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The Neurogenetic Basis of Behavioral Inhibition

A Dissertation Presented

by

Eliza Johanna Congdon

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Abstract of the Dissertation

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Altough there is increasing interest and research into the roles that genes and brain systems play in influencing psychiatric illnesses, a major obstacle in identifying these influences is the complex nature of diagnostic categories. One solution is to focus on intervening variables, or endophenotypes, that are likely more sensitive to the effects of genetic variation than are diagnostic categories. Such an endophenotype is impulsivity, the predisposition to respond to stimuli without considering the consequences. Although there is evidence supporting a neural basis of impulsivity, and evidence supporting the role of dopamine in influencing impulsivity, there have been only limited attempts to combine this information. This study tested the hypothesis that variants of two dopamine system-related gene polymorphisms (*DAT* and *COMT*) influence the neural network underlying behavioral inhibition, a more direct expression of impulsivity. Specifically, 46 healthy adults were pre-selected for genotypes of the *DAT* and *COMT* polymorphisms and performed a Stop-signal task, which measures behavioral inhibition, while undergoing functional magnetic resonance imaging (fMRI). Neural activation in a frontostriatal circuit, during trials requiring inhibition of a response, were examined across the entire group and then compared between groups with certain variants of each genotype using SPM2. Results support the role of a right-lateralized frontostriatal circuit underlying behavioral inhibition in healthy adults and support a significant role of individual differences, as neural activation varied as a function of how well individuals were able to inhibit a response. Furthermore, results of the study support 1) a significant influence of *DAT* on the neural response during inhibition; 2) a significant influence of *COMT* on the neural response during both the performance of a motor response and the inhibition of a motor response; and 3) an additive effect of *DAT* and *COMT* on neural activation during inhibition. These results further elucidate the genetic and neural basis of impulsivity, particularly with regard to

individual differences in inhibitory control. Understanding the neurogenetic basis of these individual differences will be of considerable clinical significance in advancing the prediction, diagnosis, and treatment of impulsivity-related forms of mental illness.

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Introduction

Impulsivity is the predisposition to respond to internal or external stimuli without regard to the potential negative consequences (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Ranging from normal variation to clinical manifestation, impulsivity is implicated in multiple psychiatric disorders. However, these psychiatric disorders are genetically complex, with many allelic variants of modest effect size contributing small variance to the disease, and with individual genes possibly regulating processes across diagnostic categories. These factors limit attempts to understand the biological mechanisms underlying psychiatric disorders and their relevant behaviors, such as impulsivity. A promising approach is to identify intervening variables along the pathway between genes and a behavior that are likely to be more sensitive to the effects of genetic variation using what is known as an intermediate phenotype, or endophenotype, approach (De Geus & Boomsma, 2001; Gottesman & Gould, 2003; Hamer, 2002; Hariri & Weinberger, 2003).

The purpose of the present study is to apply an intermediate phenotype approach to the construct of impulsivity, by conducting a functional magnetic resonance imaging (fMRI) study in which gene polymorphisms will be related to individual differences in brain activation during an impulsivity-related task in healthy adults. In particular, the investigation will focus on two dopamine system-related gene polymorphisms (the dopamine transporter (*DAT)* and catechol-O-methyltransferase (*COMT*)) and their effect on neural activation during behavioral inhibition using the Stop-signal task. It was predicted that levels of activation in brain regions associated with behavioral inhibition will vary as a function of genetic variation of *DAT* and *COMT* (see Tables 1-2).

Below, I will review literature on the multidimensional nature of impulsivity, which will provide support for focusing on behavioral inhibition in following an intermediate phenotype approach. I will then review literature providing support for the neural correlates of behavioral inhibition, followed by a section reviewing evidence in support of a genetic basis of impulsivity, the neuromodulatory role of dopamine, and the *DAT* and *COMT* polymorphisms. Then, I will integrate these lines of research to make predictions for the present study.

