal cortex, another important region for behavioral control (Petersen et al., 2018; Rolls, 2004; Torregrossa et al., 2008; Trujillo et al., 2019; Zeeb et al., 2010). We hypothesize that these anticorrelations reflect a cerebellar-mediated inhibitory regulation of frontal cortical areas via cerebello-thalamo-cortical networks. In ET, reductions in cerebellar coordinated prefrontal inhibition may result in poor executive functioning and behavioral dysregulation. This idea is supported by studies in animals and healthy human adults (Adamaszek et al., 2017; Miquel et al., 2019, 2016; Moulton et al., 2014), as well as in patients with ET (Hughes et al., 2019) and ataxic disorders (Chen et al., 2022). Together, these results suggest that the cerebellum is necessary for inhibitory control (Hirose et al., 2014) and future studies should integrate models of anticorrelated functional connectivity to infer cerebellar based regulation of cortical function.

Apathy-related cerebellar BOLD activity seeds revealed strong positive associations in subcortical regions of the thalamus, putamen, and caudate. Lesions to the striatum manifest with apathy, particularly in the context of action (Delgado et al., 2004; Yamada et al., 2004). The networks that subserve executive dysfunction and apathy are similar, although they differ in the thalamus, with apathy-related activity localizing more in the ventral anterior and ventral lateral nuclei, and executive dysfunction-related activity localizing more in the pulvinar region, suggesting specific outputs for each of these behavioral networks. Viral tracing studies in non-human primates show several motor and non-motor output pathways from the cerebellum to the basal ganglia via the thalamus, and are topographically organized to separate regions of the putamen and globus pallidus (reviewed in Hoshi, 2006)(Hoshi, 2006). Furthermore, there is evidence supporting direct cerebellar-basal ganglia connections, particularly from the dentate nucleus (Milardi et al., 2019). Additional research links the release of dopamine in the caudate and increased dopamine production in the substantia nigra following stimulation of the dentate nucleus in cats (A. Nieoullon et al., 1977), which suggests directional modulation of the cerebellum on the basal ganglia activity. We do not see any significant disinhibition-related BOLD activity in the basal ganglia, suggesting that dysregulation of cortical areas, specifically, medial prefrontal and orbitofrontal areas, results in lack of inhibitory control. If the cerebellum is involved in coordinating activation and inhibition of prefrontal cortical areas, the cerebellum should be included in the description of mesocorticolimbic circuitry (Miquel et al., 2019, 2016; Moulton et al., 2014).

Cerebellar regulation of appropriate timing and responsivity of prefrontal cortical regions could lead to dysfunctional communication with striatal areas also involved in behavioral regulation. Anatomical viral tracing evidence from Strick and colleagues show a “prefrontal loop” that links prefrontal cortex to the cognitive Crus I and Crus II areas of the cerebellum (R. M. Kelly & Strick, 2003; Middleton & Strick, 2000; Strick et al., 2009). Likewise, a resting state BOLD study revealed that Crus I and Crus II have high connectivity with the prefrontal cortex (O’Reilly et al., 2010).

Although our results and evidence in the literature support the notion of cerebellar regulation of cortical activity, our connectivity data do not provide a temporal or directional relationship. We speculate that correlated activity between the basal ganglia and cerebellum reflects a cerebrum-to-cerebellum directionality, whereas anticorrelations between the cerebellum and frontal cortices reflect a "bottom-up" cerebellum-to-cerebrum flow of information.

We emphasize that behavioral symptoms are assessed by caregivers, which have been shown to have more reliable responses, especially when considering a population in which introspection may be limited due to disease burden. One limitation of this study is that while we used the seed regions from the ET cohort, our functional connectivity data is based on connectivity in healthy human brains, so it is possible that this connectivity is altered in a different way in an ET cohort. We hope that these proposed networks can be assessed in future studies of ET and ataxia that assess the cerebellum and behavioral regulation. As previous studies have reported triple representation of non-motor regions in cerebellum (areas Crus I, Crus II, and lobule IX), our findings support this triplicate model of cerebellar organization. The finding of elevated levels of disinhibited behaviors in ET, and the localization to the cerebellum, should inform future investigations of ET pathology. Another limitation is a sample of 105 patients who were identified as part of a cohort eligible for Deep Brain Stimulation (DBS) surgery, which may not represent ET as a whole given that these patents have more severe and medically refractory illness. Although we acknowledge these limitations, our findings indicate significant behavioral symptoms in this population that warrant further investigation into a disease that is primarily considered a movement disorder. Future research is needed to fully elucidate the role of the cerebellum in these behaviors. These dysexecutive behaviors are likely negatively impacting patients' quality of life and should be considered by treatment providers to improve treatment planning.

5.7 CONCLUSIONS

Here we provide evidence for increased familial reported rates of three frontal behaviors in Essential Tremor, including apathy, disinhibition, and executive dysfunction, and localize these behaviors to atrophy in regions of the cerebellum thought to be involved in behavioral control. Further, we use these behavior-related atrophy changes in the cerebellum to investigate larger brain networks involved in these behaviors in a larger normative cohort. Study results emphasize the presence of clinically elevated apathy, disinhibition, and executive dysfunction in essential tremor and relationship of these behaviors to cerebellar atrophy localized to the Crus I/II and lobule IX areas. These findings expand upon previous behavioral findings in essential tremor and are the first to associate clinically elevated dysexecutive behaviors in ET to localized grey matter atrophy in the cerebellum, and the first to relate those areas in the cerebellum to larger cerebral networks. These findings will encourage future studies investigating the role of the cerebellum in behavioral regulation, biological mechanisms by which behavioral regulation from cerebellum to cerebrum occurs, and the relationship between cerebellar function and frontal behaviors.

FINAL CONCLUSIONS

This dissertation aimed to investigate behavioral symptoms and anatomical correlates with a focus on cerebellar regulation of inhibition. Overall, I found novel cerebellar relationships with impulsivity related behaviors in both Parkinson's disease and essential tremor patient populations, which should be considered when planning and developing treatment plans in these populations. Using a combination of behavioral questionnaires and imaging techniques I've shown that the mesocorticolimbic system is important in regulating impulsive behaviors, especially the ventral striatum and prefrontal cortex. Further, I have provided new evidence that the cerebellum expresses measurable dopamine receptors and likely plays a role in behavioral regulation through dopamine networks. Further research is needed to fully elucidate the role of the cerebellum in behavioral regulation and how it may fit into the mesocorticolimbic network. Use of animal models such as non-human primates, which have a more comparable cerebellum to that of humans, could provide information on anatomical connections between the cerebellum and mesocorticolimbic areas (via viral tract tracing), and measure dopamine release more directly (through cyclic voltammetry, optogenetics, or DREADDs). Understanding the role of the cerebellum in behavioral regulation could pave the way for a new therapeutic target for not just movement disorders, but other disease states in which these larger networks are implicated, such as attention deficit hyperactivity disorder (ADHD), cerebellar ataxias, autism, and/or schizophrenia.

REFERENCES

Aarsland, D., Brønnick, K., Kramberger, M. G., & Pereira, J. B. (2017). Cognitive impairment and dementia in Parkinson's disease. In *Dementia, Fifth Edition*. https://doi.org/10.1201/9781315381572

Adamaszek, M., D'Agata, F., Ferrucci, R., Habas, C., Keulen, S., Kirkby, K. C., Leggio, M., Mariën, P., Molinari, M., Moulton, E., Orsi, L., Van Overwalle, F., Papadelis, C., Priori, A., Sacchetti, B., Schutter, D. J., Styliadis, C., & Verhoeven, J. (2017). Consensus Paper: Cerebellum and Emotion. *Cerebellum*, *16*(2), 552–576. https://doi.org/10.1007/s12311-016-0815-8

Ahearn, D. J., McDonald, K., Barraclough, M., & Leroi, I. (2012a). An exploration of apathy and impulsivity in Parkinson disease. *Current Gerontology and Geriatrics Research*, *2012*, 390701. https://doi.org/10.1155/2012/390701

Ahearn, D. J., McDonald, K., Barraclough, M., & Leroi, I. (2012b). An exploration of apathy and impulsivity in Parkinson disease. *Current Gerontology and Geriatrics Research*, *2012*. https://doi.org/10.1155/2012/390701

Akkal, D., Dum, R. P., & Strick, P. L. (2007). Supplementary motor area and presupplementary motor area: Targets of basal ganglia and cerebellar output. *Journal of Neuroscience*, *27*(40), 10659–10673. https://doi.org/10.1523/JNEUROSCI.3134-07.2007

Allen, T. J., Moeller, F. G., Rhoades, H. M., & Cherek, D. R. (1998). Impulsivity and history of drug dependence. *Drug and Alcohol Dependence*. https://doi.org/10.1016/S0376-8716(98)00023-4

Ambermoon, P., Carter, A., Hall, W. D., Dissanayaka, N. N. W., & O'Sullivan, J. D. (2011). Impulse control disorders in patients with Parkinson's disease receiving dopamine replacement therapy: evidence and implications for the addictions field. *Addiction (Abingdon, England)*, *106*(2), 283–293. https://doi.org/10.1111/j.1360-0443.2010.03218.x

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. In *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*. American Psychiatric Publishing, Inc. https://doi.org/10.1176/appi.books.9780890425596.744053

Anderson, M. E. (1993). The Role of the Cerebellum in Motor Control and Motor Learning. *Physical Medicine and Rehabilitation Clinics of North America*, *4*(4), 623–636. https://doi.org/10.1016/S1047-9651(18)30550-3

Andral, G. (1848). *Clinique médicale* (4th ed.). Masson et Cie.

Andreasen, N. C., & Pierson, R. (2008). The role of the cerebellum in schizophrenia. *Biological Psychiatry*, *64*(2), 81–88. https://doi.org/10.1016/j.biopsych.2008.01.003

Antonelli, F., Ray, N., & Strafella, A. P. (2011). Impulsivity and Parkinson's disease: More than just disinhibition. *Journal of the Neurological Sciences*, *310*(1–2), 202–207. https://doi.org/10.1016/j.jns.2011.06.006

Antonini, A., Barone, P., Bonuccelli, U., Annoni, K., Asgharnejad, M., & Stanzione, P. (2017). ICARUS study: prevalence and clinical features of impulse control disorders in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *88*(4), 317–324. https://doi.org/10.1136/jnnp-2016-315277

Antonini, A., Siri, C., Santangelo, G., Cilia, R., Poletti, M., Canesi, M., Caporali, A., Mancini, F., Pezzoli, G., Ceravolo, R., Bonuccelli, U., & Barone, P. (2011). Impulsivity and compulsivity in drug-naïve patients with Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, *26*(3), 464–468. https://doi.org/10.1002/mds.23501

Aoki, S., Smith, J. B., Li, H., Yan, X., Igarashi, M., Coulon, P., Wickens, J. R., Ruigrok, T. J., & Jin, X. (2019). An open cortico-basal ganglia loop allows limbic control over motor output via the nigrothalamic pathway. *ELife*, *8*. https://doi.org/10.7554/eLife.49995

Appollonio, I. M., Grafman, J., Schwartz, V., Massaquoi, S., & Hallett, M. (1993). Memory in

patients with cerebellar degeneration. *Neurology*, *43*(8), 1536–1544. https://doi.org/10.1212/wnl.43.8.1536
Ashby, F. G., Isen, A. M., & Turken, A. U. (1999). A neuropsychological theory of positive affect and its influence on cognition. *Psychological Review*, *106*(3), 529–550. https://doi.org/10.1037/0033-295X.106.3.529
Asselin, M. C., Montgomery, A. J., Grasby, P. M., & Hume, S. P. (2007). Quantification of PET studies with the very high-affinity dopamine D 2/D3 receptor ligand [11C]FLB 457: Re-evaluation of the validity of using a cerebellar reference region. *Journal of Cerebral Blood Flow and Metabolism*, *27*(2), 378–392. https://doi.org/10.1038/sj.jcbfm.9600340
Aumann, M. A., Stark, A. J., Hughes, S. B., Lin, Y.-C., Kang, H., Bradley, E., Zald, D. H., & Claassen, D. O. (2020). Self-reported rates of impulsivity in Parkinson's Disease. *Annals of Clinical and Translational Neurology*, *7*(4), 437–448. https://doi.org/10.1002/acn3.51016
Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, J. C. (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage*, *54*(3), 2033–2044. https://doi.org/10.1016/j.neuroimage.2010.09.025
Avants, B. B., Tustison, N. J., Wu, J., Cook, P. A., & Gee, J. C. (2011). An Open Source Multivariate Framework for n-Tissue Segmentation with Evaluation on Public Data. *Neuroinformatics*, *9*(4), 381–400. https://doi.org/10.1007/s12021-011-9109-y
Bagepally, B. S., Bhatt, M. D., Chandran, V., Saini, J., Bharath, R. D., Vasudev, M., Prasad, C., Yadav, R., & Pal, P. K. (2012). Decrease in Cerebral and Cerebellar Gray Matter in Essential Tremor: A Voxel-Based Morphometric Analysis under 3T MRI. *Journal of Neuroimaging*, *22*(3), 275–278. https://doi.org/10.1111/j.1552-6569.2011.00598.x
Baillieux, H., Smet, H. J. De, Paquier, P. F., De Deyn, P. P., & Mariën, P. (2008). Cerebellar neurocognition: Insights into the bottom of the brain. *Clinical Neurology and Neurosurgery*, *110*(8), 763–773. https://doi.org/10.1016/j.clineuro.2008.05.013
Bakhshani, N.-M. (2014). Impulsivity: A Predisposition Toward Risky Behaviors. *Int J High Risk Behav Addict*, *3*(2), 20428. https://doi.org/10.5812/ijhrba.20428
Baldereschi, M., Di Carlo, A., Rocca, W. A., Vanni, P., Maggi, S., Perissinotto, E., Grigoletto, F., Amaducci, L., & Inzitari, D. (2000). Parkinson's disease and parkinsonism in a longitudinal study: Two-fold higher incidence in men. *Neurology*, *55*(9), 1358–1363. https://doi.org/10.1212/WNL.55.9.1358
Barbosa, M. T., Caramelli, P., Cunningham, M. C. Q., Maia, D. P., Lima-Costa, M. F. F., & Cardoso, F. (2013). Prevalence and clinical classification of tremor in elderly-A community-based survey in Brazil. *Movement Disorders*, *28*(5), 640–646. https://doi.org/10.1002/mds.25355
Bayard, S., Joly, E., Ghisletta, P., Rossignol, A., Herades, Y., Geny, C., Gély-Nargeot, M.-C., & Rochat, L. (2016). A multidimensional approach to impulsivity in Parkinson's disease: measurement and structural invariance of the UPPS Impulsive Behaviour Scale. *Psychological Medicine*, *46*(14), 2931–2941. https://doi.org/10.1017/S0033291716001586
Beauchaine, T. P., Hinshaw, S. P., Zisner, A. R., & Beauchaine, T. P. (2015). Midbrain Neural Mechanisms of Trait Impulsivity. In *The Oxford Handbook of Externalizing Spectrum Disorders* (pp. 184–200). Oxford University Press. https://doi.org/10.1093/oxfordhb/9780199324675.013.003
Ben-Yehudah, G., & Fiez, J. A. (2008). Impact of cerebellar lesions on reading and phonological processing. *Annals of the New York Academy of Sciences*, *1145*, 260–274. https://doi.org/10.1196/annals.1416.015
Ben-Yehudah, G., Guediche, S., & Fiez, J. A. (2007). Cerebellar contributions to verbal working memory: Beyond cognitive theory. *Cerebellum*, *6*(3), 193–201. https://doi.org/10.1080/14734220701286195
Benito-León, Julian, Bermejo-Pareja, F., & Louis, E. D. (2005). Incidence of essential tremor in

three elderly populations of Central Spain. *Neurology*, *64*(10), 1721–1725. https://doi.org/10.1212/01.WNL.0000161852.70374.01

Benito-León, Julián, & Louis, E. D. (2006). Essential tremor: emerging views of a common disorder. *Nature Clinical Practice Neurology*, *2*(12), 666–678. https://doi.org/10.1038/ncpneuro0347

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)*. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Bentivoglio, A. R., Baldonero, E., Ricciardi, L., De Nigris, F., & Daniele, A. (2013). Neuropsychological features of patients with Parkinson's disease and impulse control disorders. *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *34*(7), 1207–1213. https://doi.org/10.1007/s10072-012-1224-5

Bereczki, D. (2010). The description of all four cardinal signs of Parkinson's disease in a Hungarian medical text published in 1690. *Parkinsonism and Related Disorders*, *16*(4), 290–293. https://doi.org/10.1016/j.parkreldis.2009.11.006

Bermejo-Pareja, F. (2011). Essential tremor—a neurodegenerative disorder associated with cognitive defects? *Nature Reviews Neurology*, *7*(5), 273–282. https://doi.org/10.1038/nrneurol.2011.44

Bermejo-Pareja, F., Louis, E. D., Benito-León, J., & Neurological Disorders in Central Spain (NEDICES) Study Group. (2007). Risk of incident dementia in essential tremor: a population-based study. *Movement Disorders : Official Journal of the Movement Disorder Society*, *22*(11), 1573–1580. https://doi.org/10.1002/mds.21553

