Behavioral impulsivity and hallucinations: Insights from Parkinson's disease
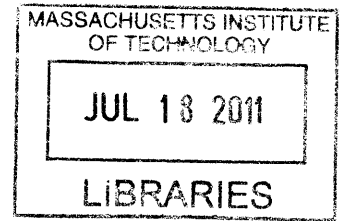
by

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Submitted to the Department of Brain and Cognitive Sciences

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Neuroscience

at the

Massachusetts Institute of Technology

September, 2011

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Abstract

Parkinson's disease (PD) is an age-related degenerative disease of the brain, characterized by motor, cognitive, and psychiatric symptoms. Neurologists and neuroscientists now understand that several symptoms of the disease, including hallucinations and impulse control behaviors, stem from the dopaminergic medications used to control the motor aspects of PD. Not all patients experience these nonmotor symptoms and tools that can predict a priori which patients are likely to have an adverse response to medication do not exist. This thesis begins to fill this gap by elucidating the mechanisms underlying the adverse effects of dopaminergic medications. Converging evidence from animals and humans shows that individual differences in particular genes that affect the dopamine system may alter the response of PD patients to dopaminergic medication. We examined the hypothesis that patients taking dopamine replacement therapy who carry candidate alleles that increase dopamine signaling experience a dopamine overdose, causing unwanted psychiatric symptoms.

Thesis Supervisor: Suzanne Corkin
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Thank you,

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Preface

This thesis is comprised of six chapters. Chapter 1, the Introduction, frames the overarching question addressed in the thesis: What are the mechanisms underlying the adverse effects of dopaminergic medications used to ameliorate motor symptoms of Parkinson's disease (PD). To tackle this question, I focus on two medication-induced side effects observed in PD: impulse control behaviors and hallucinations. Chapters 2-4 probe three distinct dimensions of impulsivity, response inhibition, delay of gratification, and reflection impulsivity. The focus of chapter 5 is hallucinations. I present each chapter with its own introduction, methods, and discussion. Chapter 6, the Conclusion, summarizes the major findings and discusses directions for future research.

1   Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disease commonly characterized by resting tremor, rigidity, slowness of movement, and postural instability. These symptoms progress relentlessly, eventually leaving most patients wheelchair bound and entirely dependent on caregivers. PD occurs worldwide and affects all races and both sexes, but with a slight predominance among males.[1] Motor symptoms of the disease typically appear when patients are in their early sixties, although up to 10% of those affected start experiencing symptoms between the ages of 30 and 60.[1,2] PD prevalence increases from roughly 0.3% in the general population to 0.6% to 1% among people 65 to 69 years of age, and 1% to 3% among people older than 70.[3] It is the second most common neurodegenerative disease, after Alzheimer's disease, and currently 40,000 to 70,000 new cases are diagnosed each year in the United States alone.[3,4] The number of individuals with PD is expected to double by the year 2030 as life expectancies increase and the global population shifts in age.[5]

James Parkinson was the first to describe the disorder in his 1817 paper, "An Essay on the Shaking Palsy",[6] although a disease named "Kampavata", described in the ancient Ayurvedic literature of India, compiled from 4500 B.C. to 1000 B.C., bears a striking resemblance to PD.[7] Parkinson reported that the "senses and intellects" remain intact in PD,[6] but we now know that the extrapyramidal symptoms are accompanied by a broad range of nonmotor symptoms.

Cognitive symptoms include visuospatial deficits and difficulty in tasks that require coordination of action and thought to achieve a goal.[2,8] Psychiatric disorders consist of anxiety, dementia, depression, impulse control behaviors, insomnia, and hallucinations.[2,8] These nonmotor aspects significantly reduce patients' quality of life, and typically do not respond to, or are worsened by, medication used to treat the motor symptoms.[2]

1.1   Neuropathology of PD

The major neuropathologic feature of idiopathic PD is selective loss of dopaminergic neurons in the midbrain. Dopaminergic degeneration in the early stages of PD is selective, targeting the ventrolateral tier of the substantia nigra pars compacta (SNpc) followed by the dorsolateral tier of SNpc. The ventral tegmental area (VTA) is relatively spared.[9-12] Patients who die with a diagnosis of PD show a 60% to 85% loss of tyrosine hydroxylase immunoreactive neurons in the SNpc, with 91% to 97% loss in the ventrolateral tier of SNpc and 40% to 50% loss in the VTA.[9,13,14]

SNpc and VTA are interconnected with the striatum in an inverse dorsal-ventral pattern.[15] The striatum—putamen and the caudate nucleus—is located in the forebrain under the frontal lobes. It is the primary input node of the basal ganglia. Ventrolateral SNpc is interconnected with the dorsal striatum (primarily putamen), while dorsolateral SNpc and VTA are interconnected with the central (head of the caudate nucleus and rostral putamen) and ventral regions of the striatum (nucleus accumbens, and rostral/ventral caudate nucleus, and putamen), respectively.[15,16] Thus, the pattern of cell loss in the early stages of PD causes severe

dopamine depletion in the dorsal striatum, moderate depletion in the central striatum, while relatively sparing dopaminergic function in the ventral striatum.[14,17,18]

Different sectors of the striatum are connected with specific regions of the cortex by functionally distinct cortico-striatal loops.[19-23] The motor loop connects motor, premotor, and supplementary motor areas with the dorsal striatum. The associative loop, which is implicated in attentional control and maintenance and manipulation of information to achieve a goal, connects dorsolateral prefrontal cortex (PFC), pre-supplementary motor area (pre-SMA), and posterior parietal cortex with the central striatum. The limbic loop, implicated in emotion, motivation, and reward processing, connects orbital/medial regions of PFC, hippocampus, amygdala, and the anterior cingulate cortex with the ventral striatum. Dopamine depletion in the dorsal striatum alters the motor loop function, causing the motor symptoms of PD.

Protective or preventive treatments for PD do not exist. The gold standard for reducing the motor symptoms is to increase dopaminergic transmission in the motor loop by giving patients the dopamine precursor levodopa or dopamine agonists. Levodopa is taken up by dopaminergic terminals and converted into dopamine by DOPA decarboxylase. Dopamine agonists, such as pramipexole, ropinirole, and bromocriptine, directly stimulate dopamine receptors. The resulting improvement in motor signs comes at a price. Use of levodopa or dopamine agonists may cause psychiatric side effects, such as hallucinations and impulse control behaviors, possibly due to over stimulation of the relatively preserved cortico-striatal loops.[24,25]

1.2　Psychiatric complications in PD

1.2.1 Impulse control behaviors

Impulsivity is "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others".[26,27] Impulsive behaviors in PD may include pathologic gambling, binge eating, hypersexuality, and excessive shopping.[27-31] The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR; American Psychiatric Association 2000), lists the criteria for impulse control disorders, but diagnostic criteria for excessive shopping and hypersexuality are lacking.[27,32] Point prevalence of at least one impulse control behavior (pathologic gambling, binge eating, hypersexuality, or excessive shopping) is 6.9% in patients taking levodopa without a dopamine agonist, and 17.1% in patients taking levodopa and dopamine agonists.[27,33,34] Pathologic gambling is one of the more common side effects of treatment with a prevalence of 6.4% in patients taking levodopa and dopamine agonists, compared to a prevalence of 1% in the general population.[27,33,35]

Manifestations of impulsivity typically result in irreversible personal, social, and financial ruin.[36,37] One study calculated that the financial loss averages more than $100,000 for patients who pathologically gamble,[36] constituting a devastating blow to families who are at retirement age and must bear the additional burden of medical expenses.

Impulsivity in PD has been studied predominantly by clinical interviews or self-report questionnaires, such as the Barratt Impulsiveness Scale (BIS-11)[38] and the Eysenck Personality

Questionnaire.[39] Although information gained from these questionnaires and interviews is invaluable, it is hard to relate aspects of impulsivity measured by these methods to underlying brain function because they are too nonspecific. Importantly, these questionnaires were not developed for studying transient medication-induced impulsivity or patients with a movement disorder.

Behavioral research on the neural and chemical underpinnings of impulsivity has focused on three domains: *response inhibition*, the ability to inhibit a prepotent response; *delay of gratification*, the ability to forgo small immediate rewards for larger delayed rewards; and *reflection impulsivity*, the ability to collect and evaluate information before making a decision.[40,41] The experiments described in **Chapters 2-4** focus on each of these domains in turn to clarify the underpinnings of medication-induced impulsivity in PD.

1.2.2 Hallucinations

According to DSM-IV-TR, a hallucination is "a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ".[42] Hallucinations in PD are predominantly visual, typically fully formed non-threatening images of people and animals. Many patients with visual hallucinations also experience auditory hallucinations.[43,44] In addition, "minor" or "benign" hallucinationatory experiences, such as a sense of presence of someone when no one is there, a sense of movement, and illusions of inanimate objects appearing as living beings, are also common.[43,45] About 30% of PD patients taking dopamine replacement therapy experience visual or auditory hallucinations.[43-45] The prevalence of hallucinations increases to 40% to 75% when minor

hallucination are also considered.[43] Once developed, hallucinations persist and progress, are associated with an increased risk of developing dementia, and are a primary risk factor for nursing home placement and its associated high mortality rates.[46-50]

The presence of formed and benign hallucinations in PD patients is typically assessed by self-report questionnaires because patients generally retain insight into their hallucinations, at least in the early stages of the disease.[43] A positive response to a screening question is followed by a structured interview to confirm the presence of major and minor hallucinations, and to assess when hallucinations first started. **Chapter 5** examines Hallucinations in PD.

1.3   Relation between psychiatric complications and medication use

Hallucinations and impulse control behaviors typically start, with variable latencies, after the introduction of dopaminergic medications or after a dose increase. They often remit when medication is decreased or discontinued.[35,43,44] All dopaminergic medications (levodopa, dopamine agonists) can induce psychiatric side effects, but agonists are more likely to do so than levodopa.[33,35,44]

While dopamine replacement therapy improves motor function in PD by increasing signaling in the dopamine-depleted cortico-striatal motor loop, it can have beneficial and deleterious effects on cognitive functions subserved by the associative and the limbic loops.[24,51,52] Early stage patients taking dopamine replacement therapy perform better than those who are off medication in tasks that engage the associative loop, such as task switching, planning and

working memory.[53] They perform worse than unmediated patients in tasks that activate the limbic loop, such as probabilistic reversal learning.[24] The idea that dopamine replacement therapy can have an opposing impact on functions that engage the associative and limbic loops, respectively, is known as the dopamine overdose hypothesis.[24] Although this hypothesis provides an explanation for the interaction between medication status and cognitive performance at a group level, it cannot account for individual variability in cognitive performance, nor is it able to predict which patients are likely to experience cognitive deterioration while receiving dopamine replacement therapy. Our goal is to flesh out this hypothesis by elucidating the mechanisms that give rise to medication-induced side effects in PD.

Insights about the mechanisms by which dopaminergic medications cause side effects come from three findings: First, not all patients taking dopamine replacement therapy develop the side effects. Second, levodopa daily dose and levodopa-equivalent daily dose (LEDD) are similar for patients who develop the side effects and those who do not.[33,35,43,44] Third, although dopamine agonists carry a higher risk for side effects, commonly prescribed dopamine agonists, such as pramipexole, ropinirole, and bromocriptine, do not differ in their association with psychiatric complications.[27,33,35,43,44] It is, therefore, likely that genetic variation plays a role in the pathogenesis of the medication-induced side effects.

1.4 Genetics of response to dopaminergic medication

Research into the genetic causes of interindividual variability in impulsivity has implicated polymorphisms in the catechol-O-methyltransferase (*COMT*), D_2 receptor (*DRD2*), D_3 receptor (*DRD3*), and D_4 receptor (*DRD4*) genes.[54-71] In healthy adults, increased risk for impulsivity is linked with allelic forms that reduce synaptic levels of dopamine (at least one *COMT* Val allele),[67,68,72-74] reduce receptor binding affinity for dopamine (presence of at least one *DRD2* 957C allele, presence of at least one *ANKK1* TaqI A1 allele,[54-58] or presence of at least one *DRD3* Ser allele[59-61,75]), or reduce receptor coupling efficacy to second messenger proteins (presence of $D_{4.7}$ allele).[63-65,76,77] In short, healthy adults with reduced dopamine signaling, conferred by the presence of one or more of the alleles noted above, show increased impulsivity.

COMT and *DRD2-4* encode proteins that directly interact with anti-Parkinsonian medications: The COMT enzyme is critical for inactivation of dopamine and levodopa in the PFC and is a target of COMT inhibitors, such as entacapone and tolcapone.[78] D_2, D_3, and D_4 receptors facilitate dopamine signaling between cells, have a high affinity for commonly prescribed dopamine agonists (bromocriptine, pramipexole, pergolide, and ropinirole),[79-81] and likely mediate the therapeutic effects of these drugs.[82] Thus, we reasoned that these polymorphisms may underlie the psychiatric side effects of dopamine replacement therapy in PD.

Although the impact of *COMT* and *DRD2-4* polymorphisms in modulating the risk for impulsivity in PD has not been studied, results on the impact of *COMT* polymorphism on working memory and attentional control are illuminating. Healthy adults with the Met/Met genotype, who have

high endogenous synaptic dopamine levels in the PFC, perform better on tests of executive function, such as attentional control and working memory, than do healthy adults with the Val/Val genotype, who have low endogenous synaptic dopamine levels.[83-86] This finding is reversed in medicated PD patients: PD patients with the Val/Val genotype exhibit better executive control than PD patients with the Met/Met genotype.[87-89] Similarly, administering d-amphetamine, which increases dopamine transmission, to healthy adults with the Val/Val genotype improves their performance on tests of executive function, while lowering the performance of individuals with the Met/Met genotype.[90] Likewise, tolcapone, a COMT inhibitor commonly used in PD treatment, significantly improves the performance of healthy Val/Val carriers on a measure of attentional set shifting, but it diminishes the performance of healthy Met/Met carriers.[91]

These seemingly contradictory effects of COMT polymorphism in medicated PD patients and healthy adults are consistent with an inverted-U dopamine response curve, whereby too much or too little dopamine results in cognitive dysfunction.[92,93] The inverted-U dopamine response curve was derived from experimental work on animals: When researchers injected a D_1 receptor agonist into the PFC of rats performing a spatial working memory task, they found that too much dopaminergic stimulation impaired spatial working memory performance.[94,95] Similarly, elevated dopamine release and turnover (induced by administration of anxiogenic β-carboline FG7142) in PFC of rats and monkeys resulted in impaired performance on a spatial working memory task.[96]

Consistent with the inverted-U hypothesis, injecting D_1 antagonists into the PFC of monkeys performing an oculomotor delayed-response task showed that too little dopamine signaling interfered with normal function.[97] Similarly, D_1 receptor antagonists in rats interfered with spatial working memory.[98] Electrophysiological studies in monkeys and rats have shown that the inverted-U curve arises because low to moderate increases in prefrontal dopamine levels suppress noisy task-unrelated neural firing, and thus focus task-relevant neural firing, while higher amounts of dopamine silence neuronal firing in the PFC.[99-101]

Investigators have hypothesized that healthy adults with reduced dopamine signaling are impulsive because they fall on the left side of the inverted-U curve (**Figure 1.1**). In contrast, the dopamine overdose hypothesis posits that medicated PD patients who experience cognitive side effects do so because they fall on the far right side of the curve.[24] Differential vulnerability of PD patients to medication-induced side effects, however, suggests that not all patients are pushed to the right side of the curve by their dopaminergic medications. We hypothesize that only those patients who carry candidate alleles that increase dopamine signaling (**Table 1.1**) fall on the far right side of the curve. Because these patients effectively experience a dopamine overdose, they are at increased risk for developing medication-induced psychiatric side effects. We expect that PD patients with alleles that confer reduced dopamine signaling will have a low risk for psychiatric side effects on medication because they fall near the peak of the curve after dopamine replacement therapy.

In summary, we hypothesize that PD patients are at risk for medication induced psychiatric side effects if they carry candidate alleles that increase dopamine signaling (**Figure 1.2**). Direct

support for this hypothesis comes from studies that have examined the impact of genetic polymorphisms on hallucinations in PD. Two studies found that the frequency of *DRD2* and *DRD3* genotypes that increase dopamine signaling are significantly higher in patients with hallucinations compared to patients without hallucinations[102,103] (but see[104,105]). Moreover, the reduction of symptoms after decrease or cessation of dopaminergic treatment,[45] and the successful treatment of hallucinations with medications that decrease dopamine signaling (quetiapine, clozapine)[106,107] suggest that dopamine overdose gives rise to the medication-induced negative side effects.

If our hypothesis is correct, it can shed light on the mechanisms by which dopaminergic medications give rise to psychiatric complications in PD.

1.5   Candidate genes

We briefly review current knowledge on select polymorphisms in *COMT, DRD2, DRD3*, and *DRD4* that alter dopamine signaling (**Table 1.1**). Variations in these genes putatively determine the pre-medicated position of an individual on the inverted-U dopamine curve. This knowledge may be useful in predicting the impact of a right-ward shift on the curve due to exogenous dopamine.[88]

1.5.1 COMT

The *COMT* Val158Met polymorphism has a significant impact on the level of dopamine signaling in the PFC.[78]   In 1957, Julius Axelrod discovered COMT, an enzyme that inactivates

catecolamines, such as dopamine.[108] The *COMT* gene is located on chromosome 22q11 and encodes two proteins: a soluble form (S-COMT) and a membrane bound form (MB-COMT).[109] MB-COMT is predominantly expressed in the brain while S-COMT is primarily present in the periphery, including blood, kidney, and liver.[73,110-113] In the brain, COMT is expressed intraneuronally in postsynaptic neurons and in astrocytic processes surrounding dopaminergic synapses, but the exact locus of COMT is not yet clear.[114-116]

Although COMT is ubiquitous in the brain,[73,110,114] it is particularly important for inactivation of dopamine in the PFC. Dopamine transporters (DAT), which provide the primary mechanism for the clearance of dopamine from synapses in the striatum, are expressed at low levels in the PFC and only at a distance from synaptic release sites.[117,118]

Several studies highlighted the critical role of COMT in deactivating dopamine in the frontal cortex.[116,119] *COMT* knockout mice had significantly elevated dopamine levels in their frontal cortices, but not in their striata.[120,121] Administering levodopa to these COMT-deficient mice significantly increased the PFC levels of dopamine, and the striatal levels of DOPAC (an MAO metabolite) and levodopa, but not dopamine.[119]

Examination of the rate of formation of 3-methoxytyramine (created when COMT methylates dopamine) in the rat revealed that COMT accounted for roughly 60% of dopamine turnover in the PFC compared to 15% in the striatum.[122] Additionally, *COMT* mRNA, which encodes the COMT enzyme, was expressed in humans and rats at higher levels in the PFC than in the striatum.[111] COMT appears to play a bigger role in primates than in mice and rats.[123] For example, DOPAC (an MAO metabolite) and HVA (metabolite of MAO and COMT) were present

in roughly equal amounts in the striatum and cerebrospinal fluid of rats and mice, whereas HVA dominated DOPAC by at least a factor of 12 in primates.[123,124]

A functional G to A single nucleotide polymorphism in COMT (rs4680) results in a valine (Val) to methionine (Met) amino acid change at codon 158 of MB-COMT (codon 108 of S-COMT). The Val isoform was more stable and active than the one with Met at physiological temperatures,[73,125] causing a 2 to 4 fold difference in COMT activity with the highest enzymatic activity observed in Val/Val, followed by moderate activity Val/Met, and lowest activity in Met/Met individuals.[73,125] The Met allele of COMT was not found in other mammals, including great apes, and thus appears to be a recent mutation in evolutionary timeline that is unique to humans.[126] Decreased COMT activity putatively increases dopamine signaling in the PFC.[73] Thus, healthy carriers of Val/Val likely fall on the left leg of the inverted-U curve, while Met/Met carries sit close to the peak.