The Multidimensionality and Clinical Significance of Impulsivity

Although impulsivity is a commonly used term in both research and clinical settings, it has a broad set of meanings and definitions. Impulsive actions tend to lack forethought or planning and often carry the connotation of being negative in that they are inaccurate or maladaptive. Behavioral manifestations are numerous, such as responding before instructions are given or completed, responding without considering all options, inability to refrain from responding to an inappropriate stimulus, or acting without considering the full set of consequences (Solanto, 2001). In addition, impulsivity has been described to manifest itself as impatience, “carelessness, risk-taking, sensation-seeking and pleasure-seeking, an underestimated sense of harm, and extroversion” (Hollander & Evers, 2001, p. 949).

Similarly, there is a wide range of impulsivity assessments, reflecting different conceptualizations of the trait. One of the most widely used measures of impulsivity, the Barratt Impulsiveness Scale-Version 11 (BIS-11), conceptualizes impulsivity in terms of three components: a nonplanning component, in which the individual does not plan or think carefully; a motor component, characterized by a tendency to act without thinking or an inability to withhold responses; and a cognitive component, characterized by a difficulty paying attention (Patton, Stanford, & Barratt, 1995). Other instruments focus on a distinction between functional and dysfunctional impulsivity (Dickman Impulsiveness Scale)(Dickman, 1990), the degree of efficiency of information processing in the face of rewarding stimuli (Lifetime History of Impulsive Behaviors Interview (Schmidt, Fallon, & Coccaro, 2004), or the distinction between conscious and unconscious risk-taking (I-7) (Eysenck, 1985).

Given that impulsivity has been conceptualized in different ways, it may not be surprising that influential trait models of personality do not regard impulsivity as a higher-order trait, but rather the combination of lower-order traits (Evenden, 1999). For example, in Costa and McCrae's five-factor model, impulsivity mostly reflects low Conscientiousness (Costa & McCrae, 1992), while in Cloninger's three-factor model, impulsivity reflects a combination of low Harm Avoidance and high Novelty Seeking (Cloninger, 1993).

There is also quantitative evidence of the multidimensional nature of impulsivity. Flory and colleagues conducted a principal components analysis of impulsivity using a range of personality assessments (Flory et al., 2006). They assessed impulsivity-related traits using the Tridimensional Personality Questionnaire (TPQ)/Temperament and Character Inventory (TCI), the Zuckerman Sensation Seeking scale (SS-V), and the Buss Perry Aggression Questionnaire (BPAQ). Principal components analysis supported a three-factor model, in which Nonplanning, Disinhibition, and Thrill-Seeking were identified as independent dimensions of impulsivity (Flory et al., 2006).

Similarly, Whiteside and Lynam (2001) conducted a factor analysis on a number of scales in an attempt to identify and separate distinct personality facets that were previously grouped under impulsivity. Their analysis provided evidence for four factors of impulsivity, including urgency (the tendency to experience and act on strong impulses, frequently under conditions of negative affect), lack of premeditation (the inability to think and reflect on consequences before engaging in an act), lack of perseverance (the inability to remain focused on a task that may be boring or difficult), and sensation seeking (the tendency to enjoy and pursue activities that are exciting and new) (Whiteside & Lynam, 2001). From their analyses, they constructed the UPPS Impulsive Behavior Scale (UPPS), which they propose assesses four "discrete psychological processes that lead individuals to engage in behavior without a proper appreciation of the potential negative consequences" (Whiteside & Lynam, 2003, p. 211; Whiteside, Lynam, Miller, & Reynolds, 2005).

The significance of impulsivity is not limited to trait models of personality, however. In its extreme form, impulsivity is associated with a number of

psychiatric disorders, including Antisocial Personality Disorder (ASPD), Borderline Personality Disorder (BPD), substance abuse and dependence, mood disorders, suicide, Impulse Control Disorders (ICD), and Attention-Deficit/Hyperactivity Disorder (ADHD), according to the American Psychological Association's (APA) *Diagnostic and Statistical Manual-IV-Text Revised (DSM-IV_TR)* (APA, 2000). Indeed, because impulsivity cuts across a number of diagnostic categories, it is highly prevalent: ICDs alone have a 12-month prevalence rate of 8.9% and a lifetime prevalence on 24.8% in the general population (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005; Kessler, Chiu, Demler, Merikangas, & Walters, 2005).