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research. Brain Research Reviews*, *28*(3), 309–369. https://doi.org/10.1016/s0165-0173(98)00019-8

Bhalsing, K. S., Upadhyay, N., Kumar, K. J., Saini, J., Yadav, R., Gupta, A. K., & Pal, P. K. (2014). Association between cortical volume loss and cognitive impairments in essential tremor. *European Journal of Neurology*, *21*(6), 874–883. https://doi.org/10.1111/ene.12399

Bhatia, K. P., Bain, P., Bajaj, N., Elble, R. J., Hallett, M., Louis, E. D., Raethjen, J., Stamelou, M., Testa, C. M., & Deuschl, G. (2018). Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Movement Disorders*, *33*(1), 75–87. https://doi.org/10.1002/mds.27121

Bhattacharjee, S. (2018a). Impulse control disorders in Parkinson's disease: Review of pathophysiology, epidemiology, clinical features, management, and future challenges. *Neurology India*, *66*(4), 967–975. https://doi.org/10.4103/0028-3886.237019

Bhattacharjee, S. (2018b). Impulse control disorders in Parkinson's disease: Review of pathophysiology, epidemiology, clinical features, management, and future challenges. *Neurology India*, *66*(4), 967. https://doi.org/10.4103/0028-3886.237019

Bloxham, C. A., Dick, D. J., & Mooret, J. M. (1987). Reaction times and attention in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *50*(9), 1178–1183. https://doi.org/10.1136/jnnp.50.9.1178

Bobée, S., Mariette, E., Tremblay-Leveau, H., & Caston, J. (2000). Effects of early midline cerebellar lesion on cognitive and emotional functions in the rat. *Behavioural Brain Research*, *112*(1–2), 107–117. https://doi.org/10.1016/s0166-4328(00)00166-2

Bonnet, L., Comte, A., Tatu, L., Millot, J. L., Moulin, T., & Medeiros De Bustos, E. (2015). The role of the amygdala in the perception of positive emotions: An "intensity detector." *Frontiers in Behavioral Neuroscience*, *9*(JULY), 1–12. https://doi.org/10.3389/fnbeh.2015.00178

Bornovalova, M. A., Lejuez, C. W., Daughters, S. B., Zachary Rosenthal, M., & Lynch, T. R. (2005). Impulsivity as a common process across borderline personality and substance use

disorders. *Clinical Psychology Review*, *25*(6), 790–812. https://doi.org/10.1016/j.cpr.2005.05.005
Bostan, A. C., Dum, R. P., & Strick, P. L. (2010). The basal ganglia communicate with the cerebellum. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(18), 8452–8456. https://doi.org/10.1073/pnas.1000496107
Bostan, A. C., & Strick, P. L. (2018). The basal ganglia and the cerebellum: nodes in an integrated network. *Nature Reviews Neuroscience*, *19*(6), 338–350. https://doi.org/10.1038/s41583-018-0002-7
Botez-Marquard, T., & Botez, M. I. (1993). Cognitive behavior in heredodegenerative ataxias. *European Neurology*, *33*(5), 351–357. https://doi.org/10.1159/000116970
Braak, H., Del Tredici, K., Rüb, U., De Vos, R. A. I., Jansen Steur, E. N. H., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, *24*(2), 197–211. https://doi.org/10.1016/S0197-4580(02)00065-9
Bracke-Tolkmitt, R., Linden, A., Canavan, A. G. M., Rockstroh, B., Scholz, E., Wessel, K., & Diener, H. C. (1989). The Cerebellum Contributes to Mental Skills. *Behavioral Neuroscience*, *103*(2), 442–446. https://doi.org/10.1037/0735-7044.103.2.442
Bromberg-Martin, E. S., Matsumoto, M., & Hikosaka, O. (2010). Dopamine in Motivational Control: Rewarding, Aversive, and Alerting. In *Neuron* (Vol. 68, Issue 5, pp. 815–834). https://doi.org/10.1016/j.neuron.2010.11.022
Bronnick, K., Emre, M., Lane, R., Tekin, S., & Aarsland, D. (2007). Profile of cognitive impairment in dementia associated with Parkinson's disease compared with Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*. https://doi.org/10.1136/jnnp.2006.108076
Brooks, D. J., & Piccini, P. (2006). Imaging in Parkinson's Disease: The Role of Monoamines in Behavior. *Biological Psychiatry*, *59*(10), 908–918. https://doi.org/10.1016/j.biopsych.2005.12.017
Brooks, V. B. (1975). Roles of cerebellum and basal ganglia in initiation and control of movements. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*, *2*(3), 265–277. https://doi.org/10.1017/s0317167100020369
Bruchhage, M. M. K., Bucci, M.-P., & Becker, E. B. E. (2018). Cerebellar involvement in autism and ADHD. *Handbook of Clinical Neurology*, *155*, 61–72. https://doi.org/10.1016/B978-0-444-64189-2.00004-4
Bruggencate, G. (1975). Functions of extrapyramidal systems in motor control II. Cortical and subcortical pathways. *Pharmacology & Therapeutics. Part B: General & Systematic Pharmacology*, *1*(4), 611–672. https://doi.org/10.1016/0306-039x(75)90022-7
Buchsbaum, M. S., Christian, B. T., Lehrer, D. S., Narayanan, T. K., Shi, B., Mantil, J., Kemether, E., Oakes, T. R., & Mukherjee, J. (2006). D2/D3 dopamine receptor binding with [F-18]fallypride in thalamus and cortex of patients with schizophrenia. *Schizophrenia Research*, *85*(1–3), 232–244. https://doi.org/10.1016/j.schres.2006.03.042
Buckholtz, J. W., Treadway, M. T., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S., Baldwin, R. M., Schwartzman, A. N., Shelby, E. S., Smith, C. E., Kessler, R. M., & Zald, D. H. (2010). Dopaminergic network differences in human impulsivity. *Science (New York, N.Y.)*, *329*(5991), 532. https://doi.org/10.1126/science.1185778
Buckner, R. L., Roffman, J. L., & Smoller, J. W. (2014). *Brain Genomics Superstruct Project (GSP)* (10th ed.). Harvard Dataverse. https://doi.org/10.7910/DVN/25833
Caprioli, D., Hong, Y. T., Sawiak, S. J., Ferrari, V., Williamson, D. J., Jupp, B., Adrian Carpenter, T., Aigbirhio, F. I., Everitt, B. J., Robbins, T. W., Fryer, T. D., & Dalley, J. W. (2013). Baseline-dependent effects of cocaine pre-exposure on impulsivity and D 2/3 receptor availability in the rat striatum: Possible relevance to the attention-deficit hyperactivity syndrome. *Neuropsychopharmacology*. https://doi.org/10.1038/npp.2013.44

Carbo-Gas, M., Vazquez-Sanroman, D., Gil-Miravet, I., De las Heras-Chanes, J., Coria-Avila, G. A., Manzo, J., Sanchis-Segura, C., & Miquel, M. (2014). Cerebellar hallmarks of conditioned preference for cocaine. *Physiology and Behavior*, *132*, 24–35. https://doi.org/10.1016/j.physbeh.2014.04.044

Carriere, N., Lopes, R., Defebvre, L., Delmaire, C., & Dujardin, K. (2015). Impaired corticostriatal connectivity in impulse control disorders in Parkinson disease. *Neurology*, *84*(21), 2116–2123. https://doi.org/10.1212/WNL.0000000000001619

Carta, I., Chen, C. H., Schott, A. L., Dorizan, S., & Khodakhah, K. (2019). Cerebellar modulation of the reward circuitry and social behavior. *Science*, *363*(6424). https://doi.org/10.1126/science.aav0581

Carvalho, J. O., Ready, R. E., Malloy, P., & Grace, J. (2013). Confirmatory Factor Analysis of the Frontal Systems Behavior Scale (FrSBe). *Assessment*, *20*(5), 632–641. https://doi.org/10.1177/1073191113492845

Cerasa, A., & Quattrone, A. (2016). Linking Essential Tremor to the Cerebellum—Neuroimaging Evidence. *Cerebellum*, *15*(3), 263–275. https://doi.org/10.1007/s12311-015-0739-8

Chandran, V., Pal, P. K., Reddy, J. Y. C., Thennarasu, K., Yadav, R., & Shivashankar, N. (2012). Non-motor features in essential tremor. *Acta Neurologica Scandinavica*, *125*(5), 332–337. https://doi.org/10.1111/j.1600-0404.2011.01573.x

Chandran, Vijay, & Pal, P. K. (2012). Essential tremor: Beyond the motor features. *Parkinsonism and Related Disorders*, *18*(5), 407–413. https://doi.org/10.1016/j.parkreldis.2011.12.003

Chatterjee, A., Jurewicz, E. C., Applegate, L. M., & Louis, E. D. (2004). Personality in essential tremor: Further evidence of non-motor manifestations of the disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *75*(7), 958–961. https://doi.org/10.1136/jnnp.2004.037176

Chen, T. X., Roy Lin, C.-Y., Aumann, M. A., Yan, Y., Amokrane, N., Desai, N. A., Kang, H., Claassen, D. O., & Kuo, S.-H. (2022). Impulsivity Trait Profiles in Patients With Cerebellar Ataxia and Parkinson Disease. *Neurology*. https://doi.org/10.1212/WNL.0000000000200349

Chillag-Talmor, O., Giladi, N., Linn, S., Gurevich, T., El-Ad, B., Silverman, B., Friedman, N., & Peretz, C. (2011). Use of a refined drug tracer algorithm to estimate prevalence and incidence of Parkinson's disease in a large israeli population. *Journal of Parkinson's Disease*, *1*(1), 35–47. https://doi.org/10.3233/JPD-2011-11024

Chudasama, Y., & Robbins, T. W. (2006). Functions of frontostriatal systems in cognition: Comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biological Psychology*, *73*(1), 19–38. https://doi.org/10.1016/j.biopsycho.2006.01.005

Ciesielska, N., Sokołowski, R., Mazur, E., Podhorecka, M., Polak-Szabela, A., & Kędziora-Kornatowska, K. (2016). Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. *Psychiatria Polska*, *50*(5), 1039–1052. https://doi.org/10.12740/PP/45368

Cilia, R., Siri, C., Marotta, G., Isaias, I. U., De Gaspari, D., Canesi, M., Pezzoli, G., & Antonini, A. (2008). Functional abnormalities underlying pathological gambling in Parkinson disease. *Archives of Neurology*, *65*(12), 1604–1611. https://doi.org/10.1001/archneur.65.12.1604

Cilia, R., & van Eimeren, T. (2011). Impulse control disorders in Parkinson's disease: seeking a roadmap toward a better understanding. *Brain Structure & Function*, *216*(4), 289–299. https://doi.org/10.1007/s00429-011-0314-0

Claassen, D. O., Van Den Wildenberg, W. P. M., Ridderinkhof, K. R., Jessup, C. K., Harrison, M. B., Wooten, G. F., & Wylie, S. A. (2011). Supplemental Material for The Risky Business of Dopamine Agonists in Parkinson Disease and Impulse Control Disorders. *Behavioral Neuroscience*. https://doi.org/10.1037/a0023795.supp

Claassen, D. O., & Wylie, S. A. (2012). Trends and issues in characterizing early cognitive changes in Parkinson's disease. *Current Neurology and Neuroscience Reports*, *12*(6), 695–702.

https://doi.org/10.1007/s11910-012-0312-5
Clark, L., Boileau, I., Zack, M., & Rakoff, V. M. (2018). Neuroimaging of reward mechanisms in Gambling disorder: an integrative review. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-018-0230-2
Cohen, O., Pullman, S., Jurewicz, E., Watner, D., & Louis, E. D. (2003). Rest Tremor in Patients With Essential Tremor. *Archives of Neurology*, *60*(3), 405. https://doi.org/10.1001/archneur.60.3.405
Combettes, M. (1831). Absence complete du cervelet, des pédoncules postérieurs et la protubérance cérébrale chez une jeune fille morte dans sa onzième année. *Bull Soc Anat Paris*, *5*, 148–157.
Constantinescu, C. C., Coleman, R. A., Pan, M.-L., & Mukherjee, J. (2011). Striatal and Extrastriatal microPET Imaging of D2/D3 Dopamine Receptors in Rat Brain with [18 F]Fallypride and [18 F]Desmethoxyfallypride. *Synapse*, *65*(8), 778–787. https://doi.org/10.1002/syn.20904
Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, *69*(12), e113-25. https://doi.org/10.1016/j.biopsych.2011.03.028
Cools, R., Nakamura, K., & Daw, N. D. (2011). Serotonin and dopamine: unifying affective, activational, and decision functions. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *36*(1), 98–113. https://doi.org/10.1038/npp.2010.121
Cosgrove, J., Alty, J. E., & Jamieson, S. (2015). Cognitive impairment in Parkinson's disease. *Postgrad Med J*, *91*, 212–220. https://doi.org/10.1136/postgradmedj-2015-133247
Cummings, J. L. (1993). Frontal-Subcortical Circuits and Human Behavior. *Archives of Neurology*, *50*(8), 873–880. https://doi.org/10.1001/archneur.1993.00540080076020
Cutando, L., Puighermanal, E., Castell, L., Tarot, P., Belle, M., Bertaso, F., Arango-Lievano, M., Ango, F., Rubinstein, M., Quintana, A., Chédotal, A., Mameli, M., & Valjent, E. (2022). Cerebellar dopamine D2 receptors regulate social behaviors. *Nature Neuroscience*. https://doi.org/10.1038/s41593-022-01092-8
Cyders, M. A., Smith, G. T., Spillane, N. S., Fischer, S., Annus, A. M., & Peterson, C. (2007). Integration of impulsivity and positive mood to predict risky behavior: development and validation of a measure of positive urgency. *Psychological Assessment*, *19*(1), 107–118. https://doi.org/10.1037/1040-3590.19.1.107
Czernecki, V., Pillon, B., Houeto, J. L., Pochon, J. B., Levy, R., & Dubois, B. (2002). Motivation, reward, and Parkinson's disease: Influence of dopatherapy. *Neuropsychologia*. https://doi.org/10.1016/S0028-3932(02)00108-2
Dalley, J. W., & Roiser, J. P. (2012). Dopamine, serotonin and impulsivity. *Neuroscience*, *215*(2012), 42–58. https://doi.org/10.1016/j.neuroscience.2012.03.065
Dalley, Jeffrey W., Everitt, B. J., & Robbins, T. W. (2011). Impulsivity, Compulsivity, and Top-Down Cognitive Control. *Neuron*, *69*(4), 680–694. https://doi.org/10.1016/J.NEURON.2011.01.020
Damian, A. M., Jacobson, S. A., Hentz, J. G., Belden, C. M., Shill, H. A., Sabbagh, M. N., Caviness, J. N., & Adler, C. H. (2011a). The montreal cognitive assessment and the mini-mental state examination as screening instruments for cognitive impairment: Item analyses and threshold scores. *Dementia and Geriatric Cognitive Disorders*. https://doi.org/10.1159/000323867
Damian, A. M., Jacobson, S. A., Hentz, J. G., Belden, C. M., Shill, H. A., Sabbagh, M. N., Caviness, J. N., & Adler, C. H. (2011b). The Montreal Cognitive Assessment and the Mini-Mental State Examination as Screening Instruments for Cognitive Impairment: Item Analyses and Threshold Scores. *Dementia and Geriatric Cognitive Disorders*, *31*(2), 126–131. https://doi.org/10.1159/000323867

Daniel, R., & Pollmann, S. (2014). A universal role of the ventral striatum in reward-based learning: evidence from human studies. *Neurobiology of Learning and Memory*, *114*, 90–100. https://doi.org/10.1016/j.nlm.2014.05.002

Daniel, S. E., & Lees, A. J. (1993). Parkinson's Disease Society Brain Bank, London: Overview and research. *Journal of Neural Transmission, Supplement*.

Dawe, S., Gullo, M. J., & Loxton, N. J. (2004). Reward drive and rash impulsiveness as dimensions of impulsivity: implications for substance misuse. *Addictive Behaviors*, *29*(7), 1389–1405. https://doi.org/10.1016/j.addbeh.2004.06.004

Dawe, S., & Loxton, N. J. (2004). The role of impulsivity in the development of substance use and eating disorders. *Neuroscience and Biobehavioral Reviews*, *28*(3), 343–351. https://doi.org/10.1016/j.neubiorev.2004.03.007

Delforge, J., Bottlaender, M., Loc'h, C., Guenther, I., Fuseau, C., Bendriem, B., Syrota, A., & Mazière, B. (1999). Quantitation of extrastriatal D2 receptors using a very high-affinity ligand (FLB 457) and the multi-injection approach. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *19*(5), 533–546. https://doi.org/10.1097/00004647-199905000-00008

Delgado, M. R., Stenger, V. A., & Fiez, J. A. (2004). Motivation-dependent Responses in the Human Caudate Nucleus. *Cortex September*, *14*, 1022–1030. https://doi.org/10.1093/cercor/bhh062

Diaz, E., Estric, C., Schandrin, A., & Lopez-Castroman, J. (2022). Neurocognitive functioning and impulsivity in first-episode psychosis with suicidal ideation and behavior: A systematic review. *Schizophrenia Research*, *241*, 130–139. https://doi.org/10.1016/j.schres.2022.01.042

Diedrichsen, J. (2006). A spatially unbiased atlas template of the human cerebellum. *NeuroImage*, *33*(1), 127–138. https://doi.org/10.1016/j.neuroimage.2006.05.056

Diedrichsen, J., Balsters, J. H., Flavell, J., Cussans, E., & Ramnani, N. (2009). A probabilistic MR atlas of the human cerebellum. *NeuroImage*, *46*(1), 39–46. https://doi.org/10.1016/j.neuroimage.2009.01.045

Donahue, K. M., Weisskoff, R. M., & Burstein, D. (n.d.). Water diffusion and exchange as they influence contrast enhancement. *Journal of Magnetic Resonance Imaging : JMRI*, *7*(1), 102–110. https://doi.org/10.1002/jmri.1880070114

Dow, R. S., & Moruzzi, G. (1958). Part II Clinical Symptomatology and Pathology. In *The Physiology and Pathology of the Cerebellum*. University of Minnesota Press.