1.5.2 DRD2

DRD2 C957T polymorphism alters the D_2 receptor affinity for dopamine and thus may alter D_2-mediated dopamine signaling. D_2 receptors are expressed at low levels across the cortex but are abundant in subcortical regions, with the highest concentrations in the striatum and limbic structures, such as the amygdala.[127-131] The DRD2 gene, which codes for dopamine receptor D_2, is located on chromosome 11q23. DRD2 C957T (rs6277) is a synonymous polymorphism (i.e., the C to T substitution does not alter the encoded amino acid due to codon redundancy) that surprisingly impacts D_2 receptor function in vitro and in vivo.

In vitro cell cultures showed that the T allele was associated with decreased mRNA stability, reduced receptor synthesis, and reduced dopamine-induced *DRD2* up-regulation, possibly due to an alteration in the folding pattern of the mRNA as a result of the C to T substitution.[132] In contrast, subsequent studies using in vivo positron emission tomography in healthy adults showed that the T allele was related to increased striatal D_2 availability, driven by enhanced D_2 binding affinity with each T allele (T/T > C/T > C/C).[133,134] The discrepancy between the in vivo and in vitro results could have been due to the complexity of dopamine transmission regulation in the human brain.[134] Still, increased binding affinity in the presence of the T allele could potentially increase the level of dopamine signaling in the brain.

Most studies to date have focused on the impact of another D_2 related polymorphism, Taq1A (rs1800497), on cognition. PET studies showed that the A1 allele of this polymorphism was associated with a 30% to 40% reduction in D_2 receptor density in striatum.[57] Newer reports, however, showed that rs1800497 was located on kinase domain containing 1 (*ANKK1*) gene downstream from the *DRD2* gene, and that *ANKK1* was not expressed in the brain.[135] Several authors reported Taq1A polymorphism was in linkage disequilibrium with *DRD2* C957T polymorphism (*d'* = 0.832 to 1, indicating strong dependence),[132,134] such that the A1 allele of Taq1A was disproportionately over- and under-represented among C/C and T/T carriers, respectively.[134,136] We chose to study the *DRD2* C957T polymorphism because it is likely that Taq1A results are indirectly due to the C957T polymorphism.[136]

1.5.3 DRD3

D_3 receptors are predominantly expressed in the nucleus accumbens, ventral tegmental area, and limbic structures, such as amygdala[127,137,138] Because nucleus accumbens is a primary target of the relatively preserved dopaminergic VTA, variations in D_3 receptors may determine whether this area will experience an overdose from exogenous dopamine.

DRD3 is located on chromosome 3q13.[139] Ser9Gly (rs6280) is a C to T substitution in the first exon of *DRD3* that results in a serine (Ser) to glycine (Gly) change at amino acid position 9 in the extracellular N-terminus of the receptor. The Gly/Gly variant in Chinese hamster ovary cells has a higher affinity for dopamine than the Ser/Ser and Ser/Gly variants, with no difference in affinity between the later two forms.[75] Using a selective D_3 ligand, however, the authors found that cells transfected with at least one Gly allele had a higher binding affinity for dopamine than those transfected with the Ser allele.[75] Similarly, in an in vitro setup with human embryonic kidney cells, the Gly variant had a 4 to 5 fold increased affinity for dopamine compared to the Ser variant.[140] In addition, cAMP inhibition was increased and MAPK signal duration was prolonged with the Gly variant relative to the Ser variant, indicating that Gly variant is associated with a more robust and prolonged activation of D_3-mediated signal transduction pathways.[140]

1.5.4 DRD4

A polymorphism in *DRD4* impacts the level of signaling of D_4 receptors. These receptors are primarily expressed in the PFC, hippocampus, amygdala, and hypothalamus.[141] *DRD4* gene is

located on chromosome 11p15 and has a 48 base-pair variable number of tandem repeats (VNTR) polymorphism in its third exon.[142] The number of repeats ranges from 2 to 11, represented as $D_{4.2}$ to $D_{4.11}$, respectively, causing a 32 to 176 amino-acid length difference in the third intracellular loop of the receptor, a region that binds to second messenger proteins.[141] The most common D_4 alleles in humans are the $D_{4.2}$, $D_{4.4}$, and $D_{4.7}$, with 5%, 70%, 20% prevalence, respectively.[143,144] In Chinese hamster ovary cells, the $D_{4.7}$ had a blunted response to dopamine compared to $D_{4.2}$ and $D_{4.4}$: The potency of dopamine to inhibit cAMP formation was reduced 2 to 3 fold with $D_{4.7}$ compared to $D_{4.2}$ and $D_{4.4}$.[76] Thus, individuals with the 7-repeat allele putatively fall on the right leg of the inverted-U curve.

1.6   Relevance to treatment of PD

The complications of dopaminergic treatment in PD include psychiatric disorders, such as hallucinations and impulse control behaviors.[27,33,35,43,145-148] Two issues demand attention: the greater vulnerability of certain patients to these side effects, and the role of genetic variation in eliciting them. Here, we propose and test a mechanism by which psychiatric side effects of dopamine replacement therapy can arise. By combining fine-tuned behavioral measures with low-cost genotyping of select dopamine gene polymorphisms, this proposal will identify biomarkers that distinguish patients who are at risk for medication-induced side effects. Individualized care for these patients will reduce their risk of incurring irreversible financial and personal costs due to medication-induced impulsivity and cognitive dysfunction.

The ultimate goal of PD research is to find the cause of and cure for the disease. In parallel to research focused on this goal, it is essential to ensure that the available medication used to ameliorate the motor symptoms of PD does not result in a degradation of the patients' quality of life. Although few alternative treatments are available for patients who show increased risk for hallucinations and impulsivity while taking dopaminergic medications, the identification of this high-risk group will permit early detection of adverse behaviors.

Table 1.1   Summary of risk alleles

Gene	Protein	Polymorphism	Risk allele	Functional significance	Proposed effect on dopamine signaling
COMT	Catechol-O-methyltransferase	Val158Met	Met	Reduced dopamine catabolism[72,73]	Increase
DRD2	D_2 receptor	C957T	T	Increased binding affinity for dopamine[133,134]	Increase
DRD3	D_3 receptor	Ser9Gly	Gly	Increased binding affinity for dopamine[75,140]	Increase
DRD4	D_4 receptor	VNTR	$D_{4.7}$-	Increased coupling to adenylyl cyclase[76,141]	Increase

* without any *DRD4* 7-repeat alleles.

Impulsivity

HC⁺ PD⁻

HC⁻

dopaminergic medication

PD⁺

high

low **Dopamine signaling** high
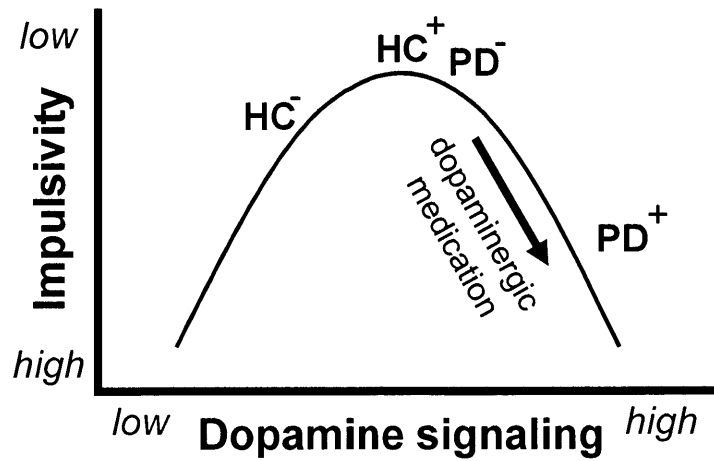
Figure 1.1   Inverted-U dopamine response curve

The inverted-U dopamine response curve has been established in animals and humans. Too little (left side of curve) and too much (right side of curve) dopamine signaling result in cognitive dysfunction. Consistent with this view, healthy adults with genotypes that reduce dopamine signaling (HC-) are impulsive. We predict that PD patients with heightened dopamine transmission (PD+) will be impulsive when receiving dopamine replacement therapy due to a dopamine overdose effect.

Dopaminergic cell degeneration

Severe (90%) dopamine loss in the nigrostriatal pathway

Moderate (30-50%) dopamine loss in the mesocorticolimbic pathway

Motor symptoms

Cognitive symptoms

Dopaminergic medication based on severity of motor symptoms

Reduced motor symptoms

Patients with low dopamine signaling do not experience medication-induced psychiatric side effects

Patients with high dopamine signaling experience dopamine overdose, causing psychiatric side effects

Figure 1.2   Model for the development of medication-induced side effects in PD

The dose of prescribed dopaminergic medications is primarily based on the severity of motor symptoms. In patients with increased dopamine signaling, medication levels that reduce motor symptoms have the potential to overdose the mesocorticolimbic pathway, which is much less affected than the nigrostriatal pathway.

2   Response inhibition

2.1   Introduction

Response inhibition is the capacity to stop a prepotent or habitual response.[149,150] Reduced inhibition is a common feature of several clinical conditions—trichotillomania (repetitive hair pulling), substance abuse, and ADHD. This impairment has, therefore, gained widespread attention in recent years.[150,151]

A common laboratory test of response inhibition, used in animals and humans, is the Stop Signal Task, which measures the ability to inhibit a motor action after it has been initiated. Participants are asked to respond as quickly as possible upon seeing a Go cue, and to inhibit this action if the Go cue is followed by a Stop cue. The Stop signal is presented only in a minority of trials, and thus responding becomes the prepotent action during the experiment. Inhibitory ability is indexed by the Stop signal reaction time (SSRT), which estimates the amount of time the brain needs to inhibit an ongoing action.

2.1.1   Neural substrates of response inhibition

The network of regions that mediates response inhibition includes the right inferior PFC (Brodmann areas 44, 45, and 47), right pre-SMA, and right subthalamic nucleus of the basal

ganglia. Here, we briefly review the evidence in support of each node's role in response inhibition.

In humans, damage to the right inferior PFC, but not the surrounding areas, resulted in slowed SSRT, and this measure was correlated with the extent of damage in this region.[152] Further, intracranial surface electrode recordings in humans showed increased activity in this region 100 to 250 msec after presentation of the Stop signal; this activity was grater when participants inhibited their movement on the Stop trials than when they failed to do so.[153]

Damage to the right pre-SMA also resulted in slowed inhibition, without affecting reaction times in trials without the Stop signal.[154] Functional MRI studies confirmed that the stopping process activated the right inferior PFC and right pre-SMA, and that greater activity in the inferior PFC was associated with better inhibitory ability.[155-157] Unlike inferior PFC, activity in the pre-SMA was not correlated with SSRT.[158] Still, temporary deactivation of the right inferior PFC or right pre-SMA using transcranial magnetic stimulation impaired inhibitory ability in healthy adults.[159,160]

Patients with cerebrovascular lesions in the basal ganglia had reduced inhibitory ability, though the authors did not identify the exact location of the basal ganglia lesions.[161] Functional MRI studies in healthy adults revealed that activation of the right subthalamic nucleus of the basal ganglia was associated with Stop, but not Go trials, and the strength of this activation was correlated with SSRT.[155,156,158]

Together, these studies suggest that the inferior PFC, pre-SMA, and subthalamic nucleus are important nodes in the response inhibition network.[151,162]

2.1.2 Response inhibition in PD

Researchers have documented reduced inhibitory ability in PD patients. In a Go/NoGo task, they responded more often than controls on trials when they should not have responded (NoGo trials).[163] Further, SSRT was significantly longer in PD patients than in age-, sex-, and education-matched controls.[164] This reduced inhibitory ability in PD was independent of general slowing and cognitive impairment,[164] indicating a selective deficit in inhibitory ability. One study showed that subthalamic nucleus stimulation in PD patients increased their inhibitory control,[165] although another demonstrated that deep brain stimulation (DBS) induced improvement was baseline dependent. Inhibitory ability increased in patients with the slowest baseline SSRTs but deteriorated in those with normal baseline SSRTs.[166] This finding is likely due an inverted-U relation between subthalamic nucleus activation and inhibitory control whereby DBS improved inhibitory ability in those with low baseline SSRTs, but impaired this ability in participants who had normal baseline response inhibition.

2.1.3 Pharmacology and genetics of response inhibition

Pharmacological studies in animals suggest that dopamine plays a critical role in modulating response inhibition: D-amphetamine, cocaine, and the dopamine reuptake inhibitor GBR 12909, all of which increase dopaminergic neurotransmission, decrease response inhibition in rats, measured by the number of premature responses in the 5-Choice Serial Reaction Time Task.[167-

[170] On this task, the dopamine antagonist alpha-flupenthixol blocked impulsivity induced by intra-accumbens injection of d-amphetamine.[167] Further, methylphenidate, which increases synaptic levels of dopamine, reduced inhibitory deficits in children and adults diagnosed with ADHD.[171-174]

The pharmacological alteration of response inhibition was baseline dependent, and improved inhibitory ability was limited to humans and rats with the worst performance at baseline.[175-179] This result is consistent with the inverted-U dopamine response hypothesis whereby only individuals on the left-leg of the inverted-U curve (i.e., those with reduced dopamine signaling) should improve when receiving dopaminergic medication.

Although hypoactivity of the serotonin system has traditionally been associated with forms of impulsivity, such as aggression and suicidality,[40,180] modulation of serotonin did not impact response inhibition measured by the Stop Signal Task. Specifically, dietary depletion of serotonin precursor tryptophan[181,182] or serotonin receptor blockade using a selective serotonin reuptake inhibitor did not impact response inhibition in rats or healthy adults.[183,184]

Genetic research also supports a role for dopamine in inhibitory control. A PET study showed that the number of D_2/D_3 receptors was lower in impulsive rats compared to non-impulsive ones.[185] Healthy adults with at least one 7-repeat allele of D_4, which reduces dopamine signaling, had longer SSRTs compared to individuals without the 7-repeat allele,[63] and children with ADHD who carried the 7-repeat allele of D_4 required higher doses of methylphenidate for symptom improvement.[65] Healthy adults with at least one Met allele of COMT showed greater

SSRT-related brain activation in the right inferior PFC than those with the Val/Val genotype,[186] which is associated with better inhibitory control.[155,186]

In summary, converging evidence from studies in animals, healthy humans, and humans with ADHD suggest that dopamine-induced changes in inhibitory ability follow and inverted-U curve, and that this curve can arise as a function of natural variation in genes that regulate the level of dopamine signaling.

2.1.4 Hypothesis

Building on prior work, we reasoned that variations in *COMT, DRD2, DRD3,* and *DRD4* would alter inhibitory ability in PD patients receiving dopamine replacement therapy. Two lines of evidence support this hypothesis: first, the baseline-dependent influence of medication on impulsivity, and second, the relation between genetic variation in the dopamine-system and activation in the network mediating response inhibition. We hypothesized that patients who carry genotypes that increase dopamine signaling would be more likely to experience deficits in response inhibition due to a dopamine overdose. We addressed four specific questions: (1) Do *COMT* Met/Met and Val/Met carriers have longer SSRTs than Val/Val carriers?, (2) Do *DRD2* T/T and C/T carriers have longer SSRTs than C/C carriers?, (3) Do *DRD3* Gly/Gly carriers have longer SSRTs than Ser/Gly and Ser/Ser carriers?, and (4) Do $D_{4.7}$- carriers have longer SSRTS than $D_{4.7}$+ carriers? We predicated that individuals with the risk variants of *COMT* (Met allele), *DRD2* (T allele), *DRD3* (Gly allele), and *DRD4* (absence of 7-repeat allele) would have longer SSRTs due to dopamine overdose.

2.2   Materials and methods

2.2.1   *Participants*

We recruited 123 patients with idiopathic PD from the Movement Disorders Units at the Massachusetts General Hospital and Brigham and Women's Hospital (**Table 2.1**). The inclusion criteria were: United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria,[187] established by collaborating neurologists; mild to moderate disease indicated by Hoehn and Yahr (H&Y) stages I-III; taking dopamine replacement therapy; no significant cognitive deficits indicated by Mini-Mental State Examination (MMSE)[188] score ≥ 26; at least 12 years of schooling; and ability to give informed consent. The exclusion criteria were: history of a brain disorder other than PD; serious medical conditions (e.g., cancer, diabetes, heart disease); and severe depression indicated by a Beck Depression Inventory (BDI)[189] score ≥18. All participants gave written informed consent using procedures approved by the MIT Committee on the Use of Humans as Experimental Subjects and by the Partners Human Research Committee.

Participants were taking their normal dose of dopaminergic medications and were optimally medicated during testing. The self-identified racial and ethnic distribution of participants was: 122 White / not Hispanic or Latino and 1 Asian.

To compare dopaminergic medication among patients, each participant's dopaminergic drug regimen was converted to a levodopa equivalent daily dose (LEDD) according to a published[146,190] formula: LEDD = levodopa/carbidopa regular (mg) + levodopa/carbidopa CR (mg) x 0.75 + [levodopa/carbidopa (mg) + levodopa/carbidopa CR (mg) x 0.75] x 0.33 if on

entacapone or tolcapone + [levodopa/carbidopa (mg) + levodopa/carbidopa CR (mg) x 0.75] x

1.2 if on 10 mg selegiline (x 1.1 if on 5 mg selegiline) + bromocriptine (mg) x 10 + pramipexole

(mg) x 67 + requip (mg) x 20 + pergolide (mg) x 100.

2.2.2 Experimental design

On each trial, a left- or right-pointing green arrow appeared on a black computer screen (**Figure**

2.1). For Go trials, participants indicated the direction of this arrow by pressing the left or right

arrow key on the keyboard as fast as possible, using their preferred index and middle fingers,

respectively. The arrow stimulus remained on the screen until participants responded (max 2.5

sec). The next trial started after a 1.5 sec interval, during which the black screen remained

blank.

On 25% of the trials, Stop trials, the arrow stimulus was replaced with a Stop signal (a red

vertical bar) after a variable delay (Stop signal delay). We asked participants to inhibit their

response when the Stop signal appeared. If they did so, the red bar remained on the screen for

2.5 sec. If participants erroneously pressed one of the arrow keys, the red bar disappeared

immediately. The next trial started after a 1.5 sec interval.

The Stop signal delay started at 250 msec and was adjusted using an adaptive staircase

method.[191] If participants successfully inhibited their response on a Stop trial, the Stop signal

delay was increased by 50 msec the next time a Stop signal appeared, thus making it harder to

exert inhibitory control. If participants failed to inhibit themselves on a Stop trial, the Stop

signal delay was decreased by 50 msec for the next Stop trial. This algorithm ensured that each

participant could inhibit roughly 50% of all Stop trials by the end of the experiment. This design allowed each participant to perform at his or her own inhibition threshold, equated the level of difficulty experienced by participants, and controlled for individual differences in speed of responding.[164]

We explained to the participants that they would not always be able to inhibit their response on Stop trials because the computer would adjust the difficulty of the task according to their performance level. We also asked them not to delay their response in anticipation of the Stop signal, but to inhibit their response when they saw the Stop signal. Participants completed 180 go and 60 Stop trials in 5 blocks with each block containing 36 Go and 12 Stop trials (240 trials total with an equal number of left- and right-pointing arrows in each block). Data analysis was limited to the fifth block to allow the staircase algorithm to converge on each participant's inhibitory threshold. Limiting the SSRT analysis to the fifth block ensured that all participants were performing at the same SSRT threshold—defined as the amount of advance warning a participant requires to be able to inhibit a habitual response 50% of the time—before they were compared with each other.