Cluster B Personality Disorders (PDs) are characterized by impulsivity (Casillas & Clark, 2002), and research related to impulsivity has been conducted on ASPD and BPD patient populations in particular. According to the DSM-IV-TR, ASPD in adults is characterized by an "impulsivity or failure to plan ahead" (APA, 2000). Indeed, studies looking at the relationship between impulsive personality traits in samples with increased antisocial traits or behaviors (Conrod, Pihl, Stewart, & Dongier, 2000; Newman, 1997; Taylor, Reeves, James, & Bobadilla, 2006) and samples with increased aggression (Barratt, Stanford, Dowdy, Liebman, & Kent, 1999; Newman, 1997; Stanford, 2003) support the centrality of impulsivity in ASPD or antisocial behaviors. BPD is characterized by "marked impulsivity beginning by early adulthood and present in a variety of contexts"; this impulsivity may manifest "in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)" or in "recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior" (APA, 2000). Support for this comes from reports that impulsivity is predictive of borderline psychopathology and poorer treatment outcome over time, is the most stable of traits associated with BPD, and is the most important distinguishing factor between persistent and remitted BPD individuals (Bagge et al., 2004; Fossati et al., 2004; Links, Heslegrave, & van Reekum, 1999).

Disorders related to abuse and addiction are also characterized by high levels of impulsivity. Although impulsivity is not explicitly listed as a criterion necessary for diagnosis, disorders of abuse and dependence are clearly characterized by deficits in inhibitory control (for a review, see Dawe, 2004). Impulsivity is significantly associated with increased rates of cocaine and alcohol abuse, in addition to higher rates of ASPD (Conrod et al., 2000; Taylor et al., 2006) or Cluster B PDs (Dom, De Wilde, Hulstijn, van den Brink, & Sabbe, 2006), and impulsivity has been shown to predict rates of substance abuse disorders, cross-sectionally and prospectively (Sher, Bartholow, & Wood, 2000).

Mood disorders, characterized by manic and depressive episodes, are also characterized by impulsivity, particularly during a manic episode (APA, 2000) (Leyton, 2001; Swann, Pazzaglia, Nicholls, Dougherty, & Moeller, 2003). However, impulsivity is not limited to manic episodes, but can remain at elevated levels in interepisode Bipolar Disorder (Swann et al., 2003). During a depressed episode, patients can become highly impulsive and this often manifests itself in recurrent suicidal ideation or attempts (APA, 2000). Indeed, suicide potential is

highest in bipolar disorder during a depressive or mixed manic episode, and increases further with comorbid substance abuse (Dougherty, Mathias, Marsh, Moeller, & Swann., 2004). In fact, suicide is a serious complication to many of the disorders reviewed here. Although not a diagnostic category in the DSM framework, there is ample evidence relating suicide to elevated impulsivity (Dougherty et al., 2004). For example, the impulsivity criteria for BPD significantly predict suicidal behaviors (Yen, 2004), leading some to suggest that impulsivity is the underlying behavior shared between ASPD, BPD, substance abuse, bipolar disorder, and suicide (Dom et al., 2006; Dougherty et al., 2004; Swann, Dougherty, Pazzaglia, Pham, & Moeller, 2004).

The prominence of impulsivity in ADHD has meant that a large portion of the literature addressing impulsivity is based on data from ADHD patients. ADHD is a childhood-onset disorder that is primarily characterized by inattention and/or hyperactivity-impulsivity. Impulsivity in ADHD "manifests itself as impatience, difficulty in delaying responses, blurting out answers before questions have been completed, difficulty awaiting one's turn, and frequently interrupting or intruding on others to the point of causing difficulties in social, academic, or occupational settings" (APA, 2000). In other words, ADHD is characterized by deficits in inhibitory control and this is readily seen in behaviors that are most relevant to individuals of this age (Avila, Cuenca, Felix, Parcet, & Miranda, 2004; Barkley, 1997; Beauchaine, Katkin, Strassberg, & Snarr, 2001; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Schachar, Tannock, & Logan, 1993).