Dumont, R., Willis, J. O., Veizel, K., & Zibulsky, J. (2014). Wechsler Adult Intelligence Scale-Fourth Edition. In *Encyclopedia of Special Education*. John Wiley & Sons, Inc. https://doi.org/10.1002/9781118660584.ese2520

Eagle, D. M., Baunez, C., Hutcheson, D. M., Lehmann, O., Shah, A. P., & Robbins, T. W. (2008). Stop-signal reaction-time task performance: Role of prefrontal cortex and subthalamic nucleus. *Cerebral Cortex*, *18*(1), 178–188. https://doi.org/10.1093/cercor/bhm044

Ebersbach, G., Baas, H., Csoti, I., Müngersdorf, M., & Deuschl, G. (2006a). Scales in Parkinson's disease. *Journal of Neurology*. https://doi.org/10.1007/s00415-006-4008-0

Ebersbach, G., Baas, H., Csoti, I., Müngersdorf, M., & Deuschl, G. (2006b). Scales in Parkinson's disease. *Journal of Neurology*, *253 Suppl 4*, IV32-5. https://doi.org/10.1007/s00415-006-4008-0

Erga, A. H., Alves, G., Larsen, J. P., Tysnes, O. B., & Pedersen, K. F. (2017). Impulsive and Compulsive Behaviors in Parkinson's Disease: The Norwegian ParkWest Study. *Journal of Parkinson's Disease*, *7*, 183–191. https://doi.org/10.3233/JPD-160977

Ersche, K. D., Meng, C., Ziauddeen, H., Stochl, J., Williams, G. B., Bullmore, E. T., & Robbins, T. W. (2020). Brain networks underlying vulnerability and resilience to drug addiction. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(26), 15253–15261. https://doi.org/10.1073/pnas.2002509117

Evans, A. H., Okai, D., Weintraub, D., Lim, S. Y., O'Sullivan, S. S., Voon, V., Krack, P., Sampaio, C., Post, B., Leentjens, A. F. G., Martinez-Martin, P., Stebbins, G. T., Goetz, C. G., Schrag, A., Bhidayasiri, R., Brown, R. G., Marinus, J., Mestre, T. A., Violante, M. R., & Skorvanek, M. (2019). Scales to assess impulsive and compulsive behaviors in Parkinson's disease: Critique and recommendations. In *Movement Disorders*. https://doi.org/10.1002/mds.27689

Evans, A. H., Pavese, N., Lawrence, A. D., Tai, Y. F., Appel, S., Doder, M., Brooks, D. J., Lees, A. J., & Piccini, P. (2006). Compulsive drug use linked to sensitized ventral striatal dopamine transmission. *Annals of Neurology*, *59*(5), 852–858. https://doi.org/10.1002/ana.20822

Evenden, J. (1999). Impulsivity: a discussion of clinical and experimental findings. *Journal of Psychopharmacology (Oxford, England)*, *13*(2), 180–192. https://doi.org/10.1177/026988119901300211

Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology*, *146*(4), 348–361. https://doi.org/10.1007/pl00005481

Everitt, B. J., Parkinson, J. A., Olmstead, M. C., Arroyo, M., Robledo, P., & Robbins, T. W. (1999). Associative processes in addiction and reward. The role of amygdala-ventral striatal subsystems. *Annals of the New York Academy of Sciences*, *877*, 412–438. https://doi.org/10.1111/j.1749-6632.1999.tb09280.x

Eysenck, S. B., & Eysenck, H. J. (1977). The place of impulsiveness in a dimensional system of personality description. *The British Journal of Social and Clinical Psychology*, *16*(1), 57–68. https://doi.org/10.1111/j.2044-8260.1977.tb01003.x

Eysenck, S. B. G., Pearson, P. R., Easting, G., & Allsopp, J. F. (1985). Age norms for impulsiveness, venturesomeness and empathy in adults. *Personality and Individual Differences*, *6*(5), 613–619. https://doi.org/10.1016/0191-8869(85)90011-X

Fahn S, Tolosa E, & Marin C. (1988). Clinical rating scale for tremor. *Parkinson's Disease and Movement Disorders*, *January 1988*, 225–234.

Fengler, S., Liepelt-Scarfone, I., Brockmann, K., Schäffer, E., Berg, D., & Kalbe, E. (2017a). Cognitive changes in prodromal Parkinson's disease: A review. *Movement Disorders*, *32*(12), 1655–1666. https://doi.org/10.1002/mds.27135

Fengler, S., Liepelt-Scarfone, I., Brockmann, K., Schäffer, E., Berg, D., & Kalbe, E. (2017b). Cognitive changes in prodromal Parkinson's disease: A review. *Movement Disorders*, *32*(12), 1655–1666. https://doi.org/10.1002/mds.27135

Figee, M., Pattij, T., Willuhn, I., Luigjes, J., van den Brink, W., Goudriaan, A., Potenza, M. N., Robbins, T. W., & Denys, D. (2016). Compulsivity in obsessive-compulsive disorder and addictions. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*, *26*(5), 856–868. https://doi.org/10.1016/j.euroneuro.2015.12.003

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., & Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. *Nature Neuroscience*, *13*(5), 538–539. https://doi.org/10.1038/nn.2516

Filip, P., Linhartová, P., Hlavatá, P., Šumec, R., Baláž, M., Bareš, M., & Kašpárek, T. (2018). Disruption of Multiple Distinctive Neural Networks Associated With Impulse Control Disorder in Parkinson's Disease. *Frontiers in Human Neuroscience*, *12*, 462. https://doi.org/10.3389/fnhum.2018.00462

First, M. B. (2015). Structured Clinical Interview for the DSM (SCID). In *The Encyclopedia of Clinical Psychology* (pp. 1–6). John Wiley & Sons, Inc. https://doi.org/10.1002/9781118625392.wbecp351

Fischman, M. W., & Foltin, R. W. (1991). Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *British Journal of Addiction*, *86*(12), 1563–1570. https://doi.org/10.1111/j.1360-0443.1991.tb01749.x

Flace, P., Livrea, P., Basile, G. A., Galletta, D., Bizzoca, A., Gennarini, G., Bertino, S., Branca, J. J. V., Gulisano, M., Bianconi, S., Bramanti, A., & Anastasi, G. (2021). The Cerebellar

Dopaminergic System. *Frontiers in Systems Neuroscience*, *15*, 650614. https://doi.org/10.3389/fnsys.2021.650614

Fleckenstein, A. E., Volz, T. J., Riddle, E. L., Gibb, J. W., & Hanson, G. R. (2007). New insights into the mechanism of action of amphetamines. *Annual Review of Pharmacology and Toxicology*, *47*, 681–698. https://doi.org/10.1146/annurev.pharmtox.47.120505.105140

Flourens, P. (1794-1867). A. du texte. (1842). *Recherches expérimentales sur les propriétés et les fonctions du système nerveux dans les animaux vertébrés* (2nd ed., Vol. 2). J.-B. Baillière (Paris). http://catalogue.bnf.fr/ark:/12148/cb30444831b

Forster, G. L., & Blaha, C. D. (2003). Pedunculopontine tegmental stimulation evokes striatal dopamine efflux by activation of acetylcholine and glutamate receptors in the midbrain and pons of the rat. *The European Journal of Neuroscience*, *17*(4), 751–762. https://doi.org/10.1046/j.1460-9568.2003.02511.x

Fotros, A., Casey, K. F., Larcher, K., Verhaeghe, J. A., Cox, S. M., Gravel, P., Reader, A. J., Dagher, A., Benkelfat, C., & Leyton, M. (2013a). Cocaine Cue-Induced Dopamine Release in Amygdala and Hippocampus: A High-Resolution PET [18F]Fallypride Study in Cocaine Dependent Participants. *Neuropsychopharmacology*, *38*, 1780–1788. https://doi.org/10.1038/npp.2013.77

Fotros, A., Casey, K. F., Larcher, K., Verhaeghe, J. A. J., Cox, S. M. L., Gravel, P., Reader, A. J., Dagher, A., Benkelfat, C., & Leyton, M. (2013b). Cocaine cue-induced dopamine release in amygdala and hippocampus: a high-resolution PET [^{18}F]fallypride study in cocaine dependent participants. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *38*(9), 1780–1788. https://doi.org/10.1038/npp.2013.77

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678. https://doi.org/10.1073/pnas.0504136102

Frankle, W. G., Paris, J., Himes, M., Mason, N. S., Mathis, C. A., & Narendran, R. (2018). Amphetamine-Induced Striatal Dopamine Release Measured With an Agonist Radiotracer in Schizophrenia. *Biological Psychiatry*, *83*(8), 707–714. https://doi.org/10.1016/j.biopsych.2017.11.032

French, S. J., & Totterdell, S. (2002). Hippocampal and prefrontal cortical inputs monosynaptically converge with individual projection neurons of the nucleus accumbens. *The Journal of Comparative Neurology*, *446*(2), 151–165. https://doi.org/10.1002/cne.10191

Friedman, J., Hastie, T., & Tibshirani, R. (2010). Regularization Paths for Generalized Linear Models via Coordinate Descent. *Journal of Statistical Software*, *33*(1), 1–22. http://www.ncbi.nlm.nih.gov/pubmed/20808728

Fudge, J. L., Kelly, E. A., Pal, R., Bedont, J. L., Park, L., & Ho, B. (2017). Beyond the Classic VTA: Extended Amygdala Projections to DA-Striatal Paths in the Primate. *Neuropsychopharmacology*, *42*(8), 1563–1576. https://doi.org/10.1038/npp.2017.38

Garcia-Ruiz, P. J., Martinez Castrillo, J. C., Alonso-Canovas, A., Herranz Barcenas, A., Vela, L., Sanchez Alonso, P., Mata, M., Olmedilla Gonzalez, N., & Mahillo Fernandez, I. (2014a). Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: A multicentre study. *Journal of Neurology, Neurosurgery and Psychiatry*, *85*(8), 841–845. https://doi.org/10.1136/jnnp-2013-306787

Garcia-Ruiz, P. J., Martinez Castrillo, J. C., Alonso-Canovas, A., Herranz Barcenas, A., Vela, L., Sanchez Alonso, P., Mata, M., Olmedilla Gonzalez, N., & Mahillo Fernandez, I. (2014b). Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(8), 840–844. https://doi.org/10.1136/jnnp-2013-306787

Gasparini, M., Bonifati, V., Fabrizio, E., Fabbrini, G., Brusa, L., Lenzi, G. L., & Meco, G. (2001).

Frontal lobe dysfunction in essential tremor. *Journal of Neurology*, *248*(5), 399–402. https://doi.org/10.1007/s004150170181

Getz, S. J., & Levin, B. (2017). Cognitive and Neuropsychiatric Features of Early Parkinson's Disease. *Archives of Clinical Neuropsychology*, *32*(7), 769–785. https://doi.org/10.1093/arclin/acx091

Gifford, A. N., Park, M. H., Kash, T. L., Herman, L. M., Park, E. H., Gatley, S. J., & Volkow, N. D. (2000). Effect of amphetamine-induced dopamine release on radiotracer binding to D1 and D2 receptors in rat brain striatal slices. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *362*(4–5), 413–418. https://doi.org/10.1007/s002100000293

Gillies, G. E., Pienaar, I. S., Vohra, S., & Qamhawi, Z. (2014). Sex differences in Parkinson's disease. *Frontiers in Neuroendocrinology*, *35*(3), 370–384. https://doi.org/10.1016/j.yfrne.2014.02.002

Gjedde, A., Kumakura, Y., Cumming, P., Linnet, J., & Møller, A. (2010). Inverted-U-shaped correlation between dopamine receptor availability in striatum and sensation seeking. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(8), 3870–3875. https://doi.org/10.1073/pnas.0912319107

Glaser, P. E. A., Surgener, S. P., Grondin, R., Gash, C. R., Palmer, M., Castellanos, F. X., & Gerhardt, G. A. (2006). Cerebellar neurotransmission in attention-deficit/hyperactivity disorder: Does dopamine neurotransmission occur in the cerebellar vermis? *Journal of Neuroscience Methods*, *151*(1), 62–67. https://doi.org/10.1016/j.jneumeth.2005.09.019

Glover, G. H. (2011). Overview of functional magnetic resonance imaging. *Neurosurgery Clinics of North America*, *22*(2), 133–139. https://doi.org/10.1016/j.nec.2010.11.001

Goetz, C. G., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stebbins, G. T., Stern, M. B., Tilley, B. C., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., … LaPelle, N. (2007). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Movement Disorders : Official Journal of the Movement Disorder Society*, *22*(1), 41–47. https://doi.org/10.1002/mds.21198

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., … LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, *23*(15), 2129–2170. https://doi.org/10.1002/mds.22340

Goldman, J. G., & Postuma, R. (2014). Premotor and nonmotor features of Parkinson's disease. In *Current Opinion in Neurology*. https://doi.org/10.1097/WCO.0000000000000112

Goris, A., Williams-Gray, C. H., Clark, G. R., Foltynie, T., Lewis, S. J. G., Brown, J., Ban, M., Spillantini, M. G., Compston, A., Burn, D. J., Chinnery, P. F., Barker, R. A., & Sawcer, S. J. (2007). Tau and α-synuclein in susceptibility to, and dementia in, Parkinson's disease. *Annals of Neurology*, *62*(2), 145–153. https://doi.org/10.1002/ana.21192

Goursaud, A. P. S., & Bachevalier, J. (2020). Altered face scanning and arousal after orbitofrontal cortex lesion in adult rhesus monkeys. *Behavioral Neuroscience*, *134*(1), 45–58. https://doi.org/10.1037/bne0000342

Gouveia, F. V., Hamani, C., Fonoff, E. T., Brentani, H., Alho, E. J. L., De Morais, R. M. C. B., De Souza, A. L., Rigonatti, S. P., & Martinez, R. C. R. (2019). Amygdala and Hypothalamus: Historical Overview with Focus on Aggression. *Clinical Neurosurgery*, *85*(1), 11–30. https://doi.org/10.1093/neuros/nyy635

Grace, J., & Malloy, P. F. (2001a). *Frontal Systems Behavior Scale (FrSBe): Professional Manual*. Psychological Assessment Resources (PAR).