2.2.3 Genotyping

We extracted DNA from the venous blood of all participants using a QIAcube robotic workstation (Qiagen, Hilden, Germany). Aliquots of DNA were sent to Partners HealthCare Center for Personalized Genetic Medicine for genotyping. The *DRD2* C957T (rs6277), *DRD3* Ser9Gly (rs6280), and *COMT* Val158Met (rs4680) polymorphisms were genotyped using Sequenom hME chemistry, and *DRD4* exon III VNTR was genotyped using a previously published

protocol.[77] In our sample, 23, 69, and 31 patients carried the *COMT* Val/Val, Val/Met, and Met/Met genotypes, respectively. The *DRD2* C957T break down was 21 C/C, 62 C/T, and 42 T/T. These distributions did not depart from the Hardy-Weinberg equilibrium (*COMT*: χ^2 = 1.975, df = 1, *p* = 0.160; *DRD2*: χ^2 = 0.132, df = 1, *p* = 0.716), indicating that allele frequencies were in equilibrium in our cohort. Because only 8 and 12 participants fell in the $D_{4.7}$+ and *DRD3* C/C groups, respectively, we excluded *DRD3* and *DRD4* from further analyses.

2.2.4 Statistical analysis

The principal dependent variable was the SSRT, measured by subtracting the average Stop signal delay from the average correct Go reaction time in the final block.[191] We also examined the participants' reaction times and error rates on Go trials. A univariate analysis of covariance (ANCOVA) compared each variable of interest among different genetic subgroups. We included age and sex in the ANCOVA as covariates because previous research uncovered age and sex differences in cognitive control ability[192,193] and COMT enzyme activity.[73] We also included LEDD, disease duration, and H&Y stage as covariates in the model to control for differences among participants in dopamine replacement dosage and the severity of motor symptoms.

To examine the impact of training on inhibitory ability, we compared SSRTs in the first and fifth blocks of the experiment. Because the staircase algorithm may not have converged to the 50% inhibitory threshold in the first block for all participants, we first corrected SSRTs for inhibition thresholds—defined as the number of successfully inhibited trials—in each block, and then carried a repeated measures ANCOVA on the adjusted SSRTs. We followed significant results

with post-hoc tests. All data were analyzed using MATLAB 2009a (MathWorks Inc., Natick, MA) and SPSS 11.5 (SPSS Inc., Chicago, IL).

2.3   Results

We characterized the participants in terms of age, sex, PD duration, H&Y stage, LEDD, number on agonists, MMSE, BDI, and education across *COMT* genotypes (**Table 2.2**). A significantly larger number of *DRD2* C/C individuals were taking dopamine agonists as compared to C/T and T/T carriers (χ^2 = 6.915, df = 2, *p* = 0.032). Individuals with the C/T genotype of *DRD2* were slightly, but significantly, older than C/C and T/T patients (C/C: *M* = 63.4, *SD* = 8.7; C/T: *M* = 68.6, *SD* = 8.4; T/T: *M* = 64.4, *SD* = 8.5; C/T vs. C/C : *p* = 0.048; C/T vs. T/T: *p* = 0.048). This age difference was taken into account by including age a covariate in all analyses. Patients were well matched on all other characteristics across *DRD2* genotypes (**Table 2.3**).

Because the green arrow in the Go trials was visible only for 2.5 seconds, we examined whether any participants missed this response window. Among the 123 participants, 117 (95.1%) never missed the window while 6 (4.9%; 2 *COMT* Val/Met & *DRD2* C/C, 3 *COMT* Val/Met & *DRD2* T/T, 1 *COMT* Met/Met & *DRD2* T/T) participants missed the window on only a single Go trial. The number of successfully inhibited trials did not differ statistically among *DRD2* and *COMT* genotypes.

We used a univariate ANCOVA with SSRT as the dependent variable and genotype as the independent factor to examine effect of *COMT* variation on SSRT (**Figure 2.2A**). Age, sex, disease duration, total LEDD, and H&Y stage were covariates in the ANCOVA. The main effect

of *COMT* on SSRT was significant ($F_{2,115}$ = 3.673, *p* = 0.028, η^2 = 6.0%). Planned post-hoc comparisons revealed that Val/Met and Met/Met participants had significantly higher SSRT thresholds than Val/Val individuals (Val/Met vs. Val/Val: *p* = 0.004 one-sided; Met/Met vs. Val/Val: *p* = 0.018 one-sided). The effect of COMT on accuracy ($F_{2,115}$ = 0.518, *p* = 0.597) and reaction times ($F_{2,115}$ = 1.852, *p* = 0.162) on Go trials was not significant (**Figure 2.2B** and **C**). The effect of *DRD2* on SSRT ($F_{2,115}$ = 0.336, *p* = 0.715), Go trial accuracy ($F_{2,115}$ = 2.696, *p* = 0.072), and Go trial reaction times ($F_{2,115}$ = 0.437, *p* = 0.647) was not significant.

To examine whether *COMT* variation interacted with training, we compared SSRTs in the first and fifth blocks. Because SSRT thresholds were significantly different between the two blocks (*p* = 4.04 x 10^{-12}), we first corrected the SSRTs in the two blocks for this threshold difference: For each block, we ran a regression with the SSRT as the dependent variable and the percentage of successfully inhibited trials as the independent variable. Then we compared the standardized residuals from the two regressions. We ran a repeated measures ANCOVA with the standardized residuals as the dependent variables, and *COMT* genotype as the between-subjects factor. In both blocks, Val/Val carriers had lower standardized residuals (indicating better inhibitory ability) than those with at least one Met allele. Neither the main effect of the experimental block ($F_{1,115}$ = 1.085, *p* = 0.300), nor the interaction between block and genotype ($F_{2,115}$ = 0.853, *p* = 0.429) were significant.

2.4   Discussion

This study examined whether polymorphisms in *COMT, DRD2, DRD3,* and *DRD4* modulate inhibitory ability in PD. We addressed four specific questions: (1) Do *COMT* Met/Met and Val/Met carriers have longer SSRTs than Val/Val carriers?, (2) Do *DRD2* T/T and C/T carriers have longer SSRTs than C/C carriers?, (3) Do *DRD3* Gly/Gly carriers have longer SSRTs than Ser/Gly and Ser/Ser carriers?, and (4) Do $D_{4.7}$- carriers have longer SSRTS than $D_{4.7}$+ carriers? We predicated that those individuals with variants that increase dopamine signaling would have reduced inhibitory ability due to a dopamine overdose in networks that are relatively preserved in the early stages of the PD. We found that patients who carried at least one Met allele of *COMT*, which confers increased dopamine levels in the PFC, had longer SSRTs than non-carriers. This reduction in inhibitory control was not accompanied by changes in accuracy or reaction times in trials without a Stop signal, indicating that increased SSRT was not due changes in performance or a general slowing of reaction times. Unlike *COMT, DRD2* variation did not alter the SSRT. Due to sample sizes, we were unable to examine the influence of *DRD3* and *DRD4* on the SSRT.

The major finding of this experiment was that the Met allele of COMT resulted in a selective decrease in inhibitory ability in PD patients taking dopamine replacement therapy. Critically, this cognitive deficit was consistent with our prediction based on previous results showing an inverted-U relation between dopamine signaling and inhibitory ability. This finding highlights the future possibility of optimizing an individual's dopamine replacement therapy regimen based on their unique genetic profile.

Impact of COMT Val158Met polymorphism on SSRT

The observed effect of the *COMT* Val158Met polymorphism is consistent with the known neural substrates of response inhibition. Investigators have shown that normal function of the PFC, particularly right inferior frontal gyrus, is essential for successful response inhibition.[151] Further, too much dopamine in the PFC results in a general reduction in neuronal activity.[99-101] In an in vitro study in mice, investigators showed that application of high concentrations of dopamine to the PFC significantly reduced the number of action potentials produced by pyramidal neurons.[100] Similarly, in well trained monkeys performing a spatial working memory tasks, high levels of D1 agonists significantly reduced the delay period activity of pyramidal neurons.[99,101] Thus, it is likely that those with at least one Met allele of COMT had slowed SSRTs because of a reduction of neural activity in the PFC due to a dopamine overdose. We cannot rule out the possibility that the impact of COMT was due to its action at other nodes of the inhibitory network (e.g. pre-SMA or STN). Future functional imaging studies on the impact of the *COMT* Val158Met variation on response inhibition in PD patients may be able to localize specific nodes of interaction between dopamine replacement therapy and *COMT* variation.

No link between DRD2 C957T polymorphism and SSRT

The lack of a *DRD2* effect on response inhibition was surprising. D_2 receptors are densely expressed in the basal ganglia (including caudate and putamen), which constitute one of the nodes of the response inhibition network. A previous study reported that healthy adults with variants of *DRD2* that increased the expression of D_2 receptors had better inhibitory control than those with reduced D_2 expression levels.[194] Similarly, alcoholic carriers of the A1 allele of

the *ANKK1* Taq1A polymorphism, which is in linkage disequilibrium with *DRD2* C957T and is associated with 30% to 40% reduced D_2 receptor density in the striatum, had worse inhibitory control than A2/A2 carriers.[195] Further, PD patients who performed at the same level as controls in the Go/NoGo task had increased activity in the right caudate relative to controls, highlighting the importance of striatum for response inhibition in PD.[196]

No interaction between COMT and DRD2 on SSRT

Several investigators have shown a significant interaction between *COMT* and *DRD2* polymorphisms in healthy adults. In a word serial position test of memory, those with *COMT* Val/Val and *DRD2* C/C genotypes performed worse than those with Met/Met and T/T genotypes.[197] Further, Met carries had significantly better working memory manipulation performance relative to Val/Val carriers, but only when they did not carry the A1 allele of the *ANKK1* Taq1A.[198] Thus, to test for a possible interaction, we ran an ANCOVA with SSRT as the dependent variable, *COMT* and *DRD2* as independent variables, and age, sex, disease duration, disease severity, and LEDD as covariates. The main effect of *COMT* remained significant in this model (p = 0.043), but as before, the main effect of *DRD2* was not significant. We did not find an interaction between *COMT* and *DRD2*. Although this finding could be due to our small sample size (only 3 people were Val/Val and C/C carriers), the results suggest that the *COMT*Cal158Met, and not *DRD2* C957T, variation is the critical determinant of inhibitory ability in PD patients who take dopamine replacement therapy.

Training did not alter inhibitory ability among COMT genotypes

An interesting question was whether PD patients could be trained to shorten their time to inhibit their response. To examine this issue, we compared the SSRTs in the first and fifth blocks of our experiment. If training were effective, then SSRTs in the fifth block would be shorter than SSRTs in the first block. This finding would indicate that due to training, the participants needed less time to successfully inhibit a habitual response in the fifth block, relative to the first block. COMT Val/Val carriers had lower SSRTs (adjusted for the difference in stopping threshold between the two blocks) than those with at least one Met allele in both blocks. The main effect of the experimental block and the interaction between block and genotype were not significant ($p > 0.05$). These results highlighted that training did not alter inhibitory ability among COMT genotypes.

DRD3 and DRD4

We were unable to examine the influence of DRD3 and DRD4 variation on inhibitory control due small sample sizes. Because studies in healthy adults have shown a significant impact of DRD4 variation on inhibitory ability, this polymorphism may play an important role in PD inhibitory ability as well.[63] D3 receptors are densely expressed in the ventral striatum, which is spared from dopamine loss in the early stages of PD.[127,137,138,199] Because most dopamine agonists have a high affinity for D_3 receptors,[80,200] variations in DRD3 may play a crucial role in determining individual risk for dopamine-induced side effects. Future studies with larger sample sizes should examine the importance of these two genes for cognition in PD.

Conclusions

The dopamine overdose hypothesis posits that dopamine replacement therapy overloads networks that are relatively spared from dopamine cell death in PD, thus adversely affecting the functions carried by them.[24,25] Here, we advance this hypothesis by showing that medication-induced changes in behaviors mediated by these circuits also depend on variation in genes of the dopamine system. Specifically, we showed that participants with at least one Met allele of COMT, which is associated with increased dopamine levels in the PFC, had significantly worse inhibitory ability than Val/Val carries. These findings suggest that Met carriers have an increased risk for developing impulse control behaviors when taking dopamine replacement therapy.

Table 2.1   Characteristics of PD patients who completed the Stop Signal Task

Variable		PD patients
No. of participants		123 (80M; 43F)
Age (yrs)		66.3 (8.7)
PD duration (yrs)		5.5 (3.8)
H&Y	Stage 1	17
	Stage 2	98
	Stage 3	8
LEDD (mg/day)		610.9 (444.3)
% taking agonists		55.3%
MMSE		28.2 (1.3)
BDI		6.1 (4.1)
Education (yrs)		16.7 (2.9)

Results are presented as mean (*SD*), number, or percentage.

Table 2.2   Characteristics of *COMT* subgroups in the Stop Signal Task

Variable		*COMT* Val/Val	Val/Met	Met/Met	*p*
No. of participants		23	69	31	
Age (yrs)		68.0 (6.7)	65.8 (8.7)	66.3 (10.2)	0.600 [§]
Sex M:F		13:10	44:25	23:8	0.382 [¥]
PD duration (yrs)		5.0 (3.8)	5.1 (3.8)	6.7 (3.8)	0.116 [§]
H&Y	Stage 1	2	9	6	
	Stage 2	19	55	24	0.770 [£]
	Stage 3	2	5	1	
LEDD (mg/day)		557.9 (378.4)	595.4 (434.7)	685.0 (510.8)	0.533 [§]
% taking agonists		52.2%	56.5%	54.8%	0.935 [¥]
MMSE		28.0 (1.5)	28.2 (1.3)	28.3 (1.3)	0.577 [§]
BDI		5.8 (3.7)	6.0 (4.0)	6.7 (4.5)	0.688 [§]
Education (yrs)		16.7 (3.4)	16.7 (3.0)	16.5 (2.4)	0.951 [§]

§ ANOVA; ¥ Chi square test; £ Fisher's exact test.
Results are presented as mean (*SD*), number, or percentage.

Table 2.3   Characteristics of *DRD2* subgroups in the Stop Signal Task

Variable		*DRD2* C/C	C/T	T/T	*p*
No. of participants		21	62	40	
Age (yrs)		63.4 (8.7)	68.6 (8.4)	64.4 (8.5)	**0.013** [§]
Sex M:F		14:7	42:20	24:16	0.715 [¥]
PD duration (yrs)		5.5 (3.3)	5.6 (4.0)	5.3 (3.9)	0.909 [§]
H&Y	Stage 1	6	7	4	0.267 [£]
	Stage 2	15	50	33	
	Stage 3	0	5	3	
LEDD (mg/day)		616.4 (325.1)	582.6 (455.8)	651.9 (485.1)	0.746 [§]
% taking agonists		81.0%	48.4%	52.5%	**0.032** [¥]
MMSE		28.5 (1.2)	28.3 (1.3)	27.8 (1.3)	0.070 [§]
BDI		6.1 (3.4)	5.7 (4.1)	6.8 (4.4)	0.404 [§]
Education (yrs)		17.2 (2.3)	16.9 (3.1)	16.2 (2.9)	0.324 [§]

§ ANOVA; ¥ Chi square test; £ Fisher's exact test.
Results are presented as mean (*SD*), number, or percentage.
Significant results are indicated in bold font.
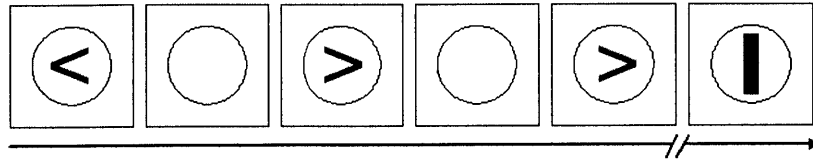
Figure 2.1   Sequence of events in the Stop Signal Task

Participants were instructed to respond in the Go trials and try to inhibit their responses in the Stop trials. Example sequence of events in the Stop Signal Task: hit left arrow key; hit right arrow key; suppress action to hit right arrow key after seeing the Stop signal (red vertical bar).
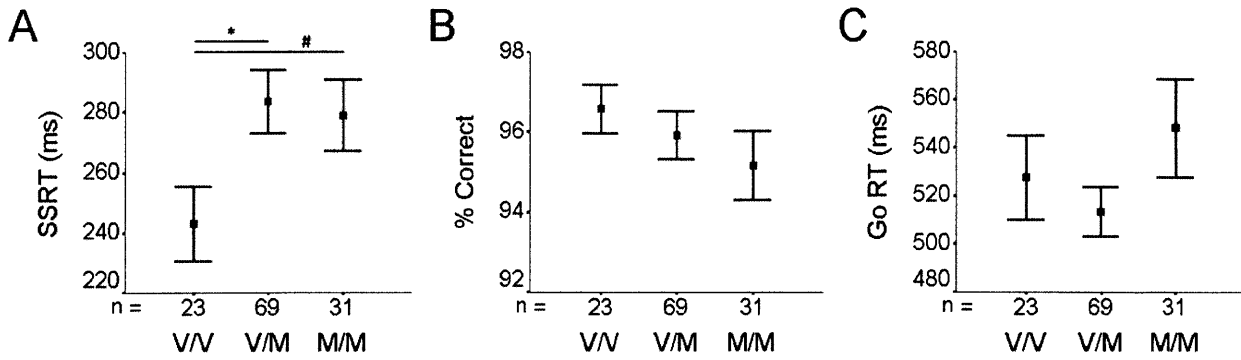
Figure 2.2   **SSRT as a function of *COMT* genotypes**

A) Patients with at least one Met allele had a significantly longer SSRT compared to Val/Val carriers. B) The groups did not differ in accuracy. C) The groups did not differ in reaction times on Go trials. Error bars depict *SEM*. * p = 0.004 one-sided; # p = 0.018 one-sided.
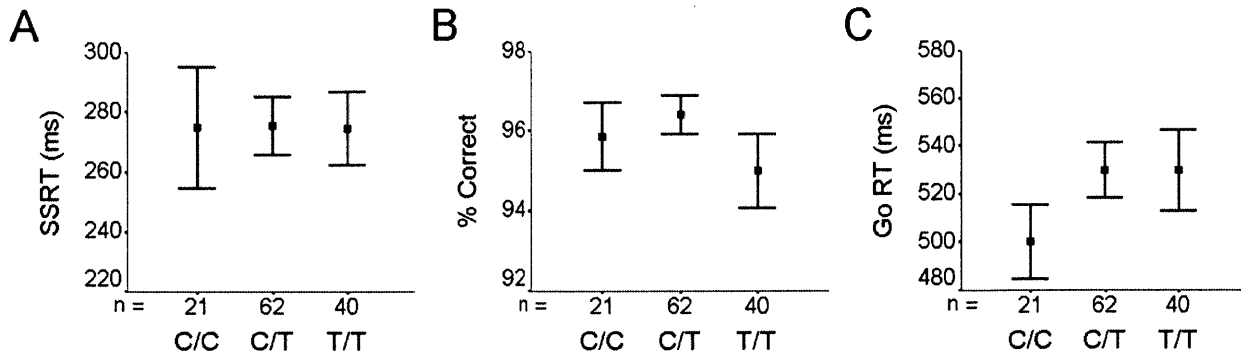
Figure 2.3   **SSRT as a function of *DRD2* genotypes**

A) *DRD2* subgroups did not differ in SSRT. B) The groups did not differ in accuracy. C) The groups did not differ in reaction times on Go trials. Error bars depict *SEM*.