Finally, the DSM recognizes a class of disorders that are primarily characterized by impulsivity, and are therefore named Impulse Control Disorders (ICDs) (APA, 2000). ICDs include Trichotillomania, Intermittent Explosive Disorder (IED), Pathological Gambling, Kleptomania, Pyromania, and Not Otherwise Specified (which includes impulsive sexual behaviors, repetitive self-mutilation, and compulsive shopping), although ICDs have been used in the literature to refer to a wider range of behaviors, including disorders relating to externalizing behavior (such as Oppositional-Defiant Disorder, Conduct Disorder, and ADHD) (Kessler, Chiu et al., 2005). These disorders are clearly characterized by a strong impulse towards an ultimately maladaptive behavior, but our understanding of ICDs is, at present, limited by the high-comorbidity of ICDs with PDs, mood disorders, substance abuse, and eating disorders (Dell'Osso, Altamura, Allen, Marazziti, & Hollander, 2006; Grant, Levine, Kim, & Potenza, 2005; Grant & Potenza, 2004; Hollander & Rosen, 2000; Kessler, Coccaro et al., 2006).

The significance of impulsivity in multiple psychiatric disorders further motivates attempts to elucidate the biological bases of impulsivity. However, current work on biological correlates of impulsivity is limited by a number of factors. First, most studies use samples constrained to diagnostic categories. This is problematic because the DSM is not rooted in biology; as a result, subjective assessments, instead of biological variables (such as markers or variants), are used to determine diagnoses (Bearden & Freimer, 2006; Leboyer, Bellivier, Nosten-Bertrand, Jouvent, Pauls, & Mallet, 1998). In addition, the DSM

creates heterogeneous groups; as a result, multiple etiologies may be represented in a single diagnostic group, thereby obscuring any relationship between a phenotype and genetic influence (Gottesman & Gould, 2003). Also as a result, impulsivity is confounded with a disease-specific symptomatology. In addition, DSM groups are categorical, which are less useful in association studies than are continuous dimensions (Plomin, Owen, & McGuffin, 1994). Second, most studies have not measured impulsivity per se, but have relied on self-reported traits such as novelty seeking. The use of self-report questionnaires is problematic because self-report may be an insensitive measure that carries only a small effect size for genetic influences (Gottesman & Gould, 2003; Hariri & Weinberger, 2003). Furthermore, different conceptualizations of personality make it difficult to identify a useful phenotype. Each of these limitations is problematic because they likely obscure any relationship between a phenotype of interest and genetic influence.

Parsing Impulsivity: Behavioral Inhibition

A way to overcome these limitations is to use an intermediate phenotype approach. Using this approach, the goal is to identify intervening variables which are more sensitive to the influence of genetic variation, but which are still related to the behavior, trait, or disorder of interest (De Geus & Boomsma, 2001; Gottesman & Gould, 2003; Hariri & Weinberger, 2003; Meyer-Lindenberg & Weinberger, 2006). The argument in support of intermediate phenotypes is not meant to imply, however, that endophenotypes are genetically less complex than the higher-order phenotype, but rather that they are closer to the influence of genetic variation and are able to be measured quantitatively (and possibly more reliably, as well) (Bearden & Freimer, 2006). In addition, it should not be overlooked that an endophenotype may not be specific to a single diagnostic category, but rather may be a common neurogenetic mechanism across disorders (Bearden & Freimer, 2006; Leboyer et al., 1998).