Grace, J., & Malloy, P. H. (2001b). *Outcome Measure Frontal Systems Behavior Scale (FrSBe)*.
Grafman, J., Litvan, I., Massaquoi, S., Stewart, M., Sirigu, A., & Hallett, M. (1992). Cognitive planning deficit in patients with cerebellar atrophy. *Neurology*, *42*(8), 1493–1496. https://doi.org/10.1212/wnl.42.8.1493
Grall-Bronnec, M., Victorri-Vigneau, C., Donnio, Y., Leboucher, J., Rousselet, M., Thiabaud, E., Zreika, N., Derkinderen, P., & Challet-Bouju, G. (2018). Dopamine Agonists and Impulse Control Disorders: A Complex Association. *Drug Safety*, *41*(1), 19–75. https://doi.org/10.1007/s40264-017-0590-6
Gray, M. A., Minati, L., Harrison, N. A., Gianaros, P. J., Napadow, V., & Critchley, H. D. (2009). Physiological recordings: Basic concepts and implementation during functional magnetic resonance imaging. *NeuroImage*, *47*(3), 1105–1115. https://doi.org/10.1016/j.neuroimage.2009.05.033
Gretton, A., Belitski, A., Murayama, Y., Schölkopf, B., & Logothetis, N. (2006). The effect of artifacts on dependence measurement in fMRI. *Magnetic Resonance Imaging*, *24*(4), 401–409. https://doi.org/10.1016/j.mri.2005.12.036
Grimaldi, G. (2013). Cerebellar Motor Disorders. In *Handbook of the Cerebellum and Cerebellar Disorders* (pp. 1595–1625). Springer Netherlands. https://doi.org/10.1007/978-94-007-1333-8_71
Guell, X., Gabrieli, J. D. E., & Schmahmann, J. D. (2018). Triple representation of language, working memory, social and emotion processing in the cerebellum: convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. *NeuroImage*, *172*(January), 437–449. https://doi.org/10.1016/j.neuroimage.2018.01.082
Guo, T., Wu, J., Zhou, C., Guan, X., Gao, T., Bai, X., Song, Z., Xuan, M., Gu, Q., Huang, P., Zhang, B., Pu, J., Xu, X., Xu, D., & Zhang, M. (2020). Aberrant Fiber Coherence of Amygdala−Accumbens−Pallidum Pathway Is Associated With Disorganized Nigrostriatal−Nigropallidal Pathway in Parkinson's Disease. *Journal of Magnetic Resonance Imaging*, *52*(6), 1799–1808. https://doi.org/10.1002/jmri.27273
Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *35*(1), 4–26. https://doi.org/10.1038/npp.2009.129
Haerer, A. F., Anderson, D. W., & Schoenberg, B. S. (1982). Prevalence of Essential Tremor: Results From the Copiah County Study. *Archives of Neurology*, *39*(12), 750–751. https://doi.org/10.1001/archneur.1982.00510240012003
Hallett, M. (2012). Parkinson's disease tremor: Pathophysiology. *Parkinsonism and Related Disorders*, *18*(SUPPL. 1), S85–S86. https://doi.org/10.1016/s1353-8020(11)70027-x
Hammes, J., Theis, H., Giehl, K., Hoenig, M. C., Greuel, A., Tittgemeyer, M., Timmermann, L., Fink, G. R., Drzezga, A., Eggers, C., & Van Eimeren, T. (2019). Dopamine metabolism of the nucleus accumbens and fronto-striatal connectivity modulate impulse control. *Brain*, *142*(3), 733–743. https://doi.org/10.1093/brain/awz007
Han, X., Jing, M. yi, Zhao, T. yun, Wu, N., Song, R., & Li, J. (2017). Role of dopamine projections from ventral tegmental area to nucleus accumbens and medial prefrontal cortex in reinforcement behaviors assessed using optogenetic manipulation. *Metabolic Brain Disease*, *32*(5), 1491–1502. https://doi.org/10.1007/s11011-017-0023-3
Hardesty, D. E., Maraganore, D. M., Matsumoto, J. Y., & Louis, E. D. (2004). Increased risk of head tremor in women with essential tremor: Longitudinal data from the Rochester Epidemiology Project. *Movement Disorders*, *19*(5), 529–533. https://doi.org/10.1002/mds.20096
Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J., & Duda, S. N. (2019). The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical*

Informatics, *95*, 103208. https://doi.org/10.1016/J.JBI.2019.103208
Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377. https://doi.org/10.1016/J.JBI.2008.08.010
Harro, J. (2015). Neuropsychiatric Adverse Effects of Amphetamine and Methamphetamine. *International Review of Neurobiology*, *120*, 179–204. https://doi.org/10.1016/bs.irn.2015.02.004
Heiden, P., Heinz, A., & Romanczuk-Seiferth, N. (2017). Pathological gambling in Parkinson's disease: what are the risk factors and what is the role of impulsivity? *European Journal of Neuroscience*, *45*(1), 67–72. https://doi.org/10.1111/ejn.13396
Helmich, R. C., Toni, I., Deuschl, G., & Bloem, B. R. (2013). The pathophysiology of essential tremor and parkinson's tremor. *Current Neurology and Neuroscience Reports*, *13*(9). https://doi.org/10.1007/s11910-013-0378-8
Herculano-Houzel, S. (2010). Coordinated scaling of cortical and cerebellar numbers of neurons. *Frontiers in Neuroanatomy*, *4*(MARCH), 1–8. https://doi.org/10.3389/fnana.2010.00012
Hett, K., Lyu, I., Trujillo, P., Lopez, A. M., Aumann, M., Larson, K. E., Hedera, P., Dawant, B., Landman, B. A., Claassen, D. O., & Oguz, I. (2021). Anatomical texture patterns identify cerebellar distinctions between essential tremor and Parkinson's disease. *Human Brain Mapping*, *42*(8), 2322–2331. https://doi.org/10.1002/hbm.25331
Hirose, S., Jimura, K., Kunimatsu, A., Abe, O., Ohtomo, K., Miyashita, Y., & Konishi, S. (2014). Changes in cerebro-cerebellar interaction during response inhibition after performance improvement. *NeuroImage*, *99*, 142–148. https://doi.org/10.1016/j.neuroimage.2014.05.007
Hisahara, S., & Shimohama, S. (2011). Dopamine receptors and Parkinson's disease. *International Journal of Medicinal Chemistry*, *2011*, 403039. https://doi.org/10.1155/2011/403039
Hlavatá, P., Linhartová, P., Šumec, R., Filip, P., Světlák, M., Baláž, M., Kašpárek, T., & Bareš, M. (2020). Behavioral and Neuroanatomical Account of Impulsivity in Parkinson's Disease. *Frontiers in Neurology*, *10*, 1338. https://doi.org/10.3389/fneur.2019.01338
Hollander, E., & Rosen, J. (2000). Impulsivity. *Journal of Psychopharmacology (Oxford, England)*, *14*(2 Suppl 1), S39-44. https://doi.org/10.1177/02698811000142S106
Holtbernd, F., & Shah, N. J. (2021). *Imaging the Pathophysiology of Essential Tremor — A Systematic Review*. *12*(June), 1–17. https://doi.org/10.3389/fneur.2021.680254
Hoops, S., Nazem, B. S., Siderowf, B. A. D., Duda, J. E., Xie, S. X., Stern, M. B., & Weintraub, D. (2009). *Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2788810/pdf/7148.pdf
Hoptman, M. J. (2015). Impulsivity and aggression in schizophrenia: a neural circuitry perspective with implications for treatment. *CNS Spectrums*, *20*(3), 280–286. https://doi.org/10.1017/S1092852915000206
Hoshi, E. (2006). Functional specialization within the dorsolateral prefrontal cortex: A review of anatomical and physiological studies of non-human primates. *Neuroscience Research*, *54*(2), 73–84. https://doi.org/10.1016/j.neures.2005.10.013
Housden, C. R., O'Sullivan, S. S., Joyce, E. M., Lees, A. J., & Roiser, J. P. (2010). Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *35*(11), 2155–2164. https://doi.org/10.1038/npp.2010.84
Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D. S., Calabresi, P. A., Pekar, J. J., van Zijl, P. C. M., & Mori, S. (2008). Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *NeuroImage*, *39*(1), 336–347. https://doi.org/10.1016/j.neuroimage.2007.07.053

Hubble, J. P., Busenbark, K. L., Pahwa, R., Lyons, K., & Koller, W. C. (1997). Clinical expression of essential tremor: Effects of gender and age. *Movement Disorders*, *12*(6), 969–972. https://doi.org/10.1002/mds.870120620

Huettel, S. A., Song, A. W., & McCarthy, G. (2009). *Functional magnetic resonance imaging* (2nd ed., Issue 8). Sinauer Associates.

Hughes, S., Claassen, D. O., van den Wildenberg, W. P. M., Phibbs, F. T., Bradley, E. B., Wylie, S. A., & van Wouwe, N. C. (2019). Action Control Deficits in Patients With Essential Tremor. *Journal of the International Neuropsychological Society : JINS*, *25*(2), 156–164. https://doi.org/10.1017/S1355617718001054

Hurley, M. J., Mash, D. C., & Jenner, P. (2003). Markers for dopaminergic neurotransmission in the cerebellum in normal individuals and patients with Parkinson's disease examined by RT-PCR. *European Journal of Neuroscience*, *18*(9), 2668–2672. https://doi.org/10.1046/j.1460-9568.2003.02963.x

Ikemoto, S. (2007). Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain Research Reviews*, *56*(1), 27–78. https://doi.org/10.1016/j.brainresrev.2007.05.004

Imperiale, F., Agosta, F., Canu, E., Markovic, V., Inuggi, A., Jecmenica-Lukic, M., Tomic, A., Copetti, M., Basaia, S., Kostic, V. S., & Filippi, M. (2018). Brain structural and functional signatures of impulsive-compulsive behaviours in Parkinson's disease. *Molecular Psychiatry*, *23*, 459–466. https://doi.org/10.1038/mp.2017.18

Ishikawa, A., Ambroggi, F., Nicola, S. M., & Fields, H. L. (2008). Contributions of the amygdala and medial prefrontal cortex to incentive cue responding. *Neuroscience*, *155*(3), 573–584. https://doi.org/10.1016/j.neuroscience.2008.06.037

Izquierdo, A., & Murray, E. A. (2004). Combined Unilateral Lesions of the Amygdala and Orbital Prefrontal Cortex Impair Affective Processing in Rhesus Monkeys. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.00968.2003

Janicki, S. C., Cosentino, S., & Louis, E. D. (2013). The cognitive side of essential tremor: What are the therapeutic implications? *Therapeutic Advances in Neurological Disorders*, *6*(6), 353–368. https://doi.org/10.1177/1756285613489591

Jellinger, K. A. (2014). Parkinson's Disease. In *Pathobiology of Human Disease* (pp. 2021–2035). Elsevier. https://doi.org/10.1016/B978-0-12-386456-7.04605-0

Jenkins, I. H., Bain, P. G., Colebatch, J. G., Thompson, P. D., Findley, L. J., Frackowiak, R. S. J., Marsden, C. D., & Brooks, D. J. (1993). A positron emission tomography study of essential tremor: Evidence for overactivity of cerebellar connections. *Annals of Neurology*, *34*(1), 82–90. https://doi.org/10.1002/ana.410340115

Jobson, D. D., Hase, Y., Clarkson, A. N., & Kalaria, R. N. (2021). The role of the medial prefrontal cortex in cognition, ageing and dementia. *Brain Communications*, *3*(3). https://doi.org/10.1093/BRAINCOMMS/FCAB125

Johanson, C. E., & Uhlenhuth, E. H. (1981). Drug preference and mood in humans: Repeated assessment of d-amphetamine. *Pharmacology, Biochemistry and Behavior*, *14*(2), 159–163. https://doi.org/10.1016/0091-3057(81)90237-9

Kehagia, A. A., Barker, R. A., & Robbins, T. W. (2010). Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *The Lancet Neurology*, *9*(12), 1200–1213. https://doi.org/10.1016/S1474-4422(10)70212-X

Kehagia, A. A., Housden, C. R., Regenthal, R., Barker, R. A., Müller, U., Rowe, J., Sahakian, B. J., & Robbins, T. W. (2014). Targeting impulsivity in Parkinson's disease using atomoxetine. *Brain : A Journal of Neurology*, *137*(Pt 7), 1986–1997. https://doi.org/10.1093/brain/awu117

Kelly, B. C., Parsons, J. T., & Wells, B. E. (2006). Prevalence and predictors of club drug use among club-going young adults in New York City. *Journal of Urban Health*, *83*(5), 884–895. https://doi.org/10.1007/s11524-006-9057-2

Kelly, R. M., & Strick, P. L. (2003). *Behavioral/Systems/Cognitive Cerebellar Loops with Motor Cortex and Prefrontal Cortex of a Nonhuman Primate*.

Kim, B., Yoon, S., Nakajima, R., Lee, H. J., Lim, H. J., Lee, Y.-K., Choi, J.-S., Yoon, B.-J., Augustine, G. J., Baik, J.-H., Designed, J.-H. B., Lee, H. J., Lim, H. J., Performed, J.-H. B., & Contributed, B.-J. Y. (2018). *Dopamine D2 receptor-mediated circuit from the central amygdala to the bed nucleus of the stria terminalis regulates impulsive behavior*. https://doi.org/10.1073/pnas.1811664115

Kim, J. H., Kim, T. H., Choi, Y. C., Chung, S. C., & Moon, S. W. (2013). Impulsive behavior and recurrent major depression associated with dandy-walker variant. *Psychiatry Investigation*, *10*(3), 303–305. https://doi.org/10.4306/pi.2013.10.3.303

King, J. A., Tenney, J., Rossi, V., Colamussi, L., & Burdick, S. (2003). Neural substrates underlying impulsivity. *Annals of the New York Academy of Sciences*, *1008*(1), 160–169. https://doi.org/10.1196/annals.1301.017

Kirkpatrick, M. G., Goldenson, N. I., Kapadia, N., Kahler, C. W., de Wit, H., Swift, R. M., McGeary, J. E., Sussman, S., & Leventhal, A. M. (2016). Emotional traits predict individual differences in amphetamine-induced positive mood in healthy volunteers. *Psychopharmacology*, *233*(1), 89–97. https://doi.org/10.1007/s00213-015-4091-y

Kish, S. J., El-Awar, M., Schut, L., Leach, L., Oscar-Berman, M., & Freedman, M. (1988). Cognitive deficits in olivopontocerebellar atrophy: Implications for the cholinergic hypothesis of Alzheimer's dementia. *Annals of Neurology*, *24*(2), 200–206. https://doi.org/10.1002/ana.410240205

Kitzman, P. H., & Bishop, G. A. (1994). The origin of serotoninergic afferents to the cat's cerebellar nuclei. *The Journal of Comparative Neurology*, *340*(4), 541–550. https://doi.org/10.1002/cne.903400407

Klomp, A., Koolschijn, P. C. M. P., Hulshoff Pol, H. E., Kahn, R. S., & Haren, N. E. M. Van. (2012). Hypothalamus and pituitary volume in schizophrenia: a structural MRI study. *The International Journal of Neuropsychopharmacology*, *15*(2), 281–288. https://doi.org/10.1017/S1461145711000794

Knoepfel, H. K., & Macken, J. (1947). Psycho-organic syndrome in heredotaxis. *Journal Belge de Neurologie et de Psychiatrie*, *47*(5), 314–323. http://www.ncbi.nlm.nih.gov/pubmed/20269896

Koh, J., Kaneoke, Y., Donishi, T., Ishida, T., Sakata, M., Hiwatani, Y., Nakayama, Y., Yasui, M., Ishiguchi, H., Hironishi, M., Murata, K. ya, Terada, M., & Ito, H. (2020). Increased large-scale inter-network connectivity in relation to impulsivity in Parkinson's disease. *Scientific Reports*, *10*(1), 11418. https://doi.org/10.1038/s41598-020-68266-x

Koller, W. C., & Rubino, F. A. (1985). Combined resting-postural tremors. *Archives of Neurology*, *42*(7), 683–684. https://doi.org/10.1001/archneur.1985.04060070073019

Kon, T., Tomiyama, M., & Wakabayashi, K. (2020). Neuropathology of Lewy body disease: Clinicopathological crosstalk between typical and atypical cases. *Neuropathology*, *40*(1), 30–39. https://doi.org/10.1111/neup.12597

Kon, T., Ueno, T., Haga, R., & Tomiyama, M. (2018). The factors associated with impulse control behaviors in Parkinson's disease: A 2-year longitudinal retrospective cohort study. *Brain and Behavior*, *8*(8), 1–11. https://doi.org/10.1002/brb3.1036

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8

Korponay, C., Dentico, D., Kral, T., Ly, M., Kruis, A., Goldman, R., Lutz, A., & Davidson, R. J. (2017). Neurobiological correlates of impulsivity in healthy adults: Lower prefrontal gray matter volume and spontaneous eye-blink rate but greater resting-state functional connectivity in basal ganglia-thalamo-cortical circuitry. *NeuroImage*, *157*, 288–296. https://doi.org/10.1016/j.neuroimage.2017.06.015

Korponay, C., & Koenigs, M. (2021). Gray matter correlates of impulsivity in psychopathy and in the general population differ by kind, not by degree: A comparison of systematic reviews. *Social Cognitive and Affective Neuroscience*, *16*(7), 683–695. https://doi.org/10.1093/scan/nsab045

Krienen, F. M., & Buckner, R. L. (2009). Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. *Cerebral Cortex*, *19*(10), 2485–2497. https://doi.org/10.1093/cercor/bhp135

Kubera, K. M., Schmitgen, M. M., Nagel, S., Hess, K., Herweh, C., Hirjak, D., Sambataro, F., & Wolf, R. C. (2019). A search for cortical correlates of trait impulsivity in Parkinson´s disease. *Behavioural Brain Research*, *369*, 111911. https://doi.org/10.1016/J.BBR.2019.111911

Kumar, A., Sundaram, S. K., Sivaswamy, L., Behen, M. E., Makki, M. I., Ager, J., Janisse, J., Chugani, H. T., & Chugani, D. C. (2010). Alterations in frontal lobe tracts and corpus callosum in young children with autism spectrum disorder. *Cerebral Cortex (New York, N.Y. : 1991)*, *20*(9), 2103–2113. https://doi.org/10.1093/cercor/bhp278

Kunwar, P. S., Zelikowsky, M., Remedios, R., Cai, H., Yilmaz, M., Meister, M., & Anderson, D. J. (2015). Ventromedial hypothalamic neurons control a defensive emotion state. *ELife*, *2015*(4). https://doi.org/10.7554/ELIFE.06633

Lammertsma, A. A., & Hume, S. P. (1996). Simplified reference tissue model for PET receptor studies. *NeuroImage*, *4*(3 Pt 1), 153–158. https://doi.org/10.1006/nimg.1996.0066