3   Delay of gratification

3.1   Introduction

Delay of gratification is the ability to exert self-control by overriding the impulse to choose a small immediate reward instead of a larger delayed one.[26,40] This dimension of impulsivity is typically examined in the laboratory using the delay discounting task, whereby participants decide between smaller-sooner and larger-later choices. Humans and animals tend to discount the value of future rewards hyperbolically, often resulting in a preference for the more immediate option.[201]

Discounting, a robust effect, has been documented with primary (food, juice) and real or hypothetical secondary (money, gift voucher) rewards.[202-204] Participants vary considerably in the level of discounting of delayed rewards. Steeper discounting curves, corresponding to a stronger desire for immediate choices, are considered impulsive. This finding is common among smokers,[205,206] obese women,[207,208] and individuals with impulse control disorders such as heroin, cocaine, and methamphetamine addicts,[209-211] alcoholics,[212,213] pathological gamblers,[214] and individuals with ADHD.[215,216] Steeper discounting curves are a risk factor for substance abuse, alcohol addiction, and smoking.[217-221]

3.1.1 Neural substrates of delay discounting

Lesion and fMRI studies have identified a network of brain regions that are engaged during delay of gratification judgments. Humans with bilateral medial orbitofrontal cortex (OFC) damage, due to traumatic brain injury or ruptured aneurysms, showed a significantly increased preference for impulsive choices, relative to controls and lesion controls with damage to regions beyond the PFC.[202] Normal function of medial OFC may be necessary for selection of delayed choices because damage to non-OFC regions of the PFC did not alter discounting.[202] In particular, participants with ventromedial, but with some sparing of the medial OFC, or dorsolateral PFC damage performed discounting tasks similarly to controls and those with damage to cortex posterior to the central sulcus.[222]

Early lesion studies in rats provided conflicting accounts of OFC's role in temporal discounting. Two laboratories[223,224] showed that bilateral OFC lesions resulted in a preference for smaller-sooner rewards, while another found that OFC lesions increased preference for larger-later ones.[225] Subsequent studies provided an explanation for these discrepant results.[226,227] Investigators noticed that baseline levels of impulsivity differed among the three studies, and that a cue marked that gap between the selection of the larger-later reward and its delivery in the first two studies but not in the third one.[223-227] In a well-controlled experiment with rats, researchers showed that delay discounting performance depended on baseline levels of impulsivity and on the presence or absence of a cue between selection and delivery of the delayed rewards: OFC inactivation increased impulsivity in less impulsive rats in the presence of a cue, but decreased impulsivity in more impulsive rats when no cue was present.[226]

The interaction between the cue and discounting may have been due to the cues acting as a conditioned reinforcer: It is possible that the presence of the cue highlighted, to the less impulsive animals, that they had chosen the delayed signal and now must wait for their reward, thus reducing the desirability of the delayed reward.[228] Given the role of OFC in monitoring and updating subjective reward values and integrating this information with goals,[229] the absence of the cue may have deprived the OFC-lesioned impulsive animals from a salient teaching signal that would allow them to lower their internal value of the delayed reward through non-OFC compensatory mechanisms, thus making them appear less impulsive.[227,230]

Lesion studies have also identified the ventral striatum, specifically the nucleus accumbens core and basolateral nucleus of the amygdala (BLA), as two other nodes in the delay of gratification network. Selective lesions of these sites increased the preference for smaller-sooner rewards over the larger-later ones.[225,231,232] Importantly, the impulsive lesioned animals were able to discriminate between the small and larger rewards and preferred the larger rewards at zero delay. This finding suggests that the nucleus accumbens core and BLA may maintain the subjective value of rewards across the delay.[225,231,233]

Two accounts of the neural substrates of delay discounting have emerged from fMRI experiments in humans. McClure and colleges (2004) reported that limbic regions (including right ventral striatum, right medial OFC, and medial PFC) were more active, relative to baseline, when healthy young adults chose between immediately available rewards or delayed rewards.[204,234] In contrast, they found that regions known to mediate cognitive control (including right dorsolateral PFC, right ventrolateral PFC, right lateral OFC, and posterior

parietal cortices) were engaged when participants made choices between immediate versus delayed and delayed versus more-delayed rewards. Further, activity in cognitive control areas was correlated with choice difficulty, and these areas were more active than limbic regions when participants chose larger-later over smaller-immediate rewards.[204,234]

Another group obtained similar results using a slightly modified task.[235] McClure and his team interpreted these findings as evidence for two separate neural systems in the brain: an impulsive "β-system" corresponding to the limbic areas and a more patient "δ-system".[204,234,236] As discussed in the **Chapter 1**, cortex and basal ganglia are connected via distinct functional loops.[19] The β- and δ-systems map on to the cognitive/motor and limbic loops, respectively. Thus, these results suggest that activity in the limbic loop would enhance the likelihood of impulsive choices, while motor and cognitive loop activations would contribute to selection of non-impulsive choices.

Some investigators have noted that the β-δ account is inconsistent with human studies showing that medial OFC lesions increased impulsive choices.[202] They argue that if activation of the β-system led to more impulsive choices, then, contrary to empirical results, removal of the medial OFC should have strengthened the δ-system relative to the β-system and thus should have reduced impulsivity.

In contrast to McClure's two component model, Kable and colleges (2007) provided evidence for a unitary delay of gratification network.[237,238] They showed that fMRI activity in left ventral striatum, left medial PFC, and left posterior cingulate cortex correlated with the subjective

value of delayed rewards: Activity in these regions increased as the magnitude of the rewards increased or as the delay to rewards decreased.

They also noted that McClure's finding of increased activity in ventral striatum, medial OFC, and medial PFC in presence of immediately available options did not necessarily imply that these regions only value immediate rewards.[237] Because the subjective value of immediate rewards was higher than later rewards, the one-component model would predict that these regions would show a stronger BOLD signal on trials with an immediately available option compared to trials with only delayed options.[237]

The unitary network is also consistent with animal studies showing that lesions in the nucleus accumbens resulted in increased impulsivity. If higher activity in the accumbens signals higher expected future rewards and induces the animal to reject the small-immediate reward, then removal of the accumbens would deprive the animal of this signal and result in increased impulsivity.[51,231]

Additional evidence for the one-component model showed that activity in a similar set of regions was correlated with discounted value of future rewards.[239] Ballard and co-workers (2009) provided further evidence for the unitary model using a delay discounting task that could distinguish neural activity due to the magnitude and delay of future rewards.[240] They found that activity in the limbic loop (right nucleus accumbens, left medial PFC, and bilateral posterior cingulate cortex) was positively correlated with reward magnitudes, while activity in the cognitive loop (left dorsolateral PFC, right posterior parietal cortex, and left temporal-parietal junction) was negatively correlated with reward delays.[240] Critically, they

demonstrated that neural activity in all identified areas correlated with participants'

discounting rates.[240]

In summary, converging evidence indicates that specific regions within the limbic and cognitive

loops, which are a target of dopaminergic projections, are critically involved in delay of

gratification calculations.[204,234,237-241] Because VTA is relatively spared from degeneration in the

early stages of PD, exogenous dopamine may alter activity in this network, resulting in

maladaptive discounting of future rewards.

3.1.2 Delay discounting in PD

Few studies have examined delay of gratification as a measure of impulsivity in PD because

reports of increased impulsivity in PD were absent from the literature until the early 2000s.[242]

In one study, Voon and colleagues (2010) examined delay of gratification in PD patients with

impulse control behaviors (compulsive shopping or pathological gambling) and those without

them.[243] They found that discounting rates were not significantly different between the two

groups when they were off pramipexole, a D_2/D_3 receptor agonist. When the patients were

taking pramipexole, however, only those with impulse control behaviors showed increased

discounting rates.[243]

A subsequent study used an expanded set of impulsive behaviors (binge eating, compulsive

medication use, compulsive shopping, hypersexuality, pathological gambling, and punding), and

confirmed the observation that temporal discounting is increased in PD patients with impulse

control behaviors.[244] This study did not find an effect of medication on impulsivity. Critically,

they found that stimulus–reward association learning was preserved in patients with impulse control behaviors, but not in those without. This finding suggests that elevated discounting of future rewards in PD patients with impulse control behaviors is not due to abnormal reward learning.[244] Rather, these data imply that aberrant dopaminergic signaling in the ventral striatum and limbic loop likely result in decreased tolerance for delayed choices.[244] This reasoning is consistent with two lines of evidence: animal studies showing increased impulsivity with limbic loop lesions;[245] and fMRI results in healthy young adults showing that levodopa significantly increased activity in the limbic loop and markedly enhanced preference for smaller-sooner rewards.[239]

3.1.3 Pharmacology and genetics of delay discounting

Animal and human studies have consistently shown that dopaminergic agents can modulate the delay of gratification. Two medications that increase dopaminergic neurotransmission, d-amphetamine and methylphenidate, successfully reduced impulsivity in patients with ADHD.[41] Low doses of these agents also decreased delay discounting in healthy adults.[246,247]

In rats, acute administration of moderate doses of d-amphetamine reduced discounting in the presence of a conditioned reinforcer.[228,248,249] Acute administration of d-amphetamine in the absence of a conditioned reinforcer,[228] or long term administration of large doses of this drug, however, significantly decreased the value of delayed rewards.[249] Critically, impact of these agents also depended on baseline levels of impulsivity: d-amphetamine increased discounting in rats with low baseline levels of impulsivity, but had the opposite effect in rats with high baseline levels of impulsivity.[179]

D_1 and D_2 receptors can both modulate discounting rates. Investigators reported that systemic injections of the D_1/D_2 antagonist α-flupenthixol, D_2 antagonist raclopride, and D_3 agonist 7-OH-DPAT, and local medial PFC infusions of the D_1 antagonist SCH 23390 and D_1/D_5 agonist SKF 38393 increased impulsive choices in rats.[226,228,248,250,251] Moreover, nucleus accumbens shell expression levels of *DRD5* and medial PFC expression levels of *DRD1*, *DRD5*, and *calcyon* (whose protein product regulates D_1 receptor affinity for dopamine) were significantly greater in rats with high baseline levels of impulsivity compared to less impulsive rats.[251] This study, however, did not find a relation between *DRD2*, *DRD4*, and *COMT* expression levels and impulsivity. This negative result does not contradict the association between polymorphisms in these genes and impulsivity because gene expression levels do not predict receptor density or function.

Pharmacological evidence that D_2—a primary target of dopaminergic drugs used in PD—plays a role in discounting judgments is consistent with genetic results showing that humans with substance abuse problems, who typically have a reduced ability to delay gratification, have decrease striatal D_2 receptor densities.[252-254] Voon et al.'s report[243] that a D_2/D_3 agonist pramipexole increased impulsivity in PD patients with existing impulse control behaviors lends credence to this hypothesis.

The finding that dopaminergic agonists and antagonists can alter impulsivity underscores the nonlinear relation between impulsivity and dopaminergic signaling: positive or negative deviations from optimal dopamine concentrations can result in maladaptive behavior. Further, the interaction between dopaminergic agents and baseline levels of impulsivity suggests that

genetic factors play an important role in the behavioral outcome of dopamine replacement therapy.

No consensus exists on whether serotonin plays a role in delay discounting. Dietary serotonin depletion studies in healthy humans found no effects[255,256] or minor ones.[257] Similarly, animal studies have not produced consistent results. One study examined the relative contribution of the dopaminergic and serotonergic systems in a discounting task where the cost was either a delay or physical effort.[258] Animals treated with the D_2 receptor antagonist, haloperidol, chose the smaller-sooner reward more often than controls. The treated animals also chose the high effort/high reward choice significantly less often than control animals. The investigators found, however, that selective blockade of tryptophan hydroxylase, a rate limiting enzyme in synthesis of serotonin, only impacted delay-based decisions: serotonin depleted rats were more likely to chose the smaller-sooner reward over the larger-later reward, but their preference for high or low effort rewards was similar.

Other studies, however, did not find a relation between serotonin and delay discounting. For example, investigators found no differences in delay of gratification between serotonin depleted rats and controls.[259] This finding was confirmed in a second study that further showed serotonin depleted animals, particularly ones with high baseline levels of delay discounting, had a muted response to d-amphetamine treatment.[260] The serotonin-dependent response to d-amphetamine treatment indicates an interaction between serotonin and dopamine.

In vivo microdialysis experiments in rats have elucidated the differential contributions of dopamine and serotonin to delay of gratification judgments. Researchers found that serotonin

levels increased in the medial PFC, but not in the OFC, whereas DOPAC, a metabolite of the dopamine, levels increased in both medial PFC and OFC of rats performing a delay discounting task for food rewards.[261] Together, these results hint at a complex interaction between dopaminergic and serotonergic systems in mediating delay of gratification.

Healthy adults with candidate alleles that reduce dopamine signaling are more likely to choose smaller-sooner rewards than individuals who do not carry these alleles.[58,66] *COMT* Val/Val genotype was associated with increased discounting compared to Val/Met and Met/Met genotypes in healthy adults and abstinent alcoholics.[66] In addition to being more impulsive, Val/Val carriers had significantly increased brain activity in the posterior parietal cortex and dorsal PFC relative to Val/Met heterozygotes,[66] suggesting that the Val allele results in inefficient cortical function due to reduced dopamine levels.

Genes that regulate D_2 receptors also play a role in delay discounting: Healthy adults with at least one A1 allele of the *ANKK1* TaqI A, which is associated with reduced D_2 receptor density in the striatum, had steeper discounting curves than A2 carriers.[58] Further, *DRD2* interacted with *DRD4* such that individuals with both A1 and $D_{4.7}$ had the steepest discounting curves.[58]

In summary, healthy adults with *COMT*, *DRD2*, and *DRD4* polymorphisms, which putatively reduce dopamine signaling, have increased discounting rates.

3.1.4 Hypothesis

We tested the hypothesis that PD patients who carry the genotypes of *COMT*, *DRD2*, *DRD3*, and *DRD4* that increase dopamine signaling are more likely to show reduced ability to delay

gratification when receiving dopamine replacement therapy. Several lines of evidence support this hypothesis. First, the neural network that subserves delay of gratification judgments receives dense dopaminergic inputs from the ventral striatum, which is relatively spared from neurodegeneration in the early stages of PD. Second, deviations from optimal dopamine levels in this network result in reduced ability to delay gratification. Third, impact of dopaminergic agents on delay of gratification depends on baseline levels of impulsivity, which are partly determined by variations in genes that regulate the dopaminergic system.

Investigators have shown that healthy adults with genotypes that reduce dopamine signaling are more likely to choose smaller-sooner rewards than individuals who do not carry them.[58,66] Because of the inverted-U relation between dopamine signaling and cognition, we hypothesized that this pattern would be reversed in PD patients receiving dopamine replacement therapy due to dopamine overdose in preserved brain circuits: Patients with the candidate genotypes that increase dopamine signaling would show reduced ability to exert self-control and delay gratification, compared to patients who are non-carriers. We addressed four specific questions: (1) Do *COMT* Met/Met and Val/Met carriers have steeper discounting curves than Val/Val carriers?, (2) Do *DRD2* T/T and C/T carriers have steeper discounting curves than C/C carriers?, (3) Do *DRD3* Gly/Gly carriers have steeper discounting curves than Ser/Gly and Ser/Ser carriers?, and (4) Do $D_{4.7}$- carriers have steeper discounting curves than $D_{4.7}$+ carriers? We predicated that individuals with the risk variants of *COMT* (Met allele), *DRD2* (T allele), *DRD3* (Gly allele), and *DRD4* (absence of 7-repeat allele) would have increased discounting stemming from dopamine overdose.

3.2 Materials and methods

3.2.1 Participants

We recruited 128 PD patients who satisfied the inclusion and exclusion criteria described in **chapter 2 (Table 3.1)**. The self-identified racial and ethnic distribution of participants was: 125 White / not Hispanic or Latino, 2 White / Hispanic or Latino, and 1 Asian.

3.2.2 Experimental design

Participants made a series of choices between a $1,000 hypothetical reward delivered after a variable delay and a lesser reward available immediately (e.g., "Would you prefer to have $600 now or $1,000 after a week?"). The delay intervals were 1 week, 1 month, 4 months, 1 year, 3 years, and 9 years. The immediate reward amounts were $999, $995, $990, $960, $940, $920, $850, $800, $750, $700, $650, $600, $550, $500, $450, $400, $350, $300, $250, $200, $150, $100, $80, $60, $40, $20, $10, $5, and $1. To minimize the motoric demands of the task, all participants indicated their choice orally by saying "now" to choose the immediate option or "later" to choose the delayed option. The examiner recorded their responses by pressing one of two designated keys on a keyboard. Trials were not timed. Over the course of the experiment, each participant received all combinations of immediate rewards and delays presented above in a randomized order (174 trials total).

3.2.3 Genotyping

Genotyping was carried out according to the protocol described in **Chapter 2**. In our sample, 24, 72, and 32 patients fell in the *COMT* Val/Val, Val/Met, and Met/Met groups, respectively. The *DRD2* C957T break down was 21 C/C, 65 C/T, and 42 T/T. These distributions did not depart from the Hardy-Weinberg equilibrium (*COMT*: χ^2 = 2.144, df = 1, *p* = 0.143; *DRD2*: χ^2 = 0.245, df = 1, *p* = 0.621). Because only 9 and 12 participants fell in the $D_{4.7}+$ and *DRD3* C/C groups, respectively, we excluded *DRD3* and *DRD4* from further analysis.

3.2.4 Statistical analysis

The principal dependent variable was the discounting rate. We used the following approach to estimate the discounting rate for each participant: First, we estimated the present value (PV) of all delayed rewards using a hyperbolic discounting function, $PV = \dfrac{1000}{1 + k \cdot D}$, where "k" is the discounting rate, and "D" is delay to reward in weeks. For each trial, we used the present values of the selected ($PV_{selected}$) and rejected ($PV_{rejected}$) choices to calculate the probability of the selected item: $p = \dfrac{PV_{selected}^a}{PV_{selected}^a + PV_{rejected}^a}$, where "a" is a positive constant. Next, we used an optimization routine to find values of "a" and "k" that minimized the sum of logarithms of probabilities over all trials during the experiment. Because discounting rate "k" is not normally distributed, we applied a logarithmic transform before further analysis to normalize "k". A univariate analysis of covariance (ANCOVA) compared the logarithm of the discounting rates among different genotypes. We included age and sex in the ANCOVA as covariates because

previous research uncovered age and sex differences in cognitive control ability[192,193] and COMT enzyme activity.[73] We also included LEDD, disease duration, and H&Y stage as covariates in the model to control for differences in dopamine replacement dosage and the severity of motor symptoms among participants. We followed significant results with post-hoc tests. All data were analyzed using MATLAB 2009a (MathWorks Inc., Natick, MA) and SPSS 11.5 (SPSS Inc., Chicago, IL).

3.3   Results

Participants were well matched in terms of age, sex, PD duration, H&Y stage, LEDD, number on agonists, MMSE, BDI, and education across *COMT* genotypes (**Table 3.2**). A significantly larger number of *DRD2* C/C individuals were taking dopamine agonists compared to C/T and T/T carriers (χ^2 = 6.546, df = 2, *p* = 0.038). In addition, *DRD2* C/T carriers were significantly older than C/C carriers (C/C: *M* = 63.4, *SD* = 8.7; C/T: *M* = 68.6, *SD* = 8.2; *p* = 0.049). This age difference was taken into account by including age a covariate in all analyses. Patients were well matched on all other characteristics across *DRD2* genotypes (**Table 3.3**).