There are multiple ways in which one can assess such intervening variables, including the use of biochemical assays; neurophysiological or neuroanatomical measures, including structural MRI; and functional imaging measures, such as fMRI, PET, and SPECT. Advantages of an intermediate phenotype approach are a 1) ten-fold increase in effect size, compared to self-report studies (Hamer, 2002), and 2) the use of objective and quantitative measures of the phenotype of interest, compared to subjective self-reports or clinical observations (Hariri & Weinberger, 2003). Indeed, the utility of an intermediate phenotype approach has already been demonstrated in research related to schizophrenia (Calkins, Curtis, Iacono, & Grove, 2004), Alzheimer's (Bookheimer et al., 2000), working memory (Egan et al., 2001; Mattay et al., 2003), and emotional processing (Hariri et al., 2005; Smolka, 2005).

In order to apply an intermediate phenotype approach to the study of impulsivity, however, it is first necessary that the phenotype of interest is adequately parsed. I reviewed evidence which suggest that the impulsivity construct itself is multidimensional and therefore may need to be defined

according to its components. Indeed, the multidimensionality of impulsivity reviewed above maps well onto a taxonomy of inhibitory control that is based on personality, behavioral, and neuroanatomical data (Nigg, 2000). This taxonomy organizes inhibitory control into a framework in which interference control, cognitive inhibition, behavioral inhibition, and oculomotor inhibition are executive inhibition processes (and can be thought of as top-down processes), while response to punishment cues and novelty are separate motivational inhibition processes (and can be thought of as bottom-up processes) (Nigg, 2000).

The importance of using such a framework extends the recognition that impulsivity is multidimensional and provides a more specific and testable approach to impulsive behavior, one that is amenable to investigations into the neural and genetic correlates of impulsivity. I have applied an intermediate phenotype approach to impulsivity, as organized by Nigg's taxonomy of inhibitory control, and this is represented in Figure 1. In particular, I have chosen to focus on the neural and genetic correlates of behavioral inhibition (also known as response inhibition), or the ability to suppress a prepotent response as opposed to the suppression of mental events (Nigg, 2000). As illustrated in Figure 1, there are other components of inhibitory control or impulsive behavior that also represent phenotypes suitable for genetic and neuroimaging investigations, such as delay of gratification and resistance to interference (Avila et al., 2004). For the present study, however, I argue that at the core of the impulsivity construct is an inability to inhibit an action. Therefore, I have chosen to focus the investigation on the neurogenetic correlates of behavioral inhibition.

The external validity of using behavioral inhibition as a proxy of impulsivity comes from studies showing that behavioral inhibition is impaired in impulsive samples [ADHD(Oosterlaan, Logan, & Sergeant, 1998; Schachar, & Logan, 1990; Schachar et al., 2005); substance abusers (Fillmore & Rush, 2002; Monterosso, 2005); CD and comorbid CD and ADHD (Oosterlaan et al., 1998)], and from evidence that behavioral inhibition is correlated with measures of self-reported impulsivity (Avila & Parcet, 2001; Logan, Schachar, & Tannock, 1997; but see Enticott et al., 2006). In particular, the association between self-reported impulsivity (as measured with the BIS-11) and a battery of neuropsychological tests revealed the strongest correlation between BIS-11 scores and performance on a standard measure of behavioral inhibition, the Go/NoGo task, in a sample of healthy adults, even after controlling for age and education (Keilp, Sackeim, & Mann, 2005).

Using behavioral inhibition within an intermediate phenotype approach to impulsive behavior provides a more specific and testable approach to the construct, and this is particularly important as I am interested in testing the influence of genetic variation on neural correlates underlying behavioral inhibition. I will next review literature that has provided converging evidence for the role of a frontostriatal circuit in behavioral inhibition, and then review evidence in support of a genetic basis of impulsivity, with specific attention given to dopamine system-related gene polymorphisms.