Lansdall, C. J., Coyle-Gilchrist, I. T. S., Jones, P. S., Rodríguez, P. V., Wilcox, A., Wehmann, E., Dick, K. M., Robbins, T. W., & Rowe, J. B. (2017). Apathy and impulsivity in frontotemporal lobar degeneration syndromes. *Brain*, *140*(6), 1792–1807. https://doi.org/10.1093/brain/awx101

Laruelle, M. (2000). Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *20*(3), 423–451. https://doi.org/10.1097/00004647-200003000-00001

Lee, A. K. W., Jerram, M., Fulwiler, C., & Gansler, D. A. (2011). Neural correlates of impulsivity factors in psychiatric patients and healthy volunteers: A voxel-based morphometry study. *Brain Imaging and Behavior*, *5*(1), 52–64. https://doi.org/10.1007/s11682-010-9112-1

Lee, J.-Y., Seo, S. H., & Kim, Y. K. (2014). Extrastriatal dopaminergic changes in Parkinson's disease patients with impulse control disorders. *J Neurol Neurosurg Psychiatry*, *85*, 23–30. https://doi.org/10.1136/jnnp-2013-305549

Lee, S. M., Kim, M., Lee, H. M., Kwon, K. Y., & Koh, S. B. (2015). Nonmotor symptoms in essential tremor: Comparison with Parkinson's disease and normal control. *Journal of the Neurological Sciences*, *349*(1–2), 168–173. https://doi.org/10.1016/j.jns.2015.01.012

Leiner, H C, Leiner, A. L., & Dow, R. S. (1993). Cognitive and language functions of the human cerebellum. *Trends in Neurosciences*, *16*(11), 444–447. https://doi.org/10.1016/0166-2236(93)90072-t

Leiner, Henrietta C., Leiner, A. L., & Dow, R. S. (1986). Does the cerebellum contribute to mental skills? *Behavioral Neuroscience*, *100*(4), 443–454. https://doi.org/10.1037//0735-7044.100.4.443

Levisohn, L., Cronin-Golomb, A., & Schmahmann, J. D. (2000). Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain : A Journal of Neurology*, *123 (Pt 5*, 1041–1050. https://doi.org/10.1093/brain/123.5.1041

Lezak, M. D. (1982). The Problem of Assessing Executive Functions. *International Journal of Psychology*, *17*(1–4), 281–297. https://doi.org/10.1080/00207598208247445

Likova, L. T., Mineff, K. N., & Nicholas, S. C. (2021). Mental Visualization in the Cerebellum: Rapid Non-motor Learning at Sub-Lobular and Causal Network Levels. *Frontiers in Systems*

Neuroscience, *15*. https://doi.org/10.3389/fnsys.2021.655514
Locke, T. M., Fujita, H., Hunker, A., Johanson, S. S., Darvas, M., du Lac, S., Zweifel, L. S., & Carlson, E. S. (2020). Purkinje Cell-Specific Knockout of Tyrosine Hydroxylase Impairs Cognitive Behaviors. *Frontiers in Cellular Neuroscience*, *14*, 228. https://doi.org/10.3389/fncel.2020.00228
Locke, T. M., Soden, M. E., Miller, S. M., Hunker, A., Knakal, C., Licholai, J. A., Dhillon, K. S., Keene, C. D., Zweifel, L. S., & Carlson, E. S. (2018). Dopamine D1 Receptor–Positive Neurons in the Lateral Nucleus of the Cerebellum Contribute to Cognitive Behavior. *Biological Psychiatry*, *84*(6), 401–412. https://doi.org/10.1016/j.biopsych.2018.01.019
Logemann, H. N. A., Lansbergen, M. M., Van Os, T. W. D. P., Böcker, K. B. E., & Kenemans, J. L. (2010). The effectiveness of EEG-feedback on attention, impulsivity and EEG: A sham feedback controlled study. *Neuroscience Letters*, *479*(1), 49–53. https://doi.org/10.1016/j.neulet.2010.05.026
Lombardi, W. J., Woolston, D. J., Roberts, J. W., & Gross, R. E. (2001). Cognitive deficits in patients with essential tremor. *Neurology*, *57*(5), 785–790. https://doi.org/10.1212/wnl.57.5.785
Louis, E D, Benito-León, J., & Bermejo-Pareja, F. (2007). Self-reported depression and anti-depressant medication use in essential tremor: cross-sectional and prospective analyses in a population-based study. *European Journal of Neurology*, *14*(10), 1138–1146. https://doi.org/10.1111/j.1468-1331.2007.01923.x
Louis, Elan D. (2009). Essential tremors: A family of neurodegenerative disorders? *Archives of Neurology*, *66*(10), 1202–1208. https://doi.org/10.1001/ARCHNEUROL.2009.217
Louis, Elan D. (2010). Essential tremor as a neuropsychiatric disorder. *Journal of the Neurological Sciences*, *289*(1–2), 144–148. https://doi.org/10.1016/j.jns.2009.08.029
Louis, Elan D. (2016). Non-motor symptoms in essential tremor: A review of the current data and state of the field. *Parkinsonism & Related Disorders*, *22 Suppl 1*, S115-8. https://doi.org/10.1016/j.parkreldis.2015.08.034
Louis, Elan D., Barnes, L., Albert, S. M., Cote, L., Schneier, F. R., Pulman, S. L., & Yu, Q. (2001). Correlates of functional disability in essential tremor. *Movement Disorders*, *16*(5), 914–920. https://doi.org/10.1002/mds.1184
Louis, Elan D., & Faust, P. L. (2020). Essential tremor: The most common form of cerebellar degeneration? *Cerebellum and Ataxias*, *7*(1), 1–10. https://doi.org/10.1186/s40673-020-00121-1
Louis, Elan D., Ford, B., Frucht, S., Barnes, L. F., X-Tang, M., & Ottman, R. (2001). Risk of tremor and impairment from tremor in relatives of patients with essential tremor: A community-based family study. *Annals of Neurology*, *49*(6), 761–769. https://doi.org/10.1002/ana.1022
Louis, Elan D., Huey, E. D., Gerbin, M., & Viner, A. S. (2012). Apathy in essential tremor, dystonia, and Parkinson's disease: a comparison with normal controls. *Movement Disorders : Official Journal of the Movement Disorder Society*, *27*(3), 432–434. https://doi.org/10.1002/mds.24049
Louis, Elan D., Ottman, R., Ford, B., Pullman, S., Martinez, M., Fahrt, S., & Hauser, W. A. (1997). The Washington Heights-Inwood Genetic Study of Essential Tremor: Methodologic Issues in Essential-Tremor Research. *Neuroepidemiology*, *16*(3), 124–133. https://doi.org/10.1159/000109681
Louis, Elan D., & Vonsattel, J. P. G. (2008). The emerging neuropathology of essential tremor. *Movement Disorders*, *23*(2), 174–182. https://doi.org/10.1002/mds.21731
Louis, Elan D, Ford, B., & Frucht, S. (2003). Factors associated with increased risk of head tremor in essential tremor: a community-based study in northern Manhattan. *Movement Disorders : Official Journal of the Movement Disorder Society*, *18*(4), 432–436.

https://doi.org/10.1002/mds.10395
Louis, Elan D, Marder, K., Cote, L., Pullman, S., Ford, B., Wilder, D., Tang, M.-X., Lantigua, R., Gurland, B., & Mayeux, R. (1995). Differences in the Prevalence of Essential Tremor Among Elderly African Americans, Whites, and Hispanics in Northern Manhattan, NY. *Archives of Neurology*, *52*(12), 1201–1205. https://doi.org/10.1001/archneur.1995.00540360079019
Luis, C. A., Keegan, A. P., & Mullan, M. (2009). Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. *International Journal of Geriatric Psychiatry*. https://doi.org/10.1002/gps.2101
Mack, J., Okai, D., Brown, R. G., Askey-Jones, S., Chaudhuri, K. R., Martin, A., Samuel, M., & David, A. S. (2013). The Role of Self-Awareness and Cognitive Dysfunction in Parkinson's Disease With and Without Impulse-Control Disorder. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *25*(2), 141–149. https://doi.org/10.1176/appi.neuropsych.12030076
MacLeod, C. M. (1991). Half a century of reseach on the stroop effect: An integrative review. *Psychological Bulletin*. https://doi.org/10.1037/0033-2909.109.2.163
Maidan, I., Jacob, Y., Giladi, N., Hausdorff, J. M., & Mirelman, A. (2019). Altered organization of the dorsal attention network is associated with freezing of gait in Parkinson's disease. *Parkinsonism & Related Disorders*. https://doi.org/10.1016/J.PARKRELDIS.2019.02.036
Malek-Ahmadi, M., Powell, J. J., Belden, C. M., O'Connor, K., Evans, L., Coon, D. W., & Nieri, W. (2015). Age- and education-adjusted normative data for the Montreal Cognitive Assessment (MoCA) in older adults age 70–99. *Aging, Neuropsychology, and Cognition*, *22*(6), 755–761. https://doi.org/10.1080/13825585.2015.1041449
Malloy, P., & Grace, J. (2005). A review of rating scales for measuring behavior change due to frontal systems damage. *Cognitive and Behavioral Neurology*, *18*(1), 18–27. http://www.ncbi.nlm.nih.gov/pubmed/15761273
Mann, L. G., Hay, K. R., Song, A. K., Errington, S. P., Trujillo, P., Zald, D. H., Yan, Y., Kang, H., Logan, G. D., & Claassen, D. O. (2021). D 2 -Like Receptor Expression in the Hippocampus and Amygdala Informs Performance on the Stop-Signal Task in Parkinson's Disease. *The Journal of Neuroscience*, *41*(48), 10023–10030. https://doi.org/10.1523/JNEUROSCI.0968-21.2021
Maréchal, E., Denoiseux, B., Thys, E., Crosiers, D., Pickut, B., & Cras, P. (2015). Impulse control disorders in Parkinson's disease: An overview from neurobiology to treatment. *Journal of Neurology*, *262*(1), 7–20. https://doi.org/10.1007/s00415-014-7361-4
Marín-Lahoz, J., Martínez-Horta, S., Sampedro, F., Pagonabarraga, J., Horta-Barba, A., Bejr-kasem, H., Botí, M., Fernández-Bobadilla, R., Pascual-Sedano, B., Pérez-Pérez, J., Aracil-Bolaños, I., Gironell, A., Gómez-Ansón, B., & Kulisevsky, J. (2020). Measuring impulsivity in Parkinson's disease: a correlational and structural neuroimaging study using different tests. *European Journal of Neurology*, *27*(8), 1478–1486. https://doi.org/10.1111/ene.14235
Marín-Lahoz, Juan, Pagonabarraga, J., Martinez-Horta, S., Fernandez de Bobadilla, R., Pascual-Sedano, B., Pérez-Pérez, J., Gironell, A., & Kulisevsky, J. (2018). Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. *Frontiers in Psychiatry*, *9*, 465. https://doi.org/10.3389/fpsyt.2018.00465
Martínez-Martín, P., Gil-Nagel, A., Gracia, L. M., Gómez, J. B., Martínez-Sarriés, J., & Bermejo, F. (1994). Unified Parkinson's disease rating scale characteristics and structure. *Movement Disorders*. https://doi.org/10.1002/mds.870090112
McHugh, M. J., Demers, C. H., Braud, J., Briggs, R., Adinoff, B., & Stein, E. A. (2013). Striatal-insula circuits in cocaine addiction: implications for impulsivity and relapse risk. *The American Journal of Drug and Alcohol Abuse*, *39*(6), 424–432. https://doi.org/10.3109/00952990.2013.847446
Meda, S. A., Stevens, M. C., Potenza, M. N., Pittman, B., Gueorguieva, R., Andrews, M. M., Thomas, A. D., Muska, C., Hylton, J. L., & Pearlson, G. D. (2009). Investigating the

behavioral and self-report constructs of impulsivity domains using principal component analysis. *Behavioural Pharmacology*, *20*(5–6), 390–399. https://doi.org/10.1097/FBP.0b013e32833113a3

Menza, M. A., Golbe, L. I., Cody, R. A., & Forman, N. E. (1993). Dopamine-related personality traits in Parkinson's disease. *Neurology*, *43*(3 Pt 1), 505–508. https://doi.org/10.1212/wnl.43.3_part_1.505

Menza, M. A., Sage, J., Marshall, E., Cody, R., & Duvoisin, R. (1990). Mood changes and "on-off" phenomena in Parkinson's disease. *Movement Disorders*, *5*(2), 148–151. https://doi.org/10.1002/mds.870050210

Mergenthaler, P., Lindauer, U., Dienel, G. A., & Meisel, A. (2013). Sugar for the brain: The role of glucose in physiological and pathological brain function. *Trends in Neurosciences*, *36*(10), 587–597. https://doi.org/10.1016/j.tins.2013.07.001

Mestre, T. A., Strafella, A. P., Thomsen, T., Voon, V., & Miyasaki, J. (2013). Diagnosis and treatment of impulse control disorders in patients with movement disorders. *Therapeutic Advances in Neurological Disorders*, *6*(3), 175–188. https://doi.org/10.1177/1756285613476127

Middleton, F. A., & Srrick, P. L. (1997). Cerebellar output channels. In *International Review of Neurobiology* (Vol. 41). ACADEMIC PRESS. https://doi.org/10.1016/s0074-7742(08)60347-5

Middleton, F. A., & Strick, P. L. (1998). The cerebellum: an overview. *Trends in Neurosciences*, *21*(9), 367–369. https://doi.org/10.1016/s0166-2236(98)01330-7

Middleton, F. A., & Strick, P. L. (2000). Basal ganglia and cerebellar loops: Motor and cognitive circuits. *Brain Research Reviews*, *31*(2–3), 236–250. https://doi.org/10.1016/S0165-0173(99)00040-5

Mikhailova, M. A., Bass, C. E., Grinevich, V. P., Chappell, A. M., Deal, A. L., Bonin, K. D., Weiner, J. L., Gainetdinov, R. R., & Budygin, E. A. (2016). Optogenetically-induced tonic dopamine release from VTA-nucleus accumbens projections inhibits reward consummatory behaviors. *Neuroscience*, *333*, 54–64. https://doi.org/10.1016/j.neuroscience.2016.07.006

Milardi, D., Quartarone, A., Bramanti, A., Anastasi, G., Bertino, S., Basile, G. A., Buonasera, P., Pilone, G., Celeste, G., Rizzo, G., Bruschetta, D., & Cacciola, A. (2019). The Cortico-Basal Ganglia-Cerebellar Network: Past, Present and Future Perspectives. *Frontiers in Systems Neuroscience*, *13*(October), 1–14. https://doi.org/10.3389/fnsys.2019.00061

Miquel, M., Nicola, S. M., Gil-Miravet, I., Guarque-Chabrera, J., & Sanchez-Hernandez, A. (2019). A working hypothesis for the role of the cerebellum in impulsivity and compulsivity. *Frontiers in Behavioral Neuroscience*, *13*(May), 1–14. https://doi.org/10.3389/fnbeh.2019.00099

Miquel, M., Vazquez-Sanroman, D., Carbo-Gas, M., Gil-Miravet, I., Sanchis-Segura, C., Carulli, D., Manzo, J., & Coria-Avila, G. A. (2016). Have we been ignoring the elephant in the room? Seven arguments for considering the cerebellum as part of addiction circuitry. *Neuroscience and Biobehavioral Reviews*, *60*, 1–11. https://doi.org/10.1016/j.neubiorev.2015.11.005

Mischel, W., Shoda, Y., & Rodriguez, M. I. (1989). Delay of gratification in children. *Science (New York, N.Y.)*, *244*(4907), 933–938. https://doi.org/10.1126/science.2658056

Mittleman, G., Goldowitz, D., Heck, D. H., & Blaha, C. D. (2008). Cerebellar modulation of frontal cortex dopamine efflux in mice: relevance to autism and schizophrenia. *Synapse (New York, N.Y.)*, *62*(7), 544–550. https://doi.org/10.1002/syn.20525

Moeller, F. G., Barratt, E. S., Dougherty, D. M., Schmitz, J. M., & Swann, A. C. (2001). Psychiatric aspects of impulsivity. *The American Journal of Psychiatry*, *158*(11), 1783–1793. https://doi.org/10.1176/appi.ajp.158.11.1783