The probability of choosing the delayed reward decreased as the amount of the immediate reward, or latency of the delayed reward, increased for both *COMT* and *DRD2* genotypes (**Figure 3.1**). This result indicated that participants attended to manipulations of reward and delay during the experiment.

The subjective value of the delayed $1000 decreased for all genotypes as delay to the reward increased (**Figure 3.2**). The discounting rates for *COMT* and *DRD2* genotypes are presented in **Figures 3.3**. To examine the effect of variation of each gene of interest on reward impulsivity, we used a univariate ANCOVA with the logarithm of the discounting rates as the dependent variable and genotype as the independent factor. Age, sex, disease duration, total LEDD, and H&Y stage were covariates in the ANCOVA. The main effect of *COMT* on the discounting rate was not significant ($F_{2,120} = 0.885$, $p = 0.415$), but the main effect of *DRD2* was significant ($F_{2,120} = 3.313$, $p = 0.040$, $\eta^2 = 5.23\%$). Planned post-hoc t tests revealed that C/T and T/T carriers had significantly higher discounting rates compared to C/C carriers (C/C: $M = -5.2$, $SD = 1.3$; C/T: $M = -4.1$, $SD = 1.6$; T/T: $M = -4.3$, $SD = 1.7$; C/C vs. C/T: $p = 0.006$ one-sided; C/C vs. T/T: $p = 0.042$ one-sided).

3.4   Discussion

The goal of this study was to examine whether select polymorphisms that putatively result in increased dopamine signaling reduce the ability to delay gratification in PD patients receiving dopamine replacement therapy. Consistent with our hypothesis, we found that PD patients with at least one T allele of *DRD2* C957T had significantly increased discounting rates relative to C/C carriers. Contrary to our hypothesis, *COMT* Val158Met variation did not alter behavioral scores.

Impact of D₂ variation on delay of gratification

D_2 receptors are densely expressed in the ventral striatum and amygdala,[127-131] which are two nodes of the delay of gratification network.[225,231,232] Functional MRI studies in humans showed that the ventral striatum tracked the subjective value of delayed rewards,[237] and lesions of ventral striatum in rats resulted in reduced ability to delay gratification.[225,231,232] Increased D_2-dependednt signaling in these areas may adversely impact their function, resulting in a reduced ability to delay gratification. These regions are interconnected with the OFC.[19] Given the importance of OFC in delay of gratification, [237,238] it is also possible that altered activity in the OFC caused the observed results.

No effect of COMT Cal158Met polymorphism on delay of gratification

The negative *COMT* finding was unexpected and demands further explanation. *COMT* has not been extensively studied in delay discounting tasks. One study showed that healthy adults and abstinent alcoholics with at least one Met allele were significantly less impulsive than Val/Val homozygotes on a discounting task with hypothetical monetary rewards.[66] A second study, however, showed that the Met/Met homozygote ADHD adolescents on drug holiday and controls had increased discounting rates relative to carriers of at least one Val allele.[262] These authors did not carry out post hoc tests, but examination of the means and standard deviations in their paper reveled that the significant main effect of *COMT* was likely due the ADHD group alone. Some reasons for the discrepancy between the two studies may be differences in disease status, participant ages, and small sample sizes. Importantly, the authors of the second study told their participants prior to the experiment that one reward amount, randomly selected, would be given to the participant at the end of the experiment, regardless of the

choice delay. This instruction effectively voided the delay to reward manipulation and complicated the interpretation of their finding. Nonetheless, both studies suggested that COMT plays a role in delay of gratification decisions.

A possible explanation emerged from a study that examined delay discounting in healthy young adults taking low doses of levodopa (a Madopar pill containing 150mg levodopa).[239] Although all participants in the study showed decreased delay discounting on levodopa, the magnitude of the change in discounting was much greater for some than others. The authors found that the level of increase in discounting of future rewards on levodopa, relative to baseline, was significantly correlated with bilateral BOLD signal in the amygdala. Thus, individual susceptibility to medication-induced delay aversion may depend on the amygdala, where D_2 receptors are densely expressed.[127-131] COMT is critical for dopamine clearance in the PFC.[78] Thus, our finding that *DRD2*, but not *COMT*, variation altered discounting behavior is consistent with the finding that amygdala activity was correlated with medication-induced changes in delay of gratification judgments.

DRD3 and DRD4

Most dopaminergic agonists have a high affinity for D_4 receptors,[263] and the interaction between *DRD2* and *DRD4* modulates ability to delay gratification.[58] *DRD3* variation may also be important in determining cognitive response to dopamine replacement therapy, but we did not have enough participants to analyze the impact of *DRD3* and *DRD4* polymorphisms. Most dopamine agonists have a high affinity for D_3 receptors,[80,200] and D_3 receptors are densely expressed in the ventral striatum and limbic cortex and strategically located to modify functions

carried by the limbic loop.[127,137,138,199] Further, repeated administration of levodopa in animal models of PD resulted in overexpression and ectopic expression of D_3 receptors in the nucleus accumbens and striatum, respectively.[264] Voon et al's report that pramipexole, which has a 5-10 fold higher selectivity for D_3 than D_2 receptors,[200] decreased delay of gratification in PD patients with impulse control disorders further highlights the importance of elucidating the impact of D_3 variation in response to dopaminergic medication.

Conclusions

The present study adds to a growing body of literature that highlights the interaction between variations in genes of the dopamine system and cognitive response to medication in PD. Specifically, we showed that carrying the T allele of the *DRD2* C957T polymorphism was linked with more impulsive choices, and thus this allele may be a risk factor for behavioral impulsivity in PD patients taking dopamine replacement therapy.

Table 3.1   Characteristics of PD patients who completed the delay discounting task

Variable		PD patients
No. of participants		128 (82M; 46F)
Age (yrs)		66.6 (8.7)
PD duration (yrs)		5.6 (3.9)
H&Y	Stage 1	17
	Stage 2	102
	Stage 3	9
LEDD (mg/day)		615.3 (440.0)
% taking agonists		56.3%
MMSE		28.2 (1.3)
BDI		6.3 (4.1)
Education (yrs)		16.6 (2.8)

Results are presented as mean (SD), number, or percentage.

Table 3.2   Characteristics of *COMT* subgroups in delay discounting task

Variable		Val/Val	Val/Met	Met/Met	p Value
No. of participants		24	72	32	
Age (yrs)		69.6 (6.7)	65.8 (8.5)	66.4 (10.0)	0.175 [§]
Sex M:F		14:10	44:28	24:8	0.320 [¥]
PD duration (yrs)		5.2 (4.1)	5.2 (3.8)	6.8 (3.8)	0.135 [§]
H&Y	Stage 1	2	9	6	
	Stage 2	20	58	24	0.839 [£]
	Stage 3	2	5	2	
LEDD (mg/day)		569.7 (384.0)	594.5 (427.0)	696.4 (506.7)	0.475 [§]
% taking agonists		54.2%	58.3%	53.1%	0.862 [¥]
MMSE		27.7 (1.5)	28.3 (1.3)	28.2 (1.3)	0.251 [§]
BDI		6.3 (3.6)	6.1 (4.1)	6.5 (4.5)	0.918 [§]
Education (yrs)		16.5 (3.2)	16.7 (3.0)	16.5 (2.3)	0.967 [§]

§ ANOVA; ¥ Chi square test; £ Fisher's exact test.
Results are presented as mean (SD), number, or percentage.

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Table 3.3   Characteristics of *DRD2* subgroups in delay discounting task

Variable		*DRD2* C/C	C/T	T/T	*p* Value
No. of participants		21	65	42	
Age (yrs)		63.4 (8.7)	68.6 (8.2)	65.3 (8.9)	**0.027** [§]
Sex M:F		14:7	44:21	24:18	0.520 [¥]
PD duration (yrs)		5.5 (3.3)	5.7 (4.1)	5.3 (3.8)	0.858 [§]
H&Y	Stage 1	6	7	4	
	Stage 2	15	53	34	0.208 [£]
	Stage 3	0	5	4	
LEDD (mg/day)		616.4 (325.1)	591.6 (453.6)	651.5 (474.0)	0.792 [§]
% taking agonists		81.0%	49.2%	54.8%	**0.038** [¥]
MMSE		28.5 (1.2)	28.3 (1.3)	27.8 (1.3)	0.065 [§]
BDI		6.1 (3.4)	5.9 (4.2)	7.0 (4.2)	0.400 [§]
Education (yrs)		17.2 (2.3)	16.8 (3.0)	16.1 (2.8)	0.274 [§]

§ ANOVA; ¥ Chi square test; £ Fisher's exact test.
Results are presented as mean (SD), number, or percentage.
Significant results are indicated in bold font.
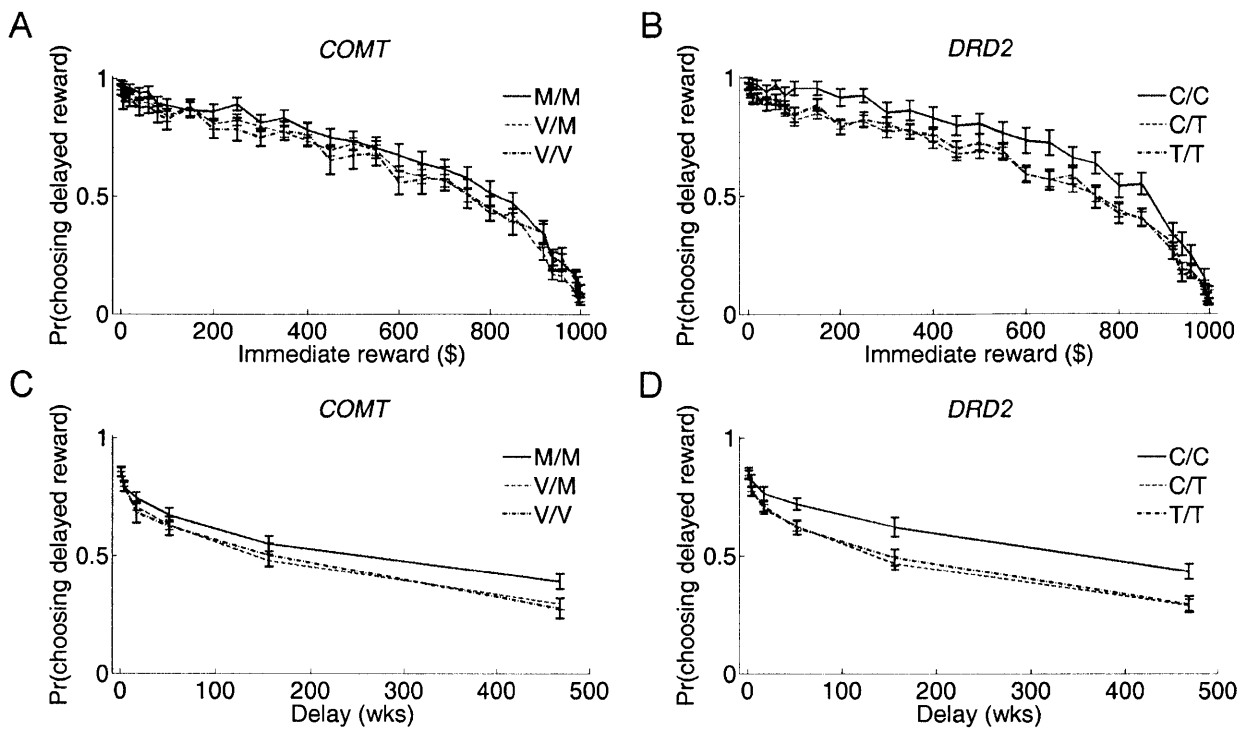
Figure 3.1 **Probability of choosing the delayed reward**

Probability of choosing the delayed reward as a function of the magnitude of the immediate reward and latency of the delayed reward. Probability of choosing the delayed reward decreased as the amount of the immediate reward increased for A) *COMT*, and B) *DRD2* genotypes. Probability of choosing the delayed reward decreased as the latency of the delayed reward increased for C) *COMT*, and D) *DRD2* genotypes. Error bars depict *SEM*. Abbreviations: M: methionine; V: valine.
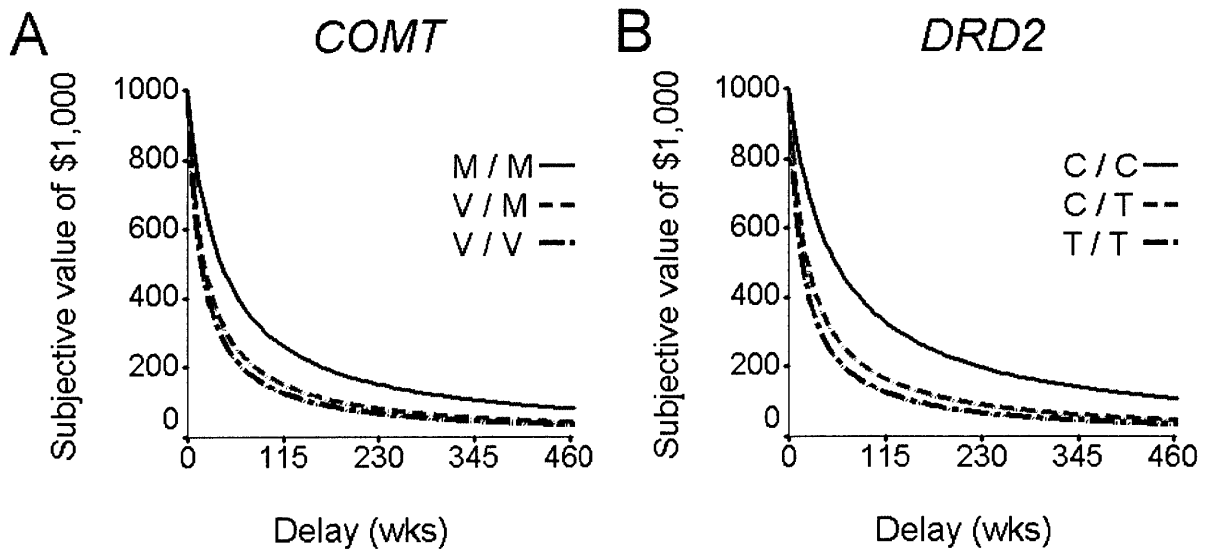
Figure 3.2   Discounting curves as a function of *COMT* and *DRD2* genotypes

Subjective value of $1,000 after delays ranging from 1 week to 9 years. Discounting functions broken down by A) *COMT* Val158Met, and B) *DRD2* C957T genotypes.
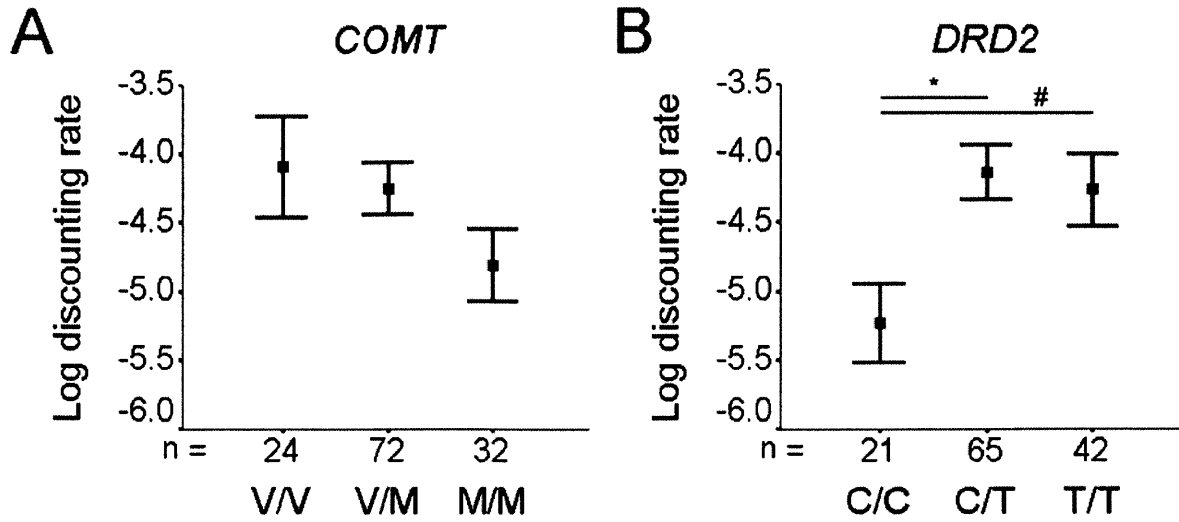
Figure 3.3   **Log-transformed discounting rates as a function of *COMT* and *DRD2* genotypes**

Smaller negative numbers reflect more reward impulsivity. A) We found no difference in discounting rates among the *COMT* genotypes. B) C/T and T/T carriers had significantly larger discounting rates compared to C/C carriers. Error bars depict *SEM*. * $p = 0.006$ one-sided; # $p = 0.042$ one-sided.

4   Reflection impulsivity

4.1   Introduction

Reflection impulsivity measures the tendency to gather and evaluate information before making a decision.[265] This often neglected dimension of impulsivity has traditionally been studied using the Matching Familiar Figures Test (MFFT), introduced by Kagan (1964).[266-268] In this task, participants view a line drawing of a familiar object (the standard) and 4, 6, or 8 probe pictures, presented below the standard picture.[267] One of them is identical to the standard while others contain slight variations in one or more features. The participants' task is to choose the probe that is identical to the standard. The critical variables are the latency of the first choice and number of errors until the correct choice is made, averaged over 12 or 20 trials.[267,268] Using the median latency of the first response and median number of errors, Kagan divided participants into four groups: Those with below median error rates and above median first-response latency were termed "reflective", whereas fast-inaccurate participants were considered "impulsive".[267] The other two groups, fast-accurate and slow-inaccurate, which constituted about a third of the participants, have received little attention.[269] Using this task, other researchers have identified several groups as reflection impulsive: children with ADHD,[269-271] current and past cigarette smokers,[272] current and past ecstasy (3,4-methylenedioxy-methamphetamine) users,[273-275] detoxified alchoholics,[276] and pathological gamblers.[277]

Some investigators have argued that the MFFT does not provide a pure measure of reflection impulsivity because it relies on latency measures, has low error rate reliability, and puts an undue burden on visual search and working memory capacities.[278-280] To overcome these shortcomings, another laboratory introduced the Information Sampling Task in 2006.[280] This task has a unitary measure of impulsivity, unlike the MFFT speed-accuracy composite score, and does not overly tax visual processing or working memory.[280] On each trial, participants explore a grid of 25 boxes that hides an underlying arrangement of two colors. Participants choose how much information they want to sample from the grid before deciding which of the two colors is in the majority among the 25 boxes. Because the explored areas remain visible during a trial, the task has a negligible working memory load. The extent of exploration before making a judgment provides an index of a participant's reflection impulsivity. Critically, fast-inaccurate responders on MFFT open significantly fewer boxes on the Information Sampling Task than slow-accurate responders, indicating that the task can successfully identify those who have traditionally been identified as reflection impulsive based on the MFFT double-median split. Similar to MFFT studies of individuals with impulse control problems, investigators have shown that alcohol-dependent individuals, problem gamblers,[281] and amphetamine, opiate,[280] and cannabis users[282] sample significantly less information than matched controls.[281]

4.1.1 Neural substrates of reflection impulsivity

Only one study has examined the neural substrates of reflection impulsivity. The investigators administered MFFT to a group of controls and individuals with OFC and non-OFC (primarily dorsolateral PFC) damage.[283,284] OFC-lesioned individuals had more errors and shorter first-

response latencies relative to controls, whereas those with non-OFC damage only had more errors.[283,284] This finding suggests that OFC plays a role in mediating reflection impulsivity. OFC receives dopaminergic inputs primarily from the VTA, which is relatively preserved in the early stages of PD. As a result, dopamine replacement therapy may cause a dopamine overdose in the OFC, resulting in reflection impulsivity.