Neural Correlates of Behavioral Inhibition

As this study is aimed at testing the neural and genetic correlates of behavioral inhibition, this review will focus on the existing literature that has used behavioral inhibition (also referred to as response inhibition) paradigms to assess group activation and individual differences in activation when suppression of a prepotent response is required. The two most commonly used tasks are the Go/NoGo and Stop-signal tasks. The Go/NoGo requires a participant to respond to a separate set of frequent stimuli (for example, every letter but "X"), but to inhibit responding to a separate set of infrequent stimuli (in this example, "X"). In this paradigm, Go stimuli are presented more frequently than NoGo stimuli. Despite its popularity, the Go/NoGo task is problematic because it does not control for the "oddball" effect, in that infrequent stimuli (in this example, "X") draw more attention than frequent stimuli (every letter but "X"). Therefore, the neural response to a NoGo stimulus confounds processes of behavioral inhibition with attentional processes that detect infrequent stimuli.

The Stop-signal task is similar to the Go/NoGo task, but it makes greater demands on a participant's inhibitory control (see Figure 2). In the Stop-signal task, participants see a series of two possible Go trials (for example, left- and rightward pointing arrows); on a subset of trials (25%), a stop signal (visual or auditory; in this example, an upwards pointing arrow) appears after the onset of a go signal, thereby requiring a participant to suppress a response that has already been initiated. The Stop-signal task also overcomes the "oddball" effect limitation of a Go/NoGo task because 1) the stop signal appears after the onset of a go stimulus, and 2) it ensures an equal number of failed and successful stop trials. A comparison of these two trial types (failed and successful stop trials) to each other eliminates the "oddball" effect.

The Stop-signal task makes greater demands on a participant's inhibitory control because the longer the delay between the go signal and the stop signal, or the closer in time that the stop signal is to the actual response, the more difficult it is to inhibit a response. This task is based on a "horse-race" model, which assumes that a go process and a stop process are in a race, and are independent of each other (Logan, 1994; Logan, & Cowan, 1984). This assumption of independence allows for the estimation of Stop-signal Reaction Time (SSRT), the primary dependent measure of the Stop-signal task, which is an estimate of the speed of the stopping process (Band, van der Molen, & Logan, 2003). A particular advantage of the SSRT is that it is an individualized measure of an participant's stopping process, or inhibitory function, after controlling for difficulty level, and it has been shown to distinguish samples with impaired inhibitory control from healthy controls (Lijffijt et al., 2005; Rucklidge & Tannock, 2002).

Neural correlates of behavioral inhibition in healthy adults.

There are a considerable number of neuroimaging studies of behavioral inhibition in healthy adults, the majority of which have outlined a right-lateralized frontostriatal circuit (Braver, Barch, Gray, Molfese, & Snyder, 2001; D'Esposito,

Postle, Jonides, & Smith, 1999; Fassbender et al., 2004; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Garavan, Ross, & Stein, 1999; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Konishi et al., 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Rubia et al., 2001; Rubia, Smith, Brammer, & Taylor, 2003) (or for a review, see Congdon & Canli, 2005)). In one of the first event-related (ER) fMRI studies to examine response inhibition, participants performed a Go/NoGo task (Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998). In response to NoGo trials, as compared to Go trials, each participant showed significant activation in the right hemisphere of the prefrontal cortex, specifically the posterior part of the right inferior frontal cortex (IFC) (also referred to as pars triangularis (Petrides & Pandya, 2002)) (Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998). Three subsequent ER-fMRI studies using Go/NoGo tasks provide further support for a right-lateralized behavioral inhibition network involving activation in the right IFC (or ventrolateral prefrontal cortex), supplementary motor area (SMA), lateral prefrontal cortex, dorsolateral prefrontal cortex, parietal areas, and the anterior cingulate cortex (ACC) (Braver et al., 2001; Garavan et al., 1999; Liddle, Kiehl, & Smith, 2001). One study included a comparison of activation in both the Go/NoGo and Stop-signal tasks and found a more strongly right-lateralized activation pattern in the Stop-signal task than the Go/NoGo task (Rubia et al., 2001). However, there was also considerable overlap in activation during both tasks, which was most consistently observed in the right IFC, a region argued to be specific to behavioral inhibition, while the other areas likely reflect other non-inhibitory areas, such as motor planning and response selection (Rubia et al., 2001).