Moers-Hornikx, V. M. P., Sesia, T., Basar, K., Lim, L. W., Hoogland, G., Steinbusch, H. W. M., Gavilanes, D. A. W. D., Temel, Y., & Vles, J. S. H. (2009). Cerebellar nuclei are involved in

impulsive behaviour. *Behavioural Brain Research*, *203*(2), 256–263. https://doi.org/10.1016/j.bbr.2009.05.011
Moises, H. C., Waterhouse, B. D., & Woodward, D. J. (1983). Locus coeruleus stimulation potentiates local inhibitory processes in rat cerebellum. *Brain Research Bulletin*, *10*(6), 795–804. https://doi.org/10.1016/0361-9230(83)90211-3
Molinari, M., Leggio, M. G., Solida, A., Ciorra, R., Misciagna, S., Silveri, M. C., & Petrosini, L. (1997). Cerebellum and procedural learning: evidence from focal cerebellar lesions. *Brain : A Journal of Neurology*, *120 (Pt 1*, 1753–1762. https://doi.org/10.1093/brain/120.10.1753
Montgomery, A. J., Lingford-Hughes, A. R., Egerton, A., Nutt, D. J., & Grasby, P. M. (2007). The effect of nicotine on striatal dopamine release in man: A [11C]raclopride PET study. *Synapse (New York, N.Y.)*, *61*(8), 637–645. https://doi.org/10.1002/syn.20419
Morean, M. E., de Wit, H., King, A. C., Sofuoglu, M., Rueger, S. Y., & O'Malley, S. S. (2013). The drug effects questionnaire: psychometric support across three drug types. *Psychopharmacology*, *227*(1), 177–192. https://doi.org/10.1007/s00213-012-2954-z
Morens, D. M., Davis, J. W., Grandinetti, A., Ross, G. W., Popper, J. S., & White, L. R. (1996). Epidemiologic observations on Parkinson's disease: Incidence and mortality in a prospective study of middle-aged men. *Neurology*, *46*(4), 1044–1050. https://doi.org/10.1212/WNL.46.4.1044
Moulton, E. A., Elman, I., Becerra, L. R., Goldstein, R. Z., & Borsook, D. (2014). The cerebellum and addiction: Insights gained from neuroimaging research. *Addiction Biology*, *19*(3), 317–331. https://doi.org/10.1111/adb.12101
Mukherjee, J, Yang, Z. Y., Brown, T., Lew, R., Wernick, M., Ouyang, X., Yasillo, N., Chen, C. T., Mintzer, R., & Cooper, M. (1999). Preliminary assessment of extrastriatal dopamine D-2 receptor binding in the rodent and nonhuman primate brains using the high affinity radioligand, 18F-fallypride. *Nuclear Medicine and Biology*, *26*(5), 519–527. https://doi.org/10.1016/s0969-8051(99)00012-8
Mukherjee, Jogeshwar, Christian, B. T., Narayanan, T. K., Shi, B., & Collins, D. (2005). Measurement of d-amphetamine-induced effects on the binding of dopamine D-2/D-3 receptor radioligand, 18F-fallypride in extrastriatal brain regions in non-human primates using PET. *Brain Research*, *1032*(1–2), 77–84. https://doi.org/10.1016/j.brainres.2004.11.005
Murray, E. A., & Izquierdo, A. (2007). Orbitofrontal cortex and amygdala contributions to affect and action in primates. *Annals of the New York Academy of Sciences*, *1121*, 273–296. https://doi.org/10.1196/annals.1401.021
Musacchio, T., Purrer, V., Papagianni, A., Fleischer, A., Mackenrodt, D., Malsch, C., Gelbrich, G., Steigerwald, F., Volkmann, J., & Klebe, S. (2016). Non-motor symptoms of essential tremor are independent of tremor severity and have an impact on quality of life. *Tremor and Other Hyperkinetic Movements*, *2016*, 1–9. https://doi.org/10.7916/D8542NCH
Nazem, S., Siderowf, A. D., Duda, J. E., Have, T. Ten, Colcher, A., Horn, S. S., Moberg, P. J., Wilkinson, J. R., Hurtig, H. I., Stern, M. B., & Weintraub, D. (2009). Montreal cognitive assessment performance in patients with Parkinson's disease with "normal" global cognition according to mini-mental state examination score. *Journal of the American Geriatrics Society*, *57*(2), 304–308. https://doi.org/10.1111/j.1532-5415.2008.02096.x
Nelson, T. E., King, J. S., & Bishop, G. A. (1997). Distribution of tyrosine hydroxylase-immunoreactive afferents to the cerebellum differs between species. *Journal of Comparative Neurology*, *379*(3), 443–454. https://doi.org/10.1002/(SICI)1096-9861(19970317)379:3<443::AID-CNE9>3.0.CO;2-3
Neve, K. A. (Ed.). (2010). *The Dopamine Receptors*. Humana Press. https://doi.org/10.1007/978-1-60327-333-6
Nieoullon, A., Cheramy, A., & Glowinski, J. (1977). Nigral and striatal dopamine release under sensory stimuli. *Nature*, *269*(5626), 340–342. https://doi.org/10.1038/269340a0

Nieoullon, André. (2002). Dopamine and the regulation of cognition and attention. *Progress in Neurobiology*, *67*(1), 53–83. https://doi.org/10.1016/s0301-0082(02)00011-4
Nombela, C., Rittman, T., Robbins, T. W., & Rowe, J. B. (2014). Multiple Modes of Impulsivity in Parkinson's Disease. *PLoS ONE*, *9*(1), e85747. https://doi.org/10.1371/journal.pone.0085747
Nomura, Y., Asano, Y., Shinoda, J., Yano, H., Ikegame, Y., Kawasaki, T., Nakayama, N., Maruyama, T., Muragaki, Y., & Iwama, T. (2018). Characteristics of time-activity curves obtained from dynamic 11 C-methionine PET in common primary brain tumors. *Journal of Neuro-Oncology*, *138*(3), 649–658. https://doi.org/10.1007/s11060-018-2834-4
O'Callaghan, C., & Lewis, S. J. G. (2017a). Cognition in Parkinson's Disease. In *International Review of Neurobiology*. https://doi.org/10.1016/bs.irn.2017.05.002
O'Callaghan, C., & Lewis, S. J. G. (2017b). Cognition in Parkinson's Disease. *International Review of Neurobiology*, *133*, 557–583. https://doi.org/10.1016/BS.IRN.2017.05.002
O'Doherty, J. P. (2004). Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Current Opinion in Neurobiology*, *14*(6), 769–776. https://doi.org/10.1016/j.conb.2004.10.016
O'Donnell, P., & Grace, A. A. (1995). Synaptic interactions among excitatory afferents to nucleus accumbens neurons: Hippocampal gating of prefrontal cortical input. *Journal of Neuroscience*, *15*(5 I), 3622–3639. https://doi.org/10.1523/jneurosci.15-05-03622.1995
O'Reilly, J. X., Beckmann, C. F., Tomassini, V., Ramnani, N., & Johansen-Berg, H. (2010). Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. *Cerebral Cortex*, *20*(4), 953–965. https://doi.org/10.1093/cercor/bhp157
O'Sullivan, S. S., Wu, K., Politis, M., Lawrence, A. D., Evans, A. H., Bose, S. K., Djamshidian, A., Lees, A. J., & Piccini, P. (2011). Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. *Brain*, *134*(4), 969–978. https://doi.org/10.1093/brain/awr003
Olsson, H., Halldin, C., & Farde, L. (2004). Differentiation of extrastriatal dopamine D2 receptor density and affinity in the human brain using PET. *NeuroImage*, *22*(2), 794–803. https://doi.org/10.1016/j.neuroimage.2004.02.002
Ongür, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex (New York, N.Y. : 1991)*, *10*(3), 206–219. https://doi.org/10.1093/cercor/10.3.206
Palmen, S. J. M. C., van Engeland, H., Hof, P. R., & Schmitz, C. (2004). Neuropathological findings in autism. *Brain : A Journal of Neurology*, *127*(Pt 12), 2572–2583. https://doi.org/10.1093/brain/awh287
Park, A., & Stacy, M. (2011). Dopamine-induced nonmotor symptoms of Parkinson's disease. *Parkinson's Disease*, *2011*, 485063. https://doi.org/10.4061/2011/485063
Parkinson, J. (2002). An essay on the shaking palsy. 1817. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *14*(2), 223–236; discussion 222. https://doi.org/10.1176/jnp.14.2.223
Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor Structure of the Barratt Impulsiveness Scale. *Journal of Clinical Psychology*, *51*(6), 768–774. http://homepages.se.edu/cvonbergen/files/2013/01/Factor-Structure-of-the-Barratt-Impulsiveness-Scale.pdf
Pauling, L., & Coryell, C. D. (1936). The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin. *Proceedings of the National Academy of Sciences*, *22*(4), 210–216. https://doi.org/10.1073/pnas.22.4.210
Petersen, K., Van Wouwe, N., Stark, A., Lin, Y.-C., Kang, H., Trujillo-Diaz, P., Kessler, R., Zald, D., Donahue, M. J., & Claassen, D. O. (2018). Ventral striatal network connectivity reflects reward learning and behavior in patients with Parkinson's disease. *Human Brain Mapping*, *39*(1), 509–521. https://doi.org/10.1002/hbm.23860
Petitet, P., Scholl, J., Attaallah, B., Drew, D., Manohar, S., & Husain, M. (2021). The relationship

between apathy and impulsivity in large population samples. *Scientific Reports*, *11*(1). https://doi.org/10.1038/S41598-021-84364-W

Piao, Y. S., Wakabayashi, K., Kakita, A., Yamada, M., Hayashi, S., Morita, T., Ikuta, F., Oyanagi, K., & Takahashi, H. (2003). Neuropathology with clinical correlations of sporadic amyotrophic lateral sclerosis: 102 Autopsy cases examined between 1962 and 2000. *Brain Pathology*, *13*(1), 10–22. https://doi.org/10.1111/j.1750-3639.2003.tb00002.x

Pierce, J. E., & Péron, J. (2020). The basal ganglia and the cerebellum in human emotion. *Social Cognitive and Affective Neuroscience*, *15*(5), 599–613. https://doi.org/10.1093/scan/nsaa076

Piercey, M. F. (1998). Pharmacology of pramipexole, a dopamine D3-preferring agonist useful in treating Parkinson's disease. In *Clinical Neuropharmacology*.

Pillon, B., Czernecki, V., & Dubois, B. (2003). Dopamine and cognitive function. In *Current Opinion in Neurology*. https://doi.org/10.1097/00019052-200312002-00004

Plichta, M. M., & Scheres, A. (2014). Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: A meta-analytic review of the fMRI literature. *Neuroscience and Biobehavioral Reviews*, *38*, 125–134. https://doi.org/10.1016/j.neubiorev.2013.07.012

Poewe, W. (2008). Non-motor symptoms in Parkinson's disease. *European Journal of Neurology*, *15 Suppl 1*(May), 14–20. https://doi.org/10.1111/j.1468-1331.2008.02056.x

Poewe, Werner, & Mahlknecht, P. (2009a). The clinical progression of Parkinson's disease. *Parkinsonism & Related Disorders*, *15 Suppl 4*, S28-32. https://doi.org/10.1016/S1353-8020(09)70831-4

Poewe, Werner, & Mahlknecht, P. (2009b). The clinical progression of Parkinson's disease. *Parkinsonism & Related Disorders*, *15*, S28–S32. https://doi.org/10.1016/S1353-8020(09)70831-4

Poewe, Werner, Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A. E., & Lang, A. E. (2017). Parkinson disease. *Nature Reviews Disease Primers*, *3*, 1–21. https://doi.org/10.1038/nrdp.2017.13

Probst, C. C., & van Eimeren, T. (2013). The functional anatomy of impulse control disorders. *Current Neurology and Neuroscience Reports*, *13*(10), 386. https://doi.org/10.1007/s11910-013-0386-8

Purves, D., Augustine, G. J., Fitzpatrick, D., Hall, W. C., LaMantia, A.-S., Mooney, R. D., Platt, M. L., & White, L. E. (2018). *Neuroscience* (6th ed.). Oxford Univeristy Press.

R Development Core Team. (2018). R: A language and environment for statistical computing. In *Vienna, Austria*. https://doi.org/R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.

Rajput, A. H., Adler, C. H., Shill, H. A., & Rajput, A. (2012). Essential tremor is not a neurodegenerative disease. *Neurodegenerative Disease Management*, *2*(3), 259–268. https://doi.org/10.2217/nmt.12.23

Rao, H., Mamikonyan, E., Detre, J. A., Siderowf, A. D., Stern, M. B., Potenza, M. N., & Weintraub, D. (2010). Decreased ventral striatal activity with impulse control disorders in Parkinson's Disease. *Movement Disorders*, *25*(11), 1660–1669. https://doi.org/10.1002/mds.23147

Rapoport, M., van Reekum, R., & Mayberg, H. (2000). The Role of the Cerebellum in Cognition and Behavior. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*(2), 193–198. https://doi.org/10.1176/jnp.12.2.193

Rautakorpi, I., Takala, J., Marttila, R. J., Sievers, K., & Rinne, U. K. (1982). Essential tremor in a Finnish population. *Acta Neurologica Scandinavica*, *66*(1), 58–67. https://doi.org/10.1111/j.1600-0404.1982.tb03129.x

Reise, S. P., Moore, T. M., Sabb, F. W., Brown, A. K., London, E. D., & Reise, S. (2013). The Barratt Impulsiveness Scale-11: Reassessment of its Structure in a Community Sample.

Psychol Assess, *25*(2), 631–642. https://doi.org/10.1037/a0032161
Rempel-Clower, N. L. (2007). Role of orbitofrontal cortex connections in emotion. *Annals of the New York Academy of Sciences*, *1121*, 72–86. https://doi.org/10.1196/annals.1401.026
Riccardi, P., Li, R., Ansari, M. S., Zald, D., Park, S., Dawant, B., Anderson, S., Doop, M., Woodward, N., Schoenberg, E., Schmidt, D., Baldwin, R., & Kessler, R. (2006). Amphetamine-induced displacement of [18F] fallypride in striatum and extrastriatal regions in humans. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *31*(5), 1016–1026. https://doi.org/10.1038/sj.npp.1300916
Riccardi, P., Park, S., Anderson, S., Doop, M., Ansari, M. S., Schmidt, D., & Baldwin, R. (2011). Sex differences in the relationship of regional dopamine release to affect and cognitive function in striatal and extrastriatal regions using positron emission tomography and [^{18}F]fallypride. *Synapse*, *65*(2), 99–102. https://doi.org/10.1002/syn.20822
Rice, M. E., Patel, J. C., & Cragg, S. J. (2011). Dopamine release in the basal ganglia. *Neuroscience*, *198*, 112–137. https://doi.org/10.1016/j.neuroscience.2011.08.066
Robert Cloninger, C. (2013). A systematic method for clinical description and classification of personality variants. *The Science of Mental Health: Volume 7: Personality and Personality Disorder*, 1–16.
Rodriguez-Jimenez, R., Avila, C., Jimenez-Arriero, M. A., Ponce, G., Monasor, R., Jimenez, M., Aragües, M., Hoenicka, J., Rubio, G., & Palomo, T. (2006). Impulsivity and Sustained Attention in Pathological Gamblers: Influence of Childhood ADHD History. *Journal of Gambling Studies*, *22*(4), 451–461. https://doi.org/10.1007/s10899-006-9028-2
Rogers, T. D., Dickson, P. E., Heck, D. H., Goldowitz, D., Mittleman, G., & Blaha, C. D. (2011). Connecting the dots of the cerebro-cerebellar role in cognitive function: neuronal pathways for cerebellar modulation of dopamine release in the prefrontal cortex. *Synapse (New York, N.Y.)*, *65*(11), 1204–1212. https://doi.org/10.1002/syn.20960
Rogers, T. D., Dickson, P. E., McKimm, E., Heck, D. H., Goldowitz, D., Blaha, C. D., & Mittleman, G. (2013). Reorganization of circuits underlying cerebellar modulation of prefrontal cortical dopamine in mouse models of autism spectrum disorder. *Cerebellum (London, England)*, *12*(4), 547–556. https://doi.org/10.1007/s12311-013-0462-2
Rolls, E. T. (2004). The functions of the orbitofrontal cortex. *Brain and Cognition*, *55*(1), 11–29. https://doi.org/10.1016/S0278-2626(03)00277-X
Roostaei, T., Nazeri, A., Sahraian, M. A., & Minagar, A. (2014). The human cerebellum: A review of physiologic neuroanatomy. *Neurologic Clinics*, *32*(4), 859–869. https://doi.org/10.1016/j.ncl.2014.07.013
Rosazza, C., & Minati, L. (2011). Resting-state brain networks: Literature review and clinical applications. *Neurological Sciences*, *32*(5), 773–785. https://doi.org/10.1007/s10072-011-0636-y
Ruitenberg, M. F. L., Wu, T., Averbeck, B. B., Chou, K. L., Koppelmans, V., & Seidler, R. D. (2018). Impulsivity in Parkinson's Disease Is Associated With Alterations in Affective and Sensorimotor Striatal Networks. *Frontiers in Neurology*, *9*, 26. https://doi.org/10.3389/fneur.2018.00279
Russel, J. S. R. (1894). Experimental Researches into the Functions o f the. In *Experimental Researches into the Functions of the Cerebellum* (pp. 819–861). London: Kegan Paul, Trench, Trübner, and Co.
Sacheli, M. A., Neva, J. L., Lakhani, B., Murray, D. K., Vafai, N., Shahinfard, E., English, C., McCormick, S., Dinelle, K., Neilson, N., McKenzie, J., Schulzer, M., McKenzie, D. C., Appel-Cresswell, S., McKeown, M. J., Boyd, L. A., Sossi, V., & Stoessl, A. J. (2019). Exercise increases caudate dopamine release and ventral striatal activation in Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, *34*(12), 1891–1900. https://doi.org/10.1002/mds.27865