4.1.2 Pharmacology and genetics of reflection impulsivity

The strongest evidence for a dopaminergic role in reflection impulsivity comes from studies of children diagnosed with ADHD. Reflection impulsivity is common in ADHD[269-271] and drugs that increase dopamine signaling—methylphenidate and amphetamine—significantly improve MFFT performance in these children.[285-287]

Investigators have also shown that bupropion, a selective dopamine and norepinephrine reuptake inhibitor,[288] was as effective as methylphenidate in reducing reflection impulsivity in children with ADHD.[289] Low doses of pramipexole—a dopamine agonist commonly used in PD—also reduced reflection impulsivity in controls who performed the Information Sampling Task.[290]

Only one study has examined reflection impulsivity in children with ADHD using the Information Sampling Task. The investigators administered this task to unmedicated and medicated (0.5 mg/Kg methylphenidate) children with ADHD, and age- and education-matched controls. The researchers found that unmedicated ADHD children opened the same number of boxes as controls but made significantly more poor decisions (i.e., they often chose the minority

color).[291] Using parametric tests, the authors did not find a difference in the performance of medicated and unmedicated children with ADHD and concluded that methylphenidate did not alter this dimension of impulsivity in ADHD. Examination of Figure 1A in their paper, however, revealed that the interquartile range of the "Total Poor Decisions on [Information Sampling Task]" for methylphenidate-treated children had a large overlap with that of controls, whereas the interquartile range of the placebo group had no overlap with controls. It is likely, therefore, that only a subgroup of the ADHD children showed improved performance on the Information Sampling Task when taking methylphenidate. Indeed, methylphenidate response in ADHD follows and inverted-U dopamine response curve: Children with the 7-repeat allele of DRD4— which reduces dopamine signaling—required higher doses of methylphenidate to reduce impulsivity and hyperactivity symptoms[65] and carriers of COMT Val allele were more likely to benefit from medication than Met carriers.[292] It is probable, therefore, that only children with reduced dopamine signaling improved in performing the Information Sampling Task when taking methylphenidate.

It is unclear whether serotonin plays a role in reflection impulsivity. Some investigators argued that because ecstasy is neurotoxic to serotonin (and to a lesser extent to dopamine) cells, increased reflection impulsivity—shorter response latencies and more errors on the MMFT[273-275]—in ecstasy users, compared to controls, indicates that serotonin modulates reflection impulsivity. This view is not accepted universally, however, because other investigators reported similar performance between ecstasy users and controls on the Information Sampling Task.[282]

Accumulating evidence shows that dopamine gene polymorphisms impact reflection impulsivity. Researchers showed that drug-naïve children diagnosed with ADHD who had the 7-repeat allele of *DRD4* were significantly more impulsive on the MFFT than children who did not carry the allele.[64] These children made significantly more errors and had significantly shorter response times.[64] Critically, the two groups did not differ in response inhibition, measured by the Stop Signal Task, indicating that differences in MFFT response latencies were not due simply to reduced motor inhibition. Another laboratory found a significant effect of variation in the dopamine beta hydroxylase gene—which encodes the protein that converts dopamine to norepinephrine—on MFFT performance in non-drug-naïve ADHD patients, though researchers could not reproduce the *DRD4* result.[293] In summary, although in their infancy, genetic studies suggest that variation in genes of the dopamine system alters reflection impulsivity.

4.1.3 Hypothesis

A lesion study in humans has linked evidence gathering to OFC function.[283] This area is susceptible to dopamine overdose in PD because dopaminergic inputs to the orbitomedial PFC are relatively spared, at least in the early stages of the disease.[24] Genetic studies showed that increasing dopaminergic signaling in children with ADHD—who putatively have low baseline levels of dopamine[294]—improved their performance on measures of reflection impulsivity.[64] Because of dopamine overdose, we hypothesized that this pattern would be reversed in PD: Patients who carry candidate alleles that increase dopamine signaling would show a reduced tendency to gather and evaluate evidence before making a decision while taking dopamine replacement therapy, compared to non-carriers. We addressed four specific questions: (1) Do

COMT Met/Met and Val/Met carriers sample less information than Val/Val carriers?, (2) Do *DRD2* T/T and C/T carriers sample less information than C/C carriers?, (3) Do *DRD3* Gly/Gly carriers sample less information than Ser/Gly and Ser/Ser carriers?, and (4) Do $D_{4.7}$- carriers sample less information than $D_{4.7}$+ carriers? We predicated that individuals with the risk variants of *COMT* (Met allele), *DRD2* (T allele), *DRD3* (Gly allele), and *DRD4* (absence of 7-repeat allele) would open fewer boxes in the Information Sampling Task, indicating increased reflection impulsivity due to dopamine overdose.

4.2 Materials and methods

4.2.1 Participants

We recruited 130 PD patients who satisfied the inclusion and exclusion criteria described in **chapter 2 (Table 4.1)**. The self-identified racial and ethnic distribution of participants was: 127 White / not Hispanic or Latino, 2 White / Hispanic or Latino, and 1 Asian.

4.2.2 Experimental design

We adapted the Information Sampling Task.[295] Participants viewed a 5x5 matrix of gray boxes that hid an underlying arrangement of two colors (**Figure 4.1**). On each trial, the two colors were selected randomly by the computer on each trial and could be blue, cyan, green, magenta, red, or yellow, with the arrangement and proportion of boxes in each color changing from trial to trial. Each gray box had a number (1 to 25). To limit the motor demands of the tasks, participants called the number on the gray box they wanted to open, and the

experimenter clicked the gray box to reveal the underlying color to the participants. Once clicked, the boxes remained visible during the remainder of the trial to minimize the memory requirements of the task. Participants uncovered as many gray boxes as they desired at their own rate. When they were ready to decide which of the two underlying colors was in the majority among the total array of boxes, they indicated their choice orally and the experimenter recorded their response by clicking one of the two dedicated boxes at the bottom of the screen. Participants received feedback on whether their choice was correct or incorrect. A correct choice earned them 100 points, while an incorrect choice resulted in a loss of 100 points. We asked the participants to maximize the number of points they earned during the experiment. If participants completed a trial in less than 30 sec, they had wait for the remainder of the 30 sec before the next trial started. This minimum trial-to-trial wait period was programmed into the experiment to deter participants from answering quickly to finish the task. Participants completed one practice trial before starting the experiment. During the experiment, they completed two trials for each of the following color proportions: 13:12, 14:11, 15:10, and 16:9 (total of 8 trials).

4.2.3 Genotyping

Genotyping was carried out according to the protocol described in **Chapter 2**. In our sample, 26, 72, and 32 patients fell in the *COMT* Val/Val, Val/Met, and Met/Met groups, respectively. The *DRD2* C957T break down was 21 C/C, 66 C/T, and 43 T/T. These distributions did not depart from the Hardy-Weinberg equilibrium (*COMT*: χ^2 = 1.575, df = 1, *p* = 0.210; *DRD2*: χ^2 =

0.267, df = 1, p = 0.605). Because only 9 and 13 participants fell in the $D_{4.7}$+ and *DRD3* C/C groups, respectively, we excluded *DRD3* and *DRD4* from further analysis.

4.2.4 Statistical analysis

The principal dependent variable was the average number of boxes that a participant opened before making their decision. A univariate analysis of covariance (ANCOVA) compared the mean number of opened boxes among different genotypes. Because previous research uncovered age and sex differences in cognitive control ability[192,193] and COMT enzyme activity,[73] we included age and sex in the ANCOVA as covariates. We also included LEDD, disease duration, and H&Y stage as covariates in the model to control for differences in dopamine replacement dosage and the severity of motor symptoms among participants. Because the number of earned points and accuracy convey the same information, we only analyzed accuracy using an ANCOVA with age, sex, disease duration, H&Y stage, and LEDD as covariates. When ANCOVAs were significant, we conducted post-hoc tests. All data were analyzed using MATLAB 2009a (MathWorks Inc., Natick, MA) and SPSS 11.5 (SPSS Inc., Chicago, IL).

4.3   Results

Participants were well matched in terms of age, sex, PD duration, H&Y stage, LEDD, number on agonists, MMSE, BDI, and education across *COMT* genotypes (**Table 4.2**). A significantly larger number of *DRD2* C/C individuals were taking dopamine agonists as compared to C/T and T/T

carriers (χ^2 = 7.450, df = 2, p = 0.024). Further, *DRD2* C/T carriers were significantly older than

C/C carriers (C/C: M = 63.4, *SD* = 8.7; C/T: M = 68.5, *SD* = 8.1; p = 0.051). This age difference

was taken into account by including age a covariate in all analyses. Patients were well matched

on all other characteristics across *DRD2* genotypes (**Table 4.3**).

To examine the effect of variation in each gene on reflection impulsivity (**Figure 4.2**), we used a

univariate ANCOVA with average number of opened boxes as the dependent variable and

genotype as the independent factor. Age, sex, disease duration, total LEDD, and H&Y stage

were covariates in the ANCOVA. The main effect of *COMT* on the number of opened boxes was

not significant ($F_{2,122}$ = 2.507, p = 0.086), but the main effect of *DRD2* was significant ($F_{2,122}$ =

3.794, p = 0.025, η^2 = 5.86%). Planned post-hoc comparisons revealed that T/T carriers opened

significantly fewer boxes than C/C carriers before making a decision, while C/T and C/C

subgroups were similar (C/C: M = 12.6, *SD* = 4.5; C/T: M = 12.8, *SD* = 5.3; T/T: M = 10.5, *SD* = 3.6;

C/C vs. T/T: p = 0.050 one-sided; C/T vs. C/C: p = 0.362 one-sided). Accuracy did not differ

among the *COMT* (Val/Val: M = 96.6%, *SD* = 9.1%; Val/Met: M = 96.9%, *SD* = 7.2%; Met/Met: M

= 96.1, *SD* = 8.1%; p = 0.826) and the *DRD2* (C/C: M = 97.6%, SD = 5.0%; C/T: M = 97.0%, *SD* =

7.9%; T/T: M = 95.6%, *SD* = 8.6%; p = 0.596) genotypes.

4.4   Discussion

This experiment tested the hypothesis that pharmacogenetic elevation of dopaminergic

signaling in PD patients would increase reflection impulsivity. Consistent with our hypothesis,

the results showed that medicated PD patients with the *DRD2* T/T genotype were significantly

more reflection impulsive than C/C carries, but C/C and C/T carriers showed similar performance.

Impact of D_2 variation on reflection impulsivity

A lesion study in humans showed that reflection impulsivity is linked with OFC function.[283] D_2 receptors are densely expressed in limbic structures, such as amygdala, [127-131] that have strong connections with the OFC.[22] Therefore, excessive D2 signaling may indirectly impair OFC function, causing increased reflection impulsivity.

COMT variation did not influence reflection impulsivity

We did not find a main effect of the *COMT* Val158Met polymorphism on reflection impulsivity. Reports of an association between *COMT* variation and cognition are primarily from tasks that have heavy executive demands, such as the Wisconsin Card Sorting Test[90,296] and the n-Back task.[90] The Wisconsin Card Sorting Test[297] uses a set of cards containing geometric figures. Participants learn—by trial and error—to sort the cards according to a rule (color, form, or number). Then, without a warning, this rule changes and they must learn to sort the cards according to a new rule. Therefore, stable maintenance of a rule while it is relevant—a task that heavily depends on PFC function[298]—is a critical requirement for successful completion of the task. In the n-Back task,[299] participants must maintain and monitor a sequence of stimuli in working memory, and respond when a stimulus is identical to one presented n-trials back. Because of its maintenance and monitoring feature, this task, similar to the WCST, relies heavily on working memory and the PFC. The lack of a *COMT* effect in this study could be due to the

low executive demands of the Information Sampling Task. Specifically, because the explored boxes remained visible during the trial, participants had immediate access to all the information they needed to make a decision. Importantly, they did not need to maintain the ratio of the explored colors in memory because this information was on the computer screen in front of them.

COMT and DRD2 interaction on reflection impulsivity

It is possible that *COMT* exerted an influence in this experiment through an interaction with *DRD2*. To examine this hypothesis directly, we combined the C/T and C/C genotypes of the *DRD2* C957T polymorphism and then ran an ANCOVA with *COMT* (Val/Val vs. Val/Met vs. Met/Met) and *DRD2* (T/T vs. C/T & C/C) as the independent factors. Age, sex, disease duration, total LEDD, and H&Y stage were covariates in this model. Similar to our previous analysis, the main effect of *DRD2* was significant ($F_{1,119}$ = 10.410, p = 0.002, η^2 = 8.04%) and the main effect of *COMT* was not ($F_{2,119}$ = 1.768, p = 0.175). Critically, the new analysis uncovered a significant interaction between *COMT* and *DRD2* ($F_{2,119}$ = 3.323, p = 0.039, η^2 = 5.29%). Carriers of the *COMT* Met/Met genotype opened more boxes (i.e., they were not reflection impulsive) but only when they did not carry the *DRD2* T/T genotype (**Figure 4.3**). *DRD2* T/T homozygotes showed increased impulsivity, independent of the number of *COMT* Met alleles they carried.

The interaction between *COMT* Val158Met and *ANKK1* Taq1a follows the inverted-U dopamine response curve. Investigators showed that Met/Met carriers performed better than Val carriers on the Stroop Task in the presence of at least one A1 allele—which results in a 30 to 40% reduction in the density of striatal D_2 receptors.[300] In the absence of the A1 allele, however,

Met/Met carriers performed worse than Val carriers. The researchers also measured prolactin levels in their participants. Because prolactin is inhibited by dopamine, levels of this protein provided an indirect measure of dopamine levels. They showed that prolactin levels were low in the Met/Met individuals who did not carry A1 (the A1- group) but were high in Met/Met and A1 carriers. This result indicated that too much dopamine in the Met/Met and A1- carriers resulted in impaired performance, whereas optimal dopamine levels in the Met/Met and A1 carriers allowed for best performance.

Our finding that Met/Met carriers who did not have the DRD2 T/T genotype had the least reflection impulsivity is consistent with the above report and the inverted-U dopamine response curve. Because DRD2 C957T and ANKK1 Taq1a are in strong linkage disequilibrium (d' = 0.832 to 1, indicating near complete dependence),[132,134] the A1 group in the above study likely corresponded to our C/C-C/T group. Met/Met carriers in the A1 group had the highest prolactin levels among all COMT and ANKK1 genotype combinations in another study,[301] indicating that the Met/Met and A1+ combination is associated with reduced dopamine levels. It is not surprising, therefore, that the Met/Met carriers in the C/C-C/T group had the best performance in our study: These individuals likely had the lowest levels of baseline dopamine, and thus did not experience a dopamine overdose while taking dopamine replacement therapy.

Conclusions

We showed that the DRD2 T/T homozygotes—who putatively have increased D_2 receptor density in the striatum and increased D_2 affinity for dopamine—had greater reflection impulsivity than C/C carriers. We also showed a significant interaction between COMT and

DRD2, whereby individuals with the lowest amounts of baseline dopamine performed better than all other groups while taking dopamine replacement therapy

Table 4.1   Characteristics of PD patients who completed the Information Sampling Task

Variable		PD patients
No. of participants		130 (84M; 46F)
Age (yrs)		66.5 (8.7)
PD duration (yrs)		5.5 (3.8)
H&Y	Stage 1	17
	Stage 2	103
	Stage 3	10
LEDD (mg/day)		617.2 (435.0)
% taking agonists		55.4%
MMSE		28.2 (1.3)
BDI		6.2 (4.1)
Education (yrs)		16.7 (2.8)

Results are presented as mean (*SD*), number, or percentage.

Table 4.2   Characteristics of *COMT* subgroups in Information Sampling Task

Variable		Val/Val	Val/Met	Met/Met	*p* Value
		COMT			
No. of participants		26	72	32	
Age (yrs)		68.8 (7.1)	65.8 (8.5)	66.4 (10.0)	0.338 [§]
Sex M:F		15:11	45:27	24:8	0.334 [¥]
PD duration (yrs)		5.3 (4.1)	5.1 (3.7)	6.8 (3.8)	0.115 [§]
H&Y	Stage 1	2	9	6	
	Stage 2	21	58	24	0.708 [£]
	Stage 3	3	5	2	
LEDD (mg/day)		583.6 (371.6)	594.1 (423.0)	695.4 (506.7)	0.496 [§]
% taking agonists		53.8%	56.9%	53.1%	0.922 [¥]
MMSE		27.8 (1.4)	28.2 (1.3)	28.2 (1.3)	0.323 [§]
BDI		6.1 (3.5)	6.1 (4.2)	6.5 (4.5)	0.890 [§]
Education (yrs)		16.7 (3.2)	16.7 (3.0)	16.5 (2.3)	0.962 [§]

§ ANOVA; ¥ Chi square test; £ Fisher's exact test.
Results are presented as mean (*SD*), number, or percentage.

Table 4.3   Characteristics of *DRD2* subgroups in Information Sampling Task

Variable		*DRD2* C/C	*DRD2* C/T	*DRD2* T/T	*p* Value
No. of participants		21	66	43	
Age (yrs)		63.4 (8.7)	68.5 (8.1)	65.1 (8.9)	**0.024** [§]
Sex M:F		14:7	45:21	25:18	0.550 [¥]
PD duration (yrs)		5.5 (3.3)	5.7 (4.1)	5.3 (3.8)	0.840 [§]
H&Y	Stage 1	6	7	4	
	Stage 2	15	53	35	0.196 [£]
	Stage 3	0	6	4	
LEDD (mg/day)		616.4 (325.1)	593.6 (446.9)	653.8 (468.6)	0.782 [§]
% taking agonists		81.0%	47.0%	55.8%	**0.024** [¥]
MMSE		28.5 (1.2)	28.3 (1.3)	27.8 (1.3)	0.082 [§]
BDI		6.1 (3.4)	5.8 (4.3)	6.9 (4.2)	0.388 [§]
Education (yrs)		17.2 (2.3)	16.8 (3.0)	16.2 (2.9)	0.362 [§]

§ ANOVA; ¥ Chi square test; £ Fisher's exact test.
Results are presented as mean (*SD*), number, or percentage.
Significant results are in bold font.
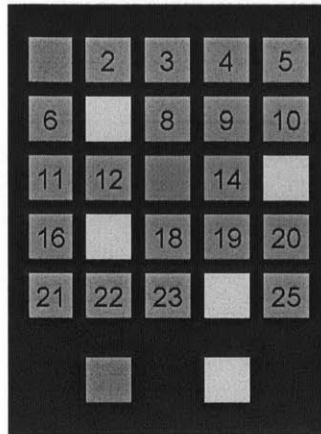
Figure 4.1   **Information Sampling Task**

In this example, a participant has revealed boxes 1, 7, 13, 15, 17, and 24 before deciding whether the green or the yellow boxes are in the majority.
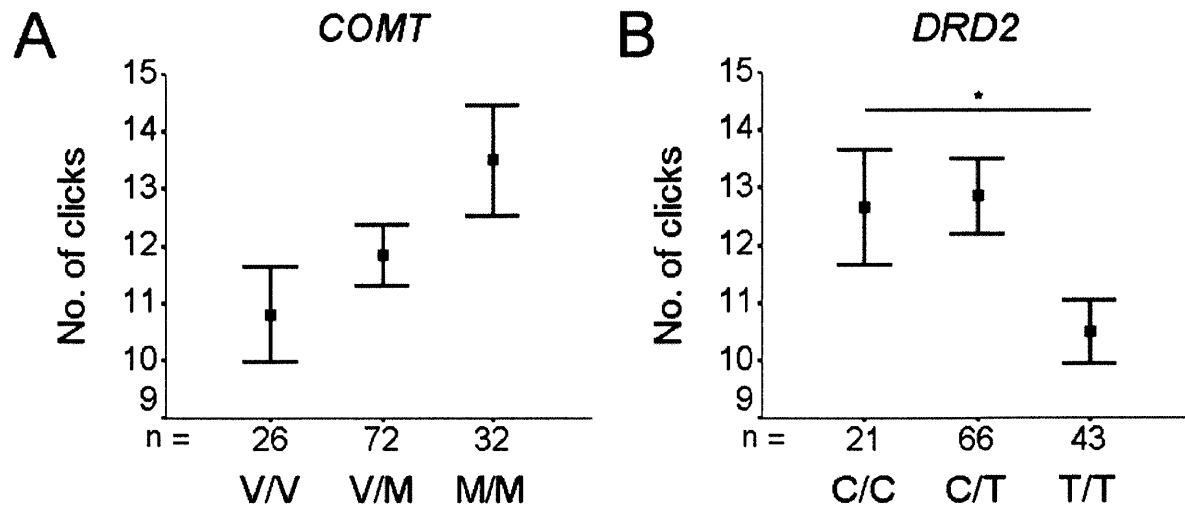
Figure 4.2   Number of explored boxes as a function of COMT and DRD2 genotypes

COMT did not have a direct effect on reflection impulsivity (A), while the T/T genotype of *DRD2* C957T polymorphism resulted in increased reflection impulsivity (B). Error bars depict *SEM*. $* p = 0.05$.
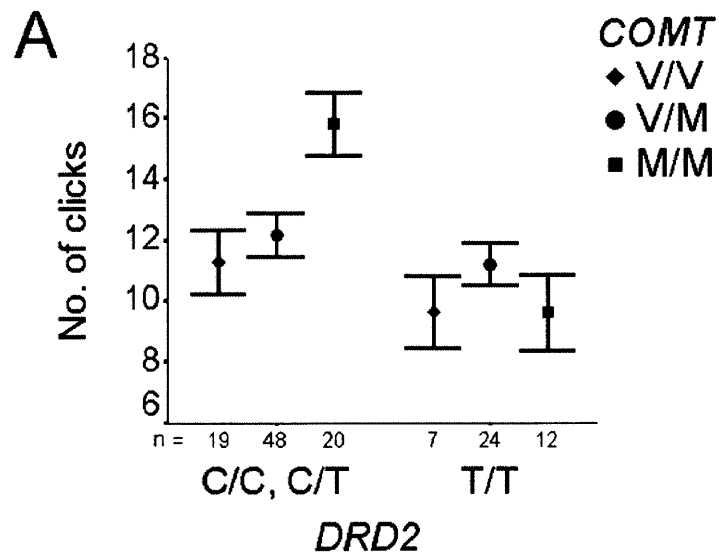
Figure 4.3   Interaction between COMT and DRD2 in the Information Sampling Task

DRD2 T/T homozygotes were reflection impulsive, independent of the number of COMT Met alleles. COMT Met/Met genotype resulted in decreased reflection impulsivity, but only in participants who did not carry the DRD2 T/T genotype.

5   Hallucinations

5.1   Introduction

Hallucinations are a common occurrence in PD and typically start several years after disease onset. Cross-sectional studies indicate that roughly a third of non-demented patients on chronic dopamine replacement therapy experience hallucinations, while longitudinal studies reveal that up to 75% of patients develop hallucinations over a 20-year period.[302] The prevalence of hallucination in PD patients with dementia is over 50%,[303] but hallucinations in that context are beyond the scope of this chapter. Our focus is on hallucinations that occur in the context of dopamine replacement therapy in patients who retained insight into the nature of their hallucinations and were awake and alert, with eyes open, when the unusual experiences occurred.

The most prevalent forms of hallucinations in PD are visual, auditory, and benign. Typical visual hallucinations consist of seeing a few people, animals, or objects, in color or black-and-white, and stationary or moving.[43] Patients are often external observers of the scene and at first cannot distinguish whether the images are real or imaginary, but, in the absence of dementia, they eventually realize that the hallucinations are unreal.[43,304] Hallucinations disappear in seconds to minutes on their own or after patients try to interact with them or touch them.[43] Visual hallucinations may occur during the day or night but are more frequent in low-light

conditions.[43] Early in the disease, they are neutral or friendly, but later on insects, rats, worms, and snakes may appear.[304,305] Auditory hallucinations may accompany visual hallucinations, where they provide the soundtrack, or they may occur independently as ringing and knocking sounds, or as music.[43] Auditory hallucinations in PD, unlike schizophrenia, are neutral and non-threatening.[43] Patients may also experience benign hallucinatory experiences, such as sensing a presence, briefly seeing a person or animal passing in their peripheral visual field, or seeing an inanimate object as animate, such as a tree branch as a cat.[43] Risk factors for hallucinations include dopamine replacement therapy, advanced age, coexistent depression, dementia, and dementia.[306]

5.1.1 Neural substrates of hallucinations

The pathogenesis of hallucinations in PD is unclear, although lines of evidence suggest that impaired visual processing plays a role in the development of visual hallucinations. First, investigators found that visual acuity—measured using an Snellen chart[307] or Landolt Cs at a distance of 5 meters[308]—was worse in patients with visual hallucinations relative to controls. Second, researchers reported that visual hallucinations disappeared after cataract surgery in two PD patients who had bilateral cataracts.[309] Third, in the Charles Bonnet syndrome, visual hallucinations develop secondary to visual loss (e.g., due to macular degeneration) in cognitively intact older individuals.[310,311] Similarities between hallucinations in PD and the Charles Bonnet syndrome—retained insight, occurrence in evening or at night, awareness of the unreal nature of complex hallucinations[308,312]—suggest that disruptions in early visual processing contribute to the development of hallucinations in PD as well. Nevertheless, visual

deficits are probably not the primary cause of hallucinations in PD because reducing dopamine replacement therapy—which impairs visual processing in PD[313,314]—remedies hallucinations.

Few functional imaging (fMRI and PET) studies have examined the neural underpinnings of hallucinations in PD.[305,315-318] These experiments have yielded heterogeneous results because 1) they were carried out when patients were not hallucinating, and 2) each study used a different cognitive task to assess cortical function (see [43] for review). Still, these reports, taken together, suggest that patients with visual hallucinations have reduced cortical activity in primary and secondary visual areas and increased activity in the PFC.[305,315-318] Some investigators have suggested that PFC dysfunction results in a lack of suppression of internally generated thoughts and images, or the misinterpretation of internal representations as external ones, thus causing hallucinations.[316,319]

5.1.2 History of hallucinations in pre- and postlevodopa eras

Prior to 1957, it was generally accepted that dopamine was simply a precursor for the neurotransmitter noradrenalin.[320] During this period, clinicians treated PD with anti-cholinergic drugs—known to be hallucinogenic—antihistamines, and amphetamines.[321-323] The beneficial effects of the anticholinergics were probably due to their interaction with midbrain dopaminergic cells because the SNpc and VTA receive dense cholinergic inputs—from the pedunculopontine and laterodorsal tegmental nuclei—and cholinergic interneurons in the striatum express D_1 and D_2 receptors.[324-326] Similarly, antihistamines likely lessened symptoms because they have some anticholinergics effects.[327]

In a groundbreaking experiment, Arvid Carlsson and colleagues (1957) injected rabbits and rats with reserpine, which depleted brain reserves of dopamine and noradrenalin. They showed that subsequent levodopa administration increased brain levels of dopamine, but not adrenaline, and reversed the reserpine-induced akinesia and sedation.[328,329] This result, suggesting that dopamine is a putative neurotransmitter in the brain, violated accepted dogma and, hence, was met with resistance.[320] Still, Carlsson's discovery, together with reports of reduced dopamine levels in the urine and brains of PD patients, suggested that increasing brain levels of dopamine would have therapeutic effects.[330]

In 1961, the first dopamine replacement therapy trials were carried out in PD patients: Barbeau and colleagues[330] in Montreal and Birkmayer and Hornykiewicz[331] in Vienna reported short-lived improvements in akinesia, rigidity, and tremor after administration of up to 200 mg of DOPA. Between 1961 and 1967 numerous groups attempted to replicate and expand these original reports.[330] Using oral and intravenous routes, investigators administered up to several grams of DOPA variants alone, together with monoamine oxidase and DOPA decarboxylase inhibitors—to reduce peripheral conversion of DOPA to dopamine—or with amphetamines.[330] Although most studies found lessening of rigidity and akinesia, the transient nature of the improvement and common reports of nausea, loss of appetite, and hypotension portended disaster for levodopa treatment.[330,332] As late as 1965, prominent investigators believed that the therapeutic results were placebo effects and recommended continuation of PD treatment with anti-cholinergic and anti-histaminic drugs.[321]

In August of 1966, however, Cotzias and colleagues at the Brookhaven National Laboratory in Long Island, New York, proved convincingly that DOPA could be used to treat PD symptoms in a sustainable manner.[333] These researchers used significantly larger doses than had been tried previously. Their insight was to increase the medication dose gradually until patients showed improvement or until side-effects set in. Patients tended to tolerate the medication well, showing fewer side effects including vomiting, nausea, loss of appetite, and hypotension.

Cotzias et al. showed that 3 to 16 grams of dl-3,4-dihydroxyphenylalanine (a mix of D-DOPA and L-DOPA) per day resulted in sustained improvement of symptoms in 8 of 16 patients.[333] Subsequently, they reported sustained improvement in 20 out of 28 patients.[334] Soon, reports appeared of hallucinations and psychiatric side effects in patients taking levodopa, particularly in those with a past history of mental illness. This literature launched the debate about the whether hallucinations are a part of the natural progression of PD.[330,335-337]

Fénelon and colleagues (2006) examined 19th and 20th century PD reports in English, French, and German for documentation of hallucinations.[338] They found that between the 1880s and 1940s investigators occasionally noted the presence of hallucinations, particularly in late-stage patients with coexistent dementia, depression, or delirium.

A critical factor complicates the interpretation of these reports as evidence that hallucinations are to be expected in PD pathophysiology: Dementia with Lewy bodies (DLB), the second most common form of dementia after Alzheimer's disease,[339] first entered the literature 1961 when Okazaki et al. presented the case report of a patient with Lewy bodies, progressive dementia, and quadriparesis.[340] DLB is characterized pathologically by the presence of cortical and

subcortical Lewy bodies and clinically identified by the presence of progressive disabling mental impairment, fluctuating cognition, Parkinsonian symptoms (bradykinesia and cogwheel rigidity, but rarely resting tremor), and visual hallucinations.[341,342] Specifically, hallucinations are present in up to 83% of DLB patients and occur early in the course of the disease.[343,344] Given that DLB has only recently entered the clinical arena (DLB was not included in DSM-IV published in 1994), it is likely that some of the early reports of hallucinations in PD patients with dementia and delirium would be characterized as DLB today.[338]

The worldwide epidemic of von Economo encephalitis (encephalitis lethargica) from 1916 to 1927, a mysterious disease that killed about 23,000 people in the US alone, complicates the interpretation of reports from the 1940s to the 1970s.[345,346] This disease, characterized by encephalitis of the midbrain and basal ganglia with lymphocyte infiltration, resulted in somnolence, lethargy, dyskinesias, hallucinations, delusions, and development of Parkinsonism.[347] Many patients who survived von Economo encephalitis developed postencephalitic Parkinsonism (PEP), and by the 1930s, PEP accounted for roughly half of all Parkinsonian cases.[348] Despite their similar clinical presentations, PEP-induced Parkinsonism differed from idiopathic PD on several dimensions: PEP patients did not present the classical "pill-roll" tremor common in idiopathic PD; PEP could occur at any age, even childhood, whereas PD typically occurs later in life; and unlike PD, which is characterized by cell loss in SN/locus ceruleus and the presence of Lewy bodies, PEP brains showed "extensive and severe bilateral diffuse degeneration and gliosis of substantia nigra and locus coeruleus in the absence of Lewy bodies".[346]

Even with these differences, the vast number of PEP cases resulted in a false view that idiopathic PD is synonymous with PEP,[346] and thus many authors did not distinguish between idiopathic PD and PEP in their studies.[338] Some even suggested that PD would "gradually disappear" by the year 1980 as the PEP cohort aged.[349] In this period, a handful of studies focused exclusively on PD without a history of encephalitis and found few patients with hallucinations (2 out of 194 in one report)[338] or none at all,[345] highlighting the rarity of hallucinations in the absence of dopamine replacement therapy.

In summary, although hallucinations did occur in pre-levodopa days in about 5% of patients,[44] they occurred primarily in the context of confusional states, depression, dementia, delirium, and anti-cholinergic medication use. Newer reports, documenting hallucinations in roughly 30% of patients, have focused primarily on hallucinations that occur with chronic dopaminergic therapy, a clear sensorium, and absence of major depressive disorders.[338] Using these criteria, investigators showed that fewer than 2% of untreated patients experience hallucinations (Aarsland et al.: n = 175; Shannon et al.: n = 164),[350,351] although one study with a small sample size (n = 30) reported a surprisingly large 27% hallucination rate among untreated patients.[352] Thus, it is possible that hallucinations are a natural component of PD progression, but their occurrence is likely facilitated by dopaminergic medications.

5.1.3 Pharmacology and genetics of hallucinations

Several lines of evidence support the hypothesis that dopamine signaling is a central factor in the development of hallucinations.[43,44,353,354] First, hallucinations are rare in PD patients who are not taking dopaminergic medications. Second, drugs that increase dopamine signaling can

induce or exacerbate hallucinations. Third, hallucinations can be treated successfully by stopping or decreasing dopaminergic agents or by reducing dopamine signaling via dopamine antagonists. In particular, investigators have shown that clozapine (a compound that blocks D_1, D_2, D_4, serotonin, α-1 adrenergic, histamine, and muscarinic receptors), reduces psychotic symptoms in 80% of PD patients,[354] and that 76% of patients relapse after clozapine is withdrawn.[355]

Although anticholinergics can induce hallucinations in PD, these hallucinations lack the clear-sensorium feature of dopaminergic-drug-induced hallucinations. Meta-analyses show that dopamine agonists are two to five times more likely to induce hallucinations than levodopa monotherapy or no therapy.[356,357] Still, investigators have not been able to find a simple dose-effect relationship between hallucinations and dopaminergic drugs. Mean daily levodopa dose, LEDD, and duration of levodopa therapy are not significantly different between those with and without hallucinations.[307,357-360] Moreover, investigators showed that high, or sudden changes in, plasma levels of levodopa may not be enough to induce hallucinations.[361] They delivered intravenous levodopa to five patients with a history of recurrent hallucinations while they stayed in a dim hospital room for two days. Although the patients had been experiencing hallucinations for an average of three years, they did not experience hallucinations under these experimental conditions. The small sample size and active hospital environment of the study, however, complicate the interpretation of the results. Nonetheless, these results suggest a complicated relation between amount of dopamine replacement therapy and onset of hallucinations.

A handful of studies that have examined the genetic basis of hallucinations in PD suggest that the development of hallucinations may be linked with polymorphisms of genes that regulate dopamine signaling. Makoff and colleagues (2000) examined the *DRD3* Ser9Gly and *DRD2* - 141C/del and *ANKK1* Taq1A polymorphisms.[102] They found that the A2/A2 genotype of *Taq*1A, which results in increased D_2 receptor density in the striatum, was disproportionately over-represented in patients who developed hallucinations later in the disease. Goetz et al. (2001) extended these results and showed that the Gly allele of the *DRD3* Ser9Gly polymorphism, which results in increased dopamine signaling, is associated with hallucinations.[362] Other studies, however, have not been able to replicate these results.[363,364]

5.1.4 Hypothesis

Neuroimaging studies suggest that hallucinations may be due to dysfunction of frontal cortical areas, which have relatively spared dopaminergic input in the early stages of PD. It is possible, therefore, that dopamine overdose may underlie the development of hallucinations in patients with increased dopamine signaling who are taking dopamine replacement therapy. Thus, we hypothesized that carriers of candidate alleles and genotypes that increase dopamine signaling would be vulnerable to developing hallucinations due to disruption of activity in frontal cortical networks that are spared from dopamine depletion early in the disease course.

5.2   Materials and methods

5.2.1 Participants

We recruited 135 PD patients who satisfied the inclusion and exclusion criteria described in chapter 2 (**Table 5.1**). The self-identified racial and ethnic distribution of participants was: 132 White / not Hispanic or Latino, 2 White / Hispanic or Latino, and 1 Asian.

5.2.2 Experimental and control groups

Patients were divided into three subgroups based on their answers to the Queen Square Visual Hallucination Inventory.[365] The benign subgroup consisted of 31 patients with benign, but not formed, hallucinations. The formed subgroup included 35 patients with formed hallucinations. All except 3 patients in this subgroup experienced benign hallucinations. Choosing a control subgroup without formed and benign hallucinations is not a trivial matter because a patient who has not developed hallucinations until the time of testing may develop hallucinations afterward. To limit the possibility of including future hallucinators in the control set, we limited this group to those patients who had had the disease for at least 5 years and had not experienced any hallucinations. The control subgroup consisted of 26 PD patients.

5.2.3 Experimental design

We used the Queen Square Visual Hallucination Inventory to document the presence of formed (visual or auditory) and benign (presence, passage, illusion) hallucinations at any time during the course of the disease.[365] The following questions from the Queen Square Visual

Hallucination Inventory examined presence, passage, and illusion hallucinations, respectively: "Have you had the vivid sensation of the presence of somebody in the room with you, when in fact there was no one there?", "Have you experienced a brief vision of movement past you, of perhaps an animal or person, when in fact there was nothing there?", "Have you looked at something and it appeared as something else for a time? For example spots in the wall appearing as insects?" Formed visual and auditory hallucinations were assessed with the following questions: "Have you had visions of people, animals, or objects that were in fact not there?", "Did you hear these people/animals/objects make any noise?", "Have you heard sounds of people talking, music, or other noises when in fact there was no sound?" We asked the participants to answer the questions based on their experiences since they were diagnosed with PD.

We also measured the patients' visual acuity and contrast sensitivity using the Freiburg Visual Acuity and Contrast Test (FrACT version 3.5).[366] The acuity test started with the presentation of a large black Landot C on a white background that could be oriented up, down, left, or right. Participants had to indicate the direction of the gap in the letter orally by saying "up", "down", "left", or "right". Using the adaptive Best PEST algorithm,[367] FrACT changes the size of the letter until it converges on the participant's acuity threshold, defined as the point of inflection in a participant's psychometric curve. The orientation of the letters changed randomly from trial to trial. A decimal acuity of 1.0 corresponds to Snellen acuity of 20/20. Contrast threshold, evaluated as Michelson contrast, was measured in the same manner as the acuity test, except that only the contrast between the original large Landot C and its background changed from trial to trial. Participants completed 30 trials for the acuity test, and 30 trials for the contrast

sensitivity test while seated comfortably at a distance of roughly 2.7 meters from the computer screen in a dimly lit room. Due to testing time restrictions, we were able to collect acuity and contrast sensitivity measures from a subset of patients in each group; hence these data are available for 16, 17, and 22 patients in the control, benign, and formed subgroups, respectively.