Sauvaget, A., Jiménez-Murcia, S., Fernández-Aranda, F., Granero, R., Grall-Bronnec, M., Victorri-Vigneau, C., Bulteau, S., Derkinderen, P., Vanelle, J. M., Hakansson, A., Mestre-Bach, G., Steward, T., & Menchón, J. M. (2017). A Comparison of Treatment-Seeking Behavioral Addiction Patients with and without Parkinson's Disease. *Frontiers in Psychiatry*, *8*, 3. https://doi.org/10.3389/fpsyt.2017.00214

Schmahmann, J. D. (2001). The cerebrocerebellar system: Anatomic substrates of the cerebellar contribution to cognition and emotion. *International Review of Psychiatry*, *13*(4), 247–260. https://doi.org/10.1080/09540260120082092

Schmahmann, J D, & Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain : A Journal of Neurology*, *121 (Pt 4*(4), 561–579. https://doi.org/10.1093/brain/121.4.561

Schmahmann, Jeremy D. (1991). An Emerging Concept. *Archives of Neurology*, *48*(11), 1178. https://doi.org/10.1001/archneur.1991.00530230086029

Schmahmann, Jeremy D., & Caplan, D. (2006). Cognition, emotion and the cerebellum. *Brain : A Journal of Neurology*, *129*(Pt 2), 290–292. https://doi.org/10.1093/brain/awh729

Schneier, F. R., Abi-Dargham, A., Martinez, D., Slifstein, M., Hwang, D.-R., Liebowitz, M. R., & Laruelle, M. (2009). Dopamine transporters, D2 receptors, and dopamine release in generalized social anxiety disorder. *Depression and Anxiety*, *26*(5), 411–418. https://doi.org/10.1002/da.20543

Schutter, D. J. L. G., Van Honk, J., D'Alfonso, A. A. L., Peper, J. S., & Panksepp, J. (2003). High frequency repetitive transcranial magnetic over the medial cerebellum induces a shift in the prefrontal electroencephalography gamma spectrum: A pilot study in humans. *Neuroscience Letters*, *336*(2), 73–76. https://doi.org/10.1016/S0304-3940(02)01077-7

Scott, B. M., Eisinger, R. S., Burns, M. R., Lopes, J., Okun, M. S., Gunduz, A., & Bowers, D. (2020). Co-occurrence of apathy and impulse control disorders in Parkinson disease. *Neurology*, *95*(20), e2769–e2780. https://doi.org/10.1212/WNL.0000000000010965

Sengul, Y., Sengul, H. S., Yucekaya, S. K., Yucel, S., Bakim, B., Pazarcı, N. K., & Özdemir, G. (2015). Cognitive functions, fatigue, depression, anxiety, and sleep disturbances: assessment of nonmotor features in young patients with essential tremor. *Acta Neurologica Belgica*, *115*(3), 281–287. https://doi.org/10.1007/s13760-014-0396-6

Sereno, M. I., Diedrichsen, J. rn, Tachrount, M., Testa-Silva, G., D Arceuil, H., & De Zeeuw, C. (2020). The human cerebellum has almost 80% of the surface area of the neocortex. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(32), 19538–19543. https://doi.org/10.1073/PNAS.2002896117

Sharma, L., Kohl, K., Morgan, T. A., & Clark, L. A. (2013). "Impulsivity": Relations between self-report and behavior. *Journal of Personality and Social Psychology*, *104*(3), 559–575. https://doi.org/10.1037/a0031181

Sierra, M., Carnicella, S., Strafella, A. P., Bichon, A., Lhommée, E., Castrioto, A., Chabardes, S., Thobois, S., & Krack, P. (2015). Apathy and impulse control disorders: Yin & yang of dopamine dependent behaviors. *Journal of Parkinson's Disease*, *5*(3), 625–636. https://doi.org/10.3233/JPD-150535

Sievers, J., Berry, M., & Baumgarten, H. (1981). The role of noradrenergic fibres in the control of post-natal cerebellar development. *Brain Research*, *207*(1), 200–208. https://doi.org/10.1016/0006-8993(81)90694-6

Slifstein, M., Kegeles, L. S., Xu, X., Thompson, J. L., Urban, N., Castrillon, J., Hackett, E., Bae, S.-A., Laruelle, M., & Abi-Dargham, A. (2010). Striatal and extrastriatal dopamine release measured with PET and [(18)F] fallypride. *Synapse (New York, N.Y.)*, *64*(5), 350–362. https://doi.org/10.1002/syn.20734

Smith, C. T., Dang, L. C., Cowan, R. L., Kessler, R. M., & Zald, D. H. (2016). Variability in paralimbic dopamine signaling correlates with subjective responses to d-amphetamine. *Neuropharmacology*, *108*, 394–402. https://doi.org/10.1016/j.neuropharm.2016.05.004

Smith, C. T., San Juan, M. D., Dang, L. C., Katz, D. T., Perkins, S. F., Burgess, L. L., Cowan, R. L., Manning, H. C., Nickels, M. L., Claassen, D. O., Samanez-Larkin, G. R., & Zald, D. H. (2018). Ventral striatal dopamine transporter availability is associated with lower trait motor impulsivity in healthy adults. *Translational Psychiatry*, *8*(1), 269. https://doi.org/10.1038/s41398-018-0328-y

Smith, P., Waterman, M., & Ward, N. (2006). Driving aggression in forensic and non-forensic populations: Relationships to self-reported levels of aggression, anger and impulsivity. *British Journal of Psychology*, *97*(3), 387–403. https://doi.org/10.1348/000712605X79111

Smulders, K., Esselink, R. A., Cools, R., & Bloem, B. R. (2014). Trait Impulsivity Is Associated with the Risk of Falls in Parkinson's Disease. *PLoS ONE*, *9*(3), e91190. https://doi.org/10.1371/journal.pone.0091190

Snider, R. S., Maiti, A., & Snider, S. R. (1976a). Cerebellar connections to catecholamine systems: anatomical and biochemical studies. *Transactions of the American Neurological Association*, *101*, 295–297. http://www.ncbi.nlm.nih.gov/pubmed/829296

Snider, R. S., Maiti, A., & Snider, S. R. (1976b). Cerebellar pathways to ventral midbrain and nigra. *Experimental Neurology*, *53*(3), 714–728. https://doi.org/10.1016/0014-4886(76)90150-3

Solano, S. M., Miller, D. W., Augood, S. J., Young, A. B., & Penney, J. B. (2000). Expression of α-synuclein, parkin, and ubiquitin carboxy-terminal hydrolase L1 mRNA in human brain: Genes associated with familial Parkinson's disease. *Annals of Neurology*, *47*(2), 201–210. https://doi.org/10.1002/1531-8249(200002)47:2<201::AID-ANA10>3.0.CO;2-F

Song, A. K., Hay, K. R., Trujillo, P., Aumann, M., Stark, A. J., Yan, Y., Kang, H., Donahue, M. J., Zald, D. H., & Claassen, D. O. (2021). Amphetamine-induced dopamine release and impulsivity in Parkinson disease. *Brain : A Journal of Neurology*. https://doi.org/10.1093/brain/awab487

Spanagel, R., & Weiss, F. (1999). The dopamine hypothesis of reward: Past and current status. *Trends in Neurosciences*, *22*(11), 521–527. https://doi.org/10.1016/S0166-2236(99)01447-2

Stanford, M. S., Mathias, C. W., Dougherty, D. M., Lake, S. L., Anderson, N. E., & Patton, J. H. (2009). Fifty years of the Barratt Impulsiveness Scale: An update and review. *Personality and Individual Differences*, *47*, 385–395. https://doi.org/10.1016/j.paid.2009.04.008

Stark, A. J., & Claassen, D. O. (2017). Positron emission tomography in Parkinson's disease: insights into impulsivity. *International Review of Psychiatry (Abingdon, England)*, *29*(6), 618–627. https://doi.org/10.1080/09540261.2017.1398139

Stark, A. J., Smith, C. T., Lin, Y.-C., Petersen, K. J., Trujillo, P., van Wouwe, N. C., Kang, H., Donahue, M. J., Kessler, R. M., Zald, D. H., & Claassen, D. O. (2018). Nigrostriatal and Mesolimbic D2/3 Receptor Expression in Parkinson's Disease Patients with Compulsive Reward-Driven Behaviors. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *38*(13), 3230–3239. https://doi.org/10.1523/JNEUROSCI.3082-17.2018

Stark, A. J., Smith, C. T., Petersen, K. J., Trujillo, P., van Wouwe, N. C., Donahue, M. J., Kessler, R. M., Deutch, A. Y., Zald, D. H., & Claassen, D. O. (2018). [18F]fallypride characterization of striatal and extrastriatal D2/3 receptors in Parkinson's disease. *NeuroImage. Clinical*, *18*(October 2017), 433–442. https://doi.org/10.1016/j.nicl.2018.02.010

Steeves, T. D. L., Miyasaki, J., Zurowski, M., Lang, A. E., Pellecchia, G., Van Eimeren, T., Rusjan, P., Houle, S., & Strafella, A. P. (2009). Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. *Brain : A Journal of Neurology*, *132*(Pt 5), 1376–1385. https://doi.org/10.1093/brain/awp054

Stoodley, C. J. (2016). The Cerebellum and Neurodevelopmental Disorders. *Cerebellum (London, England)*, *15*(1), 34–37. https://doi.org/10.1007/s12311-015-0715-3

Stoodley, C. J., & Schmahmann, J. D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex*, *46*(7), 831–

844. https://doi.org/10.1016/j.cortex.2009.11.008
Stout, J. C., Ready, R. E., Grace, J., Malloy, P. F., & Paulsen, J. S. (2003). *Factor Analysis of the Frontal Systems Behavior Scale (FrSBe)*. https://doi.org/10.1177/1073191102250339
Strahlendorf, J. C., Lee, M., & Strahlendorf, H. K. (1984). Effects of serotonin on cerebellar Purkinje cells are dependent on the baseline firing rate. *Experimental Brain Research*, *56*(1), 50–58. https://doi.org/10.1007/BF00237441
Strick, P. L., Dum, R. P., & Fiez, J. A. (2009). Cerebellum and nonmotor function. *Annual Review of Neuroscience*, *32*, 413–434. https://doi.org/10.1146/annurev.neuro.31.060407.125606
Sullivan, K. L., Hauser, R. A., & Zesiewicz, T. A. (2004). Essential tremor: Epidemiology, diagnosis, and treatment. *Neurologist*, *10*(5), 250–258. https://doi.org/10.1097/01.nrl.0000138736.07840.b2
Sulzer, D., Cragg, S. J., & Rice, M. E. (2017). Regulation of Extracellular Dopamine: Release and Uptake. *Handbook of Behavioral Neuroscience*, *24*, 373–402. https://doi.org/10.1016/B978-0-12-802206-1.00019-2
Sulzer, David, Sonders, M. S., Poulsen, N. W., & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: A review. *Progress in Neurobiology*, *75*(6), 406–433. https://doi.org/10.1016/j.pneurobio.2005.04.003
Swann, A. C. (2009). Impulsivity in mania. *Current Psychiatry Reports*, *11*(6), 481–487. https://doi.org/10.1007/s11920-009-0073-2
Swann, A. C., Bjork, J. M., Moeller, F. G., & Dougherty, D. M. (2002). *Two Models of Impulsivity: Relationship to Personality Traits and Psychopathology*. https://ac.els-cdn.com/S0006322301013579/1-s2.0-S0006322301013579-main.pdf?_tid=faa80edb-01c4-4172-b458-142ac2270737&acdnat=1546970540_773beb92ba7e7c0d5322264d20155640
Swann, A. C., Dougherty, D. M., Pazzaglia, P. J., Pham, M., & Moeller, F. G. (2004). Impulsivity: a link between bipolar disorder and substance abuse. *Bipolar Disorders*, *6*(3), 204–212. https://doi.org/10.1111/j.1399-5618.2004.00110.x
Taber, K. H., & Hurley, R. A. (2014). Volume transmission in the brain: beyond the synapse. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *26*(1), iv, 1–4. https://doi.org/10.1176/appi.neuropsych.13110351
Tajima-Pozo, K., Ruiz-Manrique, G., Yus, M., Arrazola, J., & Montañes-Rada, F. (2015). Correlation between amygdala volume and impulsivity in adults with attention-deficit hyperactivity disorder. *Acta Neuropsychiatrica*, *27*(6), 362–367. https://doi.org/10.1017/neu.2015.34
Tavano, A., Grasso, R., Gagliardi, C., Triulzi, F., Bresolin, N., Fabbro, F., & Borgatti, R. (2007). Disorders of cognitive and affective development in cerebellar malformations. *Brain*, *130*(10), 2646–2660. https://doi.org/10.1093/brain/awm201
Tetreault, A. M., Phan, T., Orlando, D., Lyu, I., Kang, H., Landman, B., & Ryan Darby, R. (2020). Network localization of clinical, cognitive, and neuropsychiatric symptoms in Alzheimer's disease. *Brain*, *143*(3), 1249–1260. https://doi.org/10.1093/brain/awaa058
Tetreault, A. M., Phan, T., Petersen, K. J., Claassen, D. O., Neth, B. J., Graff-Radford, J., Albrecht, F., Fliessbach, K., Schneider, A., Synofzik, M., Diehl-Schmid, J., Otto, M., Schroeter, M. L., & Darby, R. R. (2020). Network Localization of Alien Limb in Patients with Corticobasal Syndrome. *Annals of Neurology*, *88*(6), 1118–1131. https://doi.org/10.1002/ana.25901
Thawani, S. P., Schupf, N., & Louis, E. D. (2009). Essential tremor is associated with dementia: Prospective population-based study in New York. *Neurology*, *73*(8), 621–625. https://doi.org/10.1212/WNL.0b013e3181b389f1
Thenganatt, M. A., & Louis, E. D. (2012). Personality profile in essential tremor: A case-control study. *Parkinsonism and Related Disorders*, *18*(9), 1042–1044. https://doi.org/10.1016/j.parkreldis.2012.05.015
Thulborn, K. R. (2012). My starting point: the discovery of an NMR method for measuring blood

oxygenation using the transverse relaxation time of blood water. *NeuroImage*, *62*(2), 589–593. https://doi.org/10.1016/j.neuroimage.2011.09.070

Tibshirani, R. (1996). Regression Shrinkage and Selection Via the Lasso. *Journal of the Royal Statistical Society: Series B (Methodological)*, *58*(1), 267–288. https://doi.org/10.1111/j.2517-6161.1996.tb02080.x

Timmann, D., & Daum, I. (2007). Cerebellar contributions to cognitive functions: A progress report after two decades of research. *Cerebellum*, *6*(3), 159–162. https://doi.org/10.1080/14734220701496448

Tolosa, E., Wenning, G., & Poewe, W. (2006). The diagnosis of Parkinson's disease. In *Lancet Neurology*. https://doi.org/10.1016/S1474-4422(05)70285-4

Torregrossa, M. M., Quinn, J. J., & Taylor, J. R. (2008). Impulsivity, compulsivity, and habit: the role of orbitofrontal cortex revisited. *Biological Psychiatry*, *63*(3), 253–255. https://doi.org/10.1016/j.biopsych.2007.11.014

Triantafyllou, C., Wald, L. L., & Hoge, R. D. (2011). Echo-Time and Field Strength Dependence of BOLD Reactivity in Veins and Parenchyma Using Flow-Normalized Hypercapnic Manipulation. *PLoS ONE*, *6*(9), e24519. https://doi.org/10.1371/journal.pone.0024519

Trifilieff, P, Feng, B., Urizar, E., Winiger, V., Ward, R. D., Taylor, K. M., Martinez, D., Moore, H., Balsam, P. D., Simpson, E. H., & Javitch, J. A. (2013). Increasing dopamine D2 receptor expression in the adult nucleus accumbens enhances motivation. *Molecular Psychiatry*, *18*(9), 1025–1033. https://doi.org/10.1038/mp.2013.57

Trifilieff, Pierre, Ducrocq, F., van der Veldt, S., & Martinez, D. (2017). Blunted Dopamine Transmission in Addiction: Potential Mechanisms and Implications for Behavior. *Seminars in Nuclear Medicine*, *47*(1), 64–74. https://doi.org/10.1053/j.semnuclmed.2016.09.003

Trifilieff, Pierre, & Martinez, D. (2014). Imaging addiction: D2 receptors and dopamine signaling in the striatum as biomarkers for impulsivity. *Neuropharmacology*, *76 Pt B*, 498–509. https://doi.org/10.1016/j.neuropharm.2013.06.031

Trommer, B. L., Hoeppner, J. A., Lorber, R., & Armstrong, K. J. (1988). The go-no-go paradigm in attention deficit disorder. *Annals of Neurology*, *24*(5), 610–614. https://doi.org/10.1002/ana.410240504

Trujillo, P., van Wouwe, N. C., Lin, Y.-C., Stark, A. J., Petersen, K. J., Kang, H., Zald, D. H., Donahue, M. J., & Claassen, D. O. (2019). Dopamine effects on frontal cortical blood flow and motor inhibition in Parkinson's disease. *Cortex*, *115*(1), 99–111. https://doi.org/10.1016/j.cortex.2019.01.016