5.2.4 Genotyping

Genotyping was carried out according to the protocol described in **Chapter 2**. In our sample, 27, 76, and 32 patients fell in the *COMT* Val/Val, Val/Met, and Met/Met groups, respectively. The *DRD2* C957T break down was 21 C/C, 70 C/T, and 44 T/T. These distributions did not depart from the Hardy-Weinberg equilibrium (*COMT*: χ^2 = 2.194, df = 1, *p* = 0.139; *DRD2*: χ^2 = 0.625, df = 1, *p* = 0.429).

5.2.5 Statistical analysis

We used a chi-square test, or Fisher's exact test (if any cell count was $\leq$ 5), to compare the frequency of *COMT* and *DRD2* alleles and genotypes among the control, benign, and formed subgroups. Letter sizes in the acuity test followed a geometric progression;[368] thus, we applied a log transform (logMAR = -log[decimal acuity]) before comparing acuity between the groups.[369] All data were analyzed using MATLAB 2009a (MathWorks Inc., Natick, MA) and SPSS 11.5 (SPSS Inc., Chicago, IL).

5.3   Results

Among the 135 participants, 63 (46.7%) experienced benign hallucinations and 35 (25.9%) experienced formed visual or auditory hallucinations (**Table 5.2**). Among patients with benign hallucinations, passage hallucinations were the most prevalent (34.8%) type, followed by illusions (23.7%), and presence (17.0%) hallucinations.

Among those with formed hallucinations, purely visual experiences were the most common (17.0%). Only 4.4% experienced purely auditory hallucinations (**Table 5.3**). The majority (91.4%) of those experiencing formed hallucinations experienced benign hallucinations as well (**Table 5.4**), while 31.0% of patients without formed hallucinations experienced benign hallucinations.

A comparison of the control and benign subgroups revealed that the controls had significantly longer disease duration (control: mean disease duration = 8.3 yrs, SD = 2.7 yrs; benign: mean disease duration = 5.6 yrs, SD = 4.6 yrs, p = 0.011 two-tailed) and took significantly larger amounts of dopaminergic medications (control: mean LEDD = 891.6 mg, SD = 539.5 mg; benign: mean LEDD = 557.3 mg, SD = 422.8 mg; p = 0.011 two-tailed) (**Table 5.5**). The age at onset for the controls was significantly lower than that of the formed subgroup (control: age at onset 56.0, SD = 8.1; formed: age at onset 61.0, SD = 9.2; p = 0.030). The benign and control subgroups, and the formed and control subgroups were not significantly different with respect to sex, age, disease severity, number taking dopamine agonists, MMSE, BDI, years of education, visual acuity, or contrast sensitivity threshold.

The allele (**Table 5.6**) and genotype (**Table 5.7**) distributions for *DRD2* and *COMT* did not differ significantly between the benign and control subgroups. While the *DRD2* allele (**Table 5.8**) and genotype (**Table 5.9**) frequencies were similar between the formed and control subgroups, the Met allele of *COMT* was under-represented and the Val allele was over-represented among the formed subgroup relative to the controls (χ^2 = 4.649, df = 1, *p* = 0.031). The Val/Val genotype of COMT occurred in 72.7% of the formed subgroup but only 27.3% of the controls, while the Met/Met genotype was present in 68.8% of the controls but only 31.3% of the formed subgroup (*p* = 0.043, Fisher's exact test).

5.4   Discussion

This experiment tested the hypothesis that increased dopamine signaling is associated with the occurrence of hallucinations in PD. To answer this question, we divided a cohort of 135 patients into 3 subgroups: those with benign, but not formed, hallucinations (benign subgroup), those with formed hallucinations (formed subgroup), majority of whom also experienced benign hallucinations, and those without any hallucinations (control subgroup). To limit the possibility of including patients who may develop hallucinations at a later date, the control subgroup was limited to patients who had had PD for at least 5 years. Because of this inclusion restriction, the controls had a significantly longer disease duration and took significantly larger amounts of dopaminergic medications relative to the benign subgroup, and they had a significantly younger age at onset relative to the formed subgroup.

Visual acuity and contrast sensitivity

Visual acuity and contrast sensitivity thresholds were similar between the formed and control subgroups in our cohort. Other laboratories reported that PD patients with hallucinations, relative to those without hallucinations, had reduced visual acuity and contrast sensitivity.[307,308,370] In one study, those with hallucinations had a significantly longer disease duration relative to non hallucinators,[308] while disease duration was similar for the two groups in the other studies.[307,370] Because we limited our controls to those who had had the disease for at least five years, our controls had a significantly younger disease onset and marginally longer disease duration relative to the formed subgroup. Our negative finding, therefore, could be due to the longer disease duration of the controls, because those with longer disease durations probably had more dopamine loss in their retina than those with shorter disease durations.

Impact of D_2 variation on hallucinations

Makoff and colleagues (2000) found that the A2/A2 genotype of *ANKK1* Taq1A polymorphism, which results in increased D_2 receptor density in the striatum, was disproportionately over-represented in patients who developed hallucinations later in the disease. Kaiser et al. (2003) and Wang et al. (2004), however, were not able to replicate these results.[363,364] We did not find an association between *DRD2* C957T—which is in strong ($d' = 0.832$ to 1) linkage disequilibrium with *ANKK1* Taq1A[132,134]—and benign or formed hallucinations. It is likely, therefore, that the *ANKK1* Taq1A and *DRD2* C957T polymorphisms do not alter the risk for developing hallucinations in PD.

Another reason for the discrepant results may be due to the different methods used to document hallucinations. Makoff et al. (2000) used a semi-structured interview and included patients who experienced hallucinations (visual, auditory, tactile, olfactory, or gustatory) anytime after starting dopamine replacement therapy. Wang et al. used Makoff's method, but they included only those who experienced hallucinations for a minimum of three times a week for at least 3 months.[363] Kaiser and colleagues included patients who had a score of grater than 1 on the UPDRS "Thought Disorder" questions, indicating a presence of hallucinations or delusions.[364] Goetz and colleagues (2001) also used an interview based method, but they limited their study to those who had experienced visual hallucinations at least 3 times per week for the two months prior to the interview. We used a validated self-report questionnaire[365] to document the presence of visual and auditory hallucinations that occurred anytime after patients started taking dopamine replacement therapy. In summary, lack of a universal method of defining groups with hallucinations complicates cross study comparisons.

Impact of COMT variation on hallucinations

We found that Val allele of *COMT* was disproportionately represented among the formed subgroup, relative to the controls, and noticed a trend (p = 0.163) for overexpression of Val in the benign subgroup. Animal studies have shown that activity of neurons in the PFC follows an inverted-U curve in response to exogenous dopamine: low to moderate amounts of dopamine "focus" the activity of neurons by sharpening their tuning curves, whereas excessive amounts of dopamine silence the neurons.[99-101] Functional MRI and PET imaging studies in PD patients suggest that patients who experience hallucinations, relative to those who do not, have

increased activity in the PFC.[315,371,372] The low-activity Met allele of COMT putatively results in excessive amounts of dopamine in the frontal cortex,[78] and through suppression of neuronal activity,[99-101] likely creates an unfavorable environment for induction and maintenance of spontaneous aberrant cortical activities that would be misinterpreted as external stimuli.

Picking a PD control subgroup

No consensus exists on a method of selecting PD controls to discover genetic risk factors for hallucinations. A critical issue was the possibility that PD patients in the control group may start experiencing hallucinations after testing. Investigators have addressed this challenge in different manners. Three studies included patients with a minimum disease duration of five years in the control group to limit the possibility of including future hallucinators,[363,373,374] and another laboratory excluded patients with a disease duration of five years or less from the control group.[102] Three studies, however, did not place disease duration restrictions on the PD control set.[362,375,376] Because of this lack of consensus, we re-analyzed our data by removing the disease duration restriction from our control subgroup. The new control and formed subgroups had 69 and 35 participants, respectively. We found that the proportion of COMT Val158Met and DRD2 C957T genotypes and alleles was similar between those with formed hallucinations and PD controls (all $p > 0.27$) in the new analysis. This negative finding may be due to the inclusion of future hallucinators in the control set, or may reflect a true lack of association between COMT and DRD2 variation and hallucinations in PD.

To select an un-controversial control set, one must follow patients from the test date to death to ensure that none develops hallucinations. Given that this approach is not feasible, we

believe the next best choice is to limit the control group to those who have been taking dopamine replacement therapy for several years without experiencing any hallucinations. This group is likely more resistant to medication induced hallucinations and thus provides a rational and conservative baseline for discovering genetic risk factors.

Conclusions

We showed that the Val allele of COMT was over-represented in PD patients who experienced formed hallucinations while taking dopamine replacement therapy. When our results are validated by other investigators, Val can serve as a biomarker for early identification of at risk individuals. Careful monitoring of these patients will reduce the likelihood of undetected and untreated hallucinations.

Table 5.1 Characteristics of PD patients who completed the Queen Square Visual Hallucination Inventory

Variable		PD patients
No. of participants		135 (87M; 48F)
Age (yrs)		66.6 (8.7)
Age at PD onset		61.0 (9.5)
PD duration (yrs)		5.6 (3.8)
H&Y	Stage 1	17
	Stage 2	108
	Stage 3	10
LEDD (mg/day)		614.9 (429.6)
No. taking agonists		76 (56.3%)
MMSE		28.2 (1.3)
BDI		6.3 (4.2)
Education (yrs)		16.7 (2.9)

Results are presented as mean (*SD*), number, or percentage.

Table 5.2   **Frequency of formed and benign hallucinations**

Hallucination	No. of patients (%)
Benign	63 (46.7%)
illusions	32 (23.7%)
passage	47 (34.8%)
presence	23 (17.0%)
Formed	35 (25.9%)
visual	29 (21.5%)
auditory	12 (8.9%)

Table 5.3   Frequency of formed visual and auditory hallucinations

		Auditory		
		No	**Yes**	**Total**
Visual	**No**	100 (74.1%)	6 (4.4%)	106 (78.5%)
	Yes	23 (17.0%)	6 (4.4%)	29 (21.5%)
	Total	123 (91.1%)	12 (8.9%)	135 (100%)

Table 5.4   Overlap between formed and benign hallucinations

		Benign		
		No	**Yes**	**Total**
Formed	**No**	69 (51.1%)	31 (23.0%)	100 (74.1%)
	Yes	3 (2.2%)	32 (23.7%)	35 (25.9%)
	Total	72 (53.3%)	63 (46.7%)	135 (100%)

Table 5.5   Characteristics of patients in control, benign, and formed subgroups

Variable		Control subgroup	Benign subgroup	Formed subgroup	*p* Value Control vs. benign	*p* Value Control vs. formed
No. of participants		26	31	35		
Sex M:F		15:11	21:10	24:11	0.433 ¥	0.382 ¥
Age (yrs)		64.3 (8.3)	65.7 (8.6)	67.8 (9.4)	0.514 §	0.130 §
Age at PD onset		56.0 (8.1)	60.2 (10.8)	61.0 (9.2)	0.111 §	**0.030** §
PD duration (yrs)		8.3 (2.7)	5.6 (4.6)	6.8 (4.0)	**0.011** §	0.113 §
H&Y	Stage 1	4	2	3		
	Stage 2	19	29	27	0.069 £	0.691 £
	Stage 3	3	0	5		
LEDD (mg/day)		891.6 (539.5)	557.3 (422.8)	692.8 (422.4)	**0.011** §	0.112 §
% taking agonists		53.8%	51.6%	68.6%	0.866 ¥	0.241 ¥
Other medications						
% taking Namenda		0%	0%	2.9%		
% taking Exelon		0%	0%	5.7%		
% taking Aricept		0%	3.2%	2.9%		
% taking Artane		7.7%	6.5%	11.4%		
% taking Amantadine		15.4%	22.6%	28.6%		
% taking Bupropion		3.8%	0%	0%		
MMSE		28.1 (1.3)	28.4 (1.2)	27.8 (1.3)	0.479 §	0.354 §
BDI		5.9 (4.6)	7.2 (3.9)	6.7 (5.2)	0.252 §	0.522 §
Education (yrs)		16.5 (2.4)	16.8 (2.9)	16.5 (3.3)	0.745 §	0.975 §
Acuity (logMAR)		0.15 (0.18)	0.16 (0.19)	0.24 (0.20)	0.842 ♣	0.154 ♣
Contrast sensitivity		5.32 (3.39)	3.89 (2.29)	5.84 (4.07)	0.163 ♣	0.678 ♣

§ *t* test; ¥ Chi square test; £ Fisher's exact test; ♣ ANOVA with age as covariate.
Results are presented as mean (*SD*), number, or percentage.
Significant results are indicated in bold font.

Table 5.6   Allele frequencies of *DRD2* C957T and *COMT* Val158Met polymorphisms in control and benign subgroups

Polymorphism	Alleles	Control subgroup	Benign subgroup	*p* Value
DRD2 C957T	C	24 (52.2%)	22 (47.8%)	0.693 ¥
	T	28 (48.3%)	30 (51.7%)	
COMT Val158Met	V	18 (41.9%)	25 (58.1%)	0.163 ¥
	M	34 (55.7%)	27 (44.3%)	

¥ Chi square test.

Table 5.7   Genotype frequencies of *DRD2* C957T and *COMT* Val158Met polymorphisms in control and benign subgroups

Polymorphism	Genotype	Control subgroup	Benign subgroup	*p* Value
DRD2 C957T	C/C	5 (55.6%)	4 (44.4%)	
	C/T	14 (50.0%)	14 (50.0%)	0.484 [£]
	T/T	7 (35.0%)	13 (65.0%)	
COMT Val158Met	V/V	3 (42.9%)	4 (57.1%)	
	V/M	12 (41.4%)	17 (58.6%)	0.809 [£]
	M/M	11 (52.4%)	10 (47.6%)	

£ Fisher's exact test.

Table 5.8   Allele frequencies of *DRD2* C957T and *COMT* Val158Met polymorphisms in control and formed subgroups

Polymorphism	Allele	Control subgroup	Formed subgroup	*p* Value
DRD2 C957T	C	24 (41.4%)	34 (58.6%)	0.791 ¥
	T	28 (43.8%)	36 (56.3%)	
COMT Val158Met	V	18 (32.1%)	38 (67.9%)	**0.031** ¥
	M	34 (51.5%)	32 (48.5%)	

¥ Chi square test.

Significant results are in bold font.

Table 5.9   Genotype frequencies of *DRD2* C957T and *COMT* Val158Met polymorphisms in control and formed subgroups

Polymorphism	Genotype	Control subgroup	Formed subgroup	p Value
DRD2 C957T	C/C	5 (41.7%)	7 (58.3%)	
	C/T	14 (41.2%)	20 (58.8%)	0.940 [£]
	T/T	7 (46.7%)	8 (53.3%)	
COMT Val158Met	V/V	3 (27.3%)	8 (72.7%)	
	V/M	12 (35.3%)	22 (64.7%)	**0.043** [£]
	M/M	11 (68.8%)	5 (31.3%)	

£ Fisher's exact test.
Significant results are in bold font.

6   Conclusions

In four experiments, we tested the hypothesis that pharmacogenetic elevation of dopamine signaling in the brain regions that are relatively spared from dopamine loss in the early stages of PD would result in cognitive dysfunction. In particular, we predicted that specific alleles of *COMT* Val158Met, *DRD2* C957T, *DRD3* Ser9Gly, and *DRD4* exon III 48bp VNTR polymorphisms that putatively enhance dopamine signaling would cause impulse control behaviors and hallucinations in PD patients taking dopamine replacement therapy.

Our hypothesis stemmed from the inverted-U dopamine response curve, whereby too little or too much dopamine results in cognitive dysfunction.[92,93] Brain networks that are implicated in the occurrence of hallucinations and impulsive behaviors are primarily interconnected with the VTA, which is relatively spared from dopamine loss in the early stages of PD.[24] We reasoned that exogenous dopamine would overdose these networks in patients who carried specific polymorphisms that increase dopamine signaling, and thus, would result in psychiatric side effects.

We addressed five specific questions: (1) Are *COMT* Met/Met and Val/Met carriers more impulsive than Val/Val carriers?, (2) Are *DRD2* T/T and C/T carriers more impulsive than C/C carriers?, (3) Are *DRD3* Gly/Gly carriers more impulsive than Ser/Gly and Ser/Ser carriers?, (4) Are $D_{4.7}$- carriers more impulsive than $D_{4.7}$+ carriers?, (5) Are Met allele of *COMT*, T allele of

DRD2, Gly allele of *DRD3*, and absence of the 7-repeat allele of *DRD4* associated with hallucinations? We predicated that individuals with the variants of *COMT* (Met allele), *DRD2* (T allele), *DRD3* (Gly allele), and *DRD4* (absence of 7-repeat allele) that increase dopamine signaling would show behavioral impulsivity and would experience hallucinations due to dopamine overdose.

Consistent with our hypothesis, we found that carriers of the *COMT* Val/Met and Met/Met genotypes were more impulsive than Val/Val carriers on the Stop Signal Task (**Chapter 2**). Individuals with the T/T genotype of *DRD2* showed reduced ability to delay gratification compared to C/T and C/C carriers (**Chapter 3**). Patients with the *DRD2* T/T genotype showed more reflection impulsivity than C/C carriers. We also uncovered an interaction between *COMT* and *DRD2* whereby those individuals who had the genotype combination that is associated with high baseline dopamine levels were reflection impulsive (**Chapter 4**). Contrary to our hypothesis, we found that the Val allele of *COMT* was associated with hallucinations (**Chapter 5**). We could not study *DRD3* and *DRD4* due to the small number of Gly and $D_{4.7}$+ carriers.

Our results suggest that pharmacogenetic elevation of dopamine signaling results in increased impulsivity, and thus maybe cause impulse control behaviors—binge eating, excessive shopping, pathological gambling, and hypersexuality—in patients who are taking dopamine replacement therapy. This finding provides a springboard for future work that will directly examine whether medication-induced impulse control behaviors in PD are linked with polymorphisms in *COMT* and *DRD2*. We only examined one single nucleotide polymorphism on each gene. Future studies should examine multiple polymorphisms on each gene to assess

whether the combination of these polymorphisms provides increased predictive power. They should also attempt to measure dopamine levels—perhaps by examination of prolactin levels—to provide needed empirical support for gene-dopamine interactions.

Over-representation of the *COMT* Val—and under-representation of the *COMT* Met—allele in individuals with hallucinations provides an immediate biomarker for early identification of at risk individuals. Hallucinations are a side effect of dopamine replacement therapy and are linked with hyperactivity in the PFC.[43,44,303] Pharmacological experiments in animals showed that too much dopamine in the PFC resulted in a general silencing of neuronal firing.[99-101] We posit that excessive PFC dopamine levels, due to exogenous dopamine and the presence of the COMT Met isoform, would not allow the occurrence of self-organized spontaneous neuronal activations that would be misinterpreted as external stimuli, i.e., a hallucination.

Because hallucinations in PD are predominantly friendly or non-threatening, many patients do not report them to their neurologists. If not treated early, however, hallucinations persist and progress and are a significant risk factor for dementia, nursing home placement (and thus increased mortality rates).[46-50] An objective hallucination risk biomarker will allow neurologists to carefully monitor treatment levels for these patients to reduce the risk of hallucinations and institutionalization.

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