Turner, B. M., Paradiso, S., Marvel, C. L., Pierson, R., Boles Ponto, L. L., Hichwa, R. D., & Robinson, R. G. (2007). The cerebellum and emotional experience. *Neuropsychologia*, *45*(6), 1331–1341. https://doi.org/10.1016/j.neuropsychologia.2006.09.023

Tustison, N. J., Avants, B. B., Cook, P. A., Yuanjie Zheng, Egan, A., Yushkevich, P. A., & Gee, J. C. (2010). N4ITK: Improved N3 Bias Correction. *IEEE Transactions on Medical Imaging*, *29*(6), 1310–1320. https://doi.org/10.1109/TMI.2010.2046908

Valente, E. M., Nuovo, S., & Doherty, D. (2018). Genetics of cerebellar disorders. In *Handbook of Clinical Neurology* (1st ed., Vol. 154, pp. 267–286). Elsevier B.V. https://doi.org/10.1016/B978-0-444-63956-1.00016-3

Van Kammen, D. P., & Murphy, D. L. (1975). Attenuation of the euphoriant and activating effects of d- and l-amphetamine by lithium carbonate treatment. *Psychopharmacologia*, *44*(3), 215–224. https://doi.org/10.1007/BF00428897

van Wouwe, N. C., van den Wildenberg, W. P. M., Claassen, D. O., Kanoff, K., Bashore, T. R., & Wylie, S. A. (2014). Speed pressure in conflict situations impedes inhibitory action control in Parkinson's disease. *Biological Psychology*, *101*, 44–60. https://doi.org/10.1016/j.biopsycho.2014.07.002

Vandehey, N. T., Moirano, J. M., Converse, A. K., Holden, J. E., Mukherjee, J., Murali, D.,

Nickles, R. J., Davidson, R. J., Schneider, M. L., & Christian, B. T. (2010a). High-affinity dopamine D2/D3 PET radioligands 18F-fallypride and 11C-FLB457: A comparison of kinetics in extrastriatal regions using a multiple-injection protocol. *Journal of Cerebral Blood Flow and Metabolism*, *30*(5), 994–1007. https://doi.org/10.1038/jcbfm.2009.270

Vandehey, N. T., Moirano, J. M., Converse, A. K., Holden, J. E., Mukherjee, J., Murali, D., Nickles, R. J., Davidson, R. J., Schneider, M. L., & Christian, B. T. (2010b). High-affinity dopamine D2/D3 PET radioligands 18F-fallypride and 11C-FLB457: a comparison of kinetics in extrastriatal regions using a multiple-injection protocol. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *30*(5), 994–1007. https://doi.org/10.1038/jcbfm.2009.270

Visanji, N. P., Brooks, P. L., Hazrati, L. N., & Lang, A. E. (2014). The prion hypothesis in Parkinson's disease: Braak to the future. *Acta Neuropathologica Communications*, *2*(1), 1. https://doi.org/10.1186/2051-5960-1-2

Volkow, N. D., Michaelides, M., & Baler, R. (2019). The neuroscience of drug reward and addiction. *Physiological Reviews*, *99*(4), 2115–2140. https://doi.org/10.1152/physrev.00014.2018

Volkow, N. D., Wise, R. A., & Baler, R. (2017). *The dopamine motive system: implications for drug and food addiction*. https://doi.org/10.1038/nrn.2017.130

Voon, V, Hassan, ; K, Zurowski, ; M, De Souza, ; M, Thomsen, ; T, Fox, ; S, Lang, ; A E, & Miyasaki, J. (2006). *Prevalence of repetitive and reward-seeking behaviors in Parkinson disease*. www.neurology.org.

Voon, Valerie, & Fox, S. H. (2007). Medication-related impulse control and repetitive behaviors in Parkinson disease. *Archives of Neurology*, *64*(8), 1089–1096. https://doi.org/10.1001/archneur.64.8.1089

Voon, Valerie, Rizos, A., Chakravartty, R., Mulholland, N., Robinson, S., Howell, N. A., Harrison, N., Vivian, G., & Ray Chaudhuri, K. (2014). Impulse control disorders in Parkinson's disease: decreased striatal dopamine transporter levels. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(2), 148–152. https://doi.org/10.1136/jnnp-2013-305395

Voon, Valerie, Sohr, M., Lang, A. E., Potenza, M. N., Siderowf, A. D., Whetteckey, J., Weintraub, D., Wunderlich, G. R., & Stacy, M. (2011). Impulse control disorders in parkinson disease: A multicenter case-control study. *Annals of Neurology*, *69*(6), 986–996. https://doi.org/10.1002/ana.22356

Voon, Valerie, Thomsen, T., Miyasaki, J. M., de Souza, M., Shafro, A., Fox, S. H., Duff-Canning, S., Lang, A. E., & Zurowski, M. (2007). Factors Associated With Dopaminergic Drug–Related Pathological Gambling in Parkinson Disease. *Archives of Neurology*, *64*(2), 212. https://doi.org/10.1001/archneur.64.2.212

Wakabayashi, K., Tanji, K., Odagiri, S., Miki, Y., Mori, F., & Takahashi, H. (2013). The Lewy body in Parkinson's disease and related neurodegenerative disorders. *Molecular Neurobiology*, *47*(2), 495–508. https://doi.org/10.1007/s12035-012-8280-y

Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., Hua, K., Zhang, J., Jiang, H., Dubey, P., Blitz, A., van Zijl, P., & Mori, S. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage*, *36*(3), 630–644. https://doi.org/10.1016/j.neuroimage.2007.02.049

Wallesch, C. W., & Horn, A. (1990). Long-term effects of cerebellar pathology on cognitive functions. *Brain and Cognition*, *14*(1), 19–25. https://doi.org/10.1016/0278-2626(90)90057-u

Wang, G. J., Volkow, N. D., Logan, J., Pappas, N. R., Wong, C. T., Zhu, W., Netusil, N., & Fowler, J. S. (2001). Brain dopamine and obesity. *Lancet (London, England)*, *357*(9253), 354–357. https://doi.org/10.1016/s0140-6736(00)03643-6

Wang, S.-M., & Tickle-Degnen, L. (2018). Emotional cues from expressive behavior of women and men with Parkinson's disease. *PloS One*, *13*(7), e0199886.

https://doi.org/10.1371/journal.pone.0199886
Wardle, M. C., & De Wit, H. (2012). Effects of amphetamine on reactivity to emotional stimuli. *Psychopharmacology*, *220*(1), 143–153. https://doi.org/10.1007/s00213-011-2498-7
Wardle, M. C., Garner, M. J., Munafò, M. R., & de Wit, H. (2012). Amphetamine as a social drug: effects of d-amphetamine on social processing and behavior. *Psychopharmacology*, *223*(2), 199–210. https://doi.org/10.1007/s00213-012-2708-y
Watabe-Uchida, M., Zhu, L., Ogawa, S. K., Vamanrao, A., & Uchida, N. (2012). Whole-Brain Mapping of Direct Inputs to Midbrain Dopamine Neurons. *Neuron*, *74*(5), 858–873. https://doi.org/10.1016/j.neuron.2012.03.017
Watson, D, Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology*, *54*(6), 1063–1070. https://doi.org/10.1037//0022-3514.54.6.1063
Watson, David, Clark, L. A., & Tellegen, A. (1988). Development and Validation of Brief Measures of Positive and Negative Affect: The PANAS Scales. *Journal of Personality and Social Psychology*. https://doi.org/10.1037/0022-3514.54.6.1063
Watson, T. C., Becker, N., Apps, R., & Jones, M. W. (2014). Back to front: Cerebellar connections and interactions with the prefrontal cortex. *Frontiers in Systems Neuroscience*, *8*(FEB), 1–11. https://doi.org/10.3389/fnsys.2014.00004
Wegener, S., Wu, W. C., Perthen, J. E., & Wong, E. C. (2007). Quantification of rodent Cerebral Blood Flow (CBF) in normal and high flow states using pulsed arterial spin labeling magnetic resonance imaging. *Journal of Magnetic Resonance Imaging*. https://doi.org/10.1002/jmri.21045
Weiland, B. J., Heitzeg, M. M., Zald, D., Cummiford, C., Love, T., Zucker, R. A., & Zubieta, J.-K. (2014). Relationship between impulsivity, prefrontal anticipatory activation, and striatal dopamine release during rewarded task performance. *Psychiatry Research*, *223*(3), 244–252. https://doi.org/10.1016/j.pscychresns.2014.05.015
Weintraub, D., & Claassen, D. O. (2017). *Impulse Control and Related Disorders in Parkinson's Disease* (pp. 679–717). https://doi.org/10.1016/bs.irn.2017.04.006
Weintraub, D., Hoops, S., Shea, J. A., Lyons, K. E., Pahwa, R., Driver-Dunckley, E. D., Adler, C. H., Potenza, M. N., Miyasaki, J., Siderowf, A. D., Duda, J. E., Hurtig, H. I., Colcher, A., Horn, S. S., Stern, M. B., & Voon, V. (2009a). Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, *24*(10), 1461–1467. https://doi.org/10.1002/mds.22571
Weintraub, D., Hoops, S., Shea, J. A., Lyons, K. E., Pahwa, R., Driver-Dunckley, E. D., Adler, C. H., Potenza, M. N., Miyasaki, J., Siderowf, A. D., Duda, J. E., Hurtig, H. I., Colcher, A., Horn, S. S., Stern, M. B., & Voon, V. (2009b). Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Movement Disorders*, *24*(10), 1461–1467. https://doi.org/10.1002/mds.22571
Weintraub, D., Koester, J., Potenza, M. N., Siderowf, A. D., Stacy, M., Voon, V., Whetteckey, J., Wunderlich, G. R., & Lang, A. E. (2010). Impulse Control Disorders in Parkinson Disease. *Archives of Neurology*, *67*(5), 589–595. https://doi.org/10.1001/archneurol.2010.65
Weintraub, D., & Mamikonyan, E. (2019). The Neuropsychiatry of Parkinson Disease: A Perfect Storm. *The American Journal of Geriatric Psychiatry*, *27*(9), 998–1018. https://doi.org/10.1016/j.jagp.2019.03.002
Weintraub, D., Mamikonyan, E., Papay, K., Shea, J. A., Xie, S. X., & Siderowf, A. (2012). Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. *Movement Disorders : Official Journal of the Movement Disorder Society*, *27*(2), 242–247. https://doi.org/10.1002/mds.24023
Weiss, H. D., & Marsh, L. (2012a). Impulse control disorders and compulsive behaviors associated with dopaminergic therapies in Parkinson disease. *Neurology. Clinical Practice*, *2*(4), 267–

274. https://doi.org/10.1212/CPJ.0b013e318278be9b
Weiss, H. D., & Marsh, L. (2012b). Impulse control disorders and compulsive behaviors associated with dopaminergic therapies in Parkinson disease. *Neurology: Clinical Practice*, *2*(4), 267. https://doi.org/10.1212/CPJ.0B013E318278BE9B
Weisskoff, R M, Zuo, C. S., Boxerman, J. L., & Rosen, B. R. (1994). Microscopic susceptibility variation and transverse relaxation: theory and experiment. *Magnetic Resonance in Medicine*, *31*(6), 601–610. https://doi.org/10.1002/mrm.1910310605
Weisskoff, Robert M. (2012). The characterization of dynamic susceptibility effects. *NeuroImage*, *62*(2), 1014–1016. https://doi.org/10.1016/j.neuroimage.2012.01.019
Welton, T., Cardoso, F., Carr, J. A., Chan, L. L., Deuschl, G., Jankovic, J., & Tan, E. K. (2021). Essential tremor. *Nature Reviews Disease Primers*, *7*(1). https://doi.org/10.1038/s41572-021-00314-w
Wen, M. C., Chan, L. L., Tan, L. C. S., & Tan, E. K. (2016). Depression, anxiety, and apathy in Parkinson's disease: Insights from neuroimaging studies. *European Journal of Neurology*, *23*(6), 1001–1019. https://doi.org/10.1111/ene.13002
Whiteside, S. P., & Lynam, D. R. (2001). The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. *Personality and Individual Differences*, *30*(4), 669–689. https://doi.org/10.1016/S0191-8869(00)00064-7
Wills, A. J., Jenkins, I. H., Thompson, P. D., Findley, L. J., & Brooks, D. J. (1995). A positron emission tomography study of cerebral activation associated with essential and writing tremor. *Archives of Neurology*, *52*(3), 299–305. https://doi.org/10.1001/archneur.1995.00540270095025
Winstanley, C. A., Eagle, D. M., & Robbins, T. W. (2006). Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. *Clinical Psychology Review*, *26*(4), 379–395. https://doi.org/10.1016/j.cpr.2006.01.001
Wise, R. A., & Rompre, P. P. (1989). Brain dopamine and reward. *Annual Review of Psychology*, *40*(1), 191–225. https://doi.org/10.1146/annurev.ps.40.020189.001203
Woodward, D. J., Moises, H. C., Waterhouse, B. D., Yeh, H. H., & Cheun, J. E. (1991). The cerebellar norepinephrine system: inhibition, modulation, and gating. *Progress in Brain Research*, *88*, 331–341. https://doi.org/10.1016/s0079-6123(08)63820-0
Woodward, N. D., Zald, D. H., Ding, Z., Riccardi, P., Ansari, M. S., Baldwin, R. M., Cowan, R. L., Li, R., & Kessler, R. M. (2009). Cerebral morphology and dopamine D2/D3 receptor distribution in humans: A combined [18F]fallypride and voxel-based morphometry study. *NeuroImage*, *46*(1), 31–38. https://doi.org/10.1016/j.neuroimage.2009.01.049
Wylie, S. A., van Wouwe, N. C., Godfrey, S. G., Bissett, P. G., Logan, G. D., Kanoff, K. E., Claassen, D. O., Neimat, J. S., & van den Wildenberg, W. P. M. (2018). Dopaminergic medication shifts the balance between going and stopping in Parkinson's disease. *Neuropsychologia*, *109*, 262–269. https://doi.org/10.1016/j.neuropsychologia.2017.12.032
Xiao, Y., Fonov, V., Bériault, S., Subaie, F. Al, Chakravarty, M. M., Sadikot, A. F., Pike, G. B., & Collins, D. L. (2015). Multi-contrast unbiased MRI atlas of a Parkinson's disease population. *International Journal of Computer Assisted Radiology and Surgery*, *10*(3), 329–341. https://doi.org/10.1007/s11548-014-1068-y
Yacoub, E., Van De Moortele, P. F., Shmuel, A., & Uğurbil, K. (2005). Signal and noise characteristics of Hahn SE and GE BOLD fMRI at 7 T in humans. *NeuroImage*, *24*(3), 738–750. https://doi.org/10.1016/j.neuroimage.2004.09.002
Yamada, H., Matsumoto, N., & Kimura, M. (2004). Tonically Active Neurons in the Primate Caudate Nucleus and Putamen Differentially Encode Instructed Motivational Outcomes of Action. *Journal of Neuroscience*, *24*(14), 3500–3510. https://doi.org/10.1523/JNEUROSCI.0068-04.2004
Yin, H. H., & Knowlton, B. J. (2006). The role of the basal ganglia in habit formation. *Nature*

Reviews. Neuroscience, *7*(6), 464–476. https://doi.org/10.1038/nrn1919
Yoo, S. W., Oh, Y. S., Hwang, E. J., Ryu, D. W., Lee, K. S., Lyoo, C. H., & Kim, J. S. (2019). "Depressed" caudate and ventral striatum dopamine transporter availability in de novo Depressed Parkinson's disease. *Neurobiology of Disease*, *132*(August), 104563. https://doi.org/10.1016/j.nbd.2019.104563
Zald, D. H., Boileau, I., El-Dearedy, W., Gunn, R., McGlone, F., Dichter, G. S., & Dagher, A. (2004). Dopamine transmission in the human striatum during monetary reward tasks. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *24*(17), 4105–4112. https://doi.org/10.1523/JNEUROSCI.4643-03.2004
Zeeb, F. D., Floresco, S. B., & Winstanley, C. A. (2010). Contributions of the orbitofrontal cortex to impulsive choice: interactions with basal levels of impulsivity, dopamine signalling, and reward-related cues. *Psychopharmacology*, *211*(1), 87–98. https://doi.org/10.1007/s00213-010-1871-2
Zgaljardic, D., Borod, J., Foldi, N., Mattis, P., Gordon, M., Feigin, A., & Eidelberg, D. (2006). An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, *28*(7), 1127–1144. https://doi.org/10.1080/13803390500246910
Zgaljardic, D. J., Borod, J. C., Foldi, N. S., & Mattis, P. (2003). A Review of the Cognitive and Behavioral Sequelae of Parkinson's Disease: Relationship to Frontostriatal Circuitry. In *Cognitive and Behavioral Neurology*. https://doi.org/10.1097/00146965-200312000-00001
Zhang, G., Zhang, Z., Liu, L., Yang, J., Huang, J., Xiong, N., & Wang, T. (2014). Impulsive and compulsive behaviors in Parkinson's disease. *Frontiers in Aging Neuroscience*, *6*, 318. https://doi.org/10.3389/fnagi.2014.00318