The central role of the right IFC in behavioral inhibition has been more formally recognized in a meta-analysis of studies using the WCST, task-switching, and Go/NoGo paradigms (Buchsbaum, Greer, Chang, & Berman, 2005). These imaging studies are further supported by data from lesion (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Rieger, Gauggel, & Burmeister, 2003) and transcranial magnetic stimulation (TMS) (Chambers et al., 2006) studies. Specifically, a study of brain-damaged patients compared performance on a Stop-signal task between patients with unilateral right frontal lobe lesions and non-lesioned controls and found that only the inferior frontal gyrus (IFG) (specifically the pars opercularis) was critical for response inhibition (Aron et al., 2003). Furthermore, the extent of right IFG damage (particularly in the pars opercularis), as measured with MRI, correlated with SSRT, such that greater damage was associated with slower inhibition (Aron et al., 2003). This finding was replicated using a different measure of inhibitory control, task-switching, in a larger sample of 17 left prefrontal lesioned patients, 19 right prefrontal lesioned patients, and 20 non-lesioned controls (Aron, Monsell, Sahakian, & Robbins, 2004). Based on this larger sample, they further demonstrated that the association between IFG damage (particularly the pars opercularis) and inhibitory control was specific for the right hemisphere. In support of these findings, temporary deactivation of the right IFC with TMS impairs the ability to stop an initiated action, but not the ability to execute an action (Chambers et al., 2006).

The role of key subcortical regions in the suppression of a motor response that has already been initiated has been carefully delineated by Aron and Poldrack (2006, 2007). Using a tracking Stop-signal task, in order to ensure an equal number of successful and failed inhibition trials, they were able to define the pattern of activation underlying response execution, successful inhibition and failed inhibition. Their analyses revealed that successful inhibition was characterized by activation in both cortical regions (the right IFC, pre-supplementary motor area (pre-SMA), right parietal cortex), as well as several subcortical regions, including the insula and regions within the basal ganglia, particularly the globus pallidus (GP) and subthalamic nucleus (STN) (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron & Poldrack, 2006)

Beyond group activation seen in an fMRI studies, though, there is evidence for white matter tract connections between three key right-lateralized regions: the IFC, pre-SMA, and STN. By conducing fMRI studies and using diffusion-weighted imaging (DWI) tractography (in order to map fiber connections between regions known to be engaged in functional studies), Aron and Poldrack were able to outline a three-way functional-anatomical network that is responsible for stopping a response that has already been initiated (Aron et al., 2007; Aron & Poldrack, 2006).

As a result, there is strong evidence for the role of a right-lateralized frontostriatal network underlying Go and Stop processes. Specifically, the data suggests that, for the Go process, premotor areas project to the basal ganglia and activate a direct pathway, which in turn excites primary motor cortex and results in a directed movement via brainstem motor program commands. The Stop process acts to suppress the Go process, and likely does this through a direct connection from the right IFC (and pre-SMA) to the STN, which in turn activates the GP to re-establish inhibition over the direct motor pathway (thereby suppressing the directed movement) (see Figure 3, which is adapted from Grillner, Hellgren, Menard, Saitoh, & Wikstrom, 2005))(Frank, 2006). This pathway is called the hyperdirect pathway, in contrast to the direct pathway or slower indirect pathway, and acts via the basal ganglia (STN and GP) to brake output from the primary motor cortex (Aron et al., 2007; Aron & Poldrack, 2006; Frank, 2006; Mink, 1996; Nambu, Tokuno, & Takada, 2002).

Data from neuroimaging studies to support the role of a right-lateralized frontostriatal circuit underlying behavioral inhibition largely comes from samples composed exclusively of healthy adults. In addition, we can draw inferences about the role of this circuit in behavioral inhibition from samples characterized by varying ages or by samples characterized by impaired inhibitory control, as well as by examining the relationship between activation or structure and individual differences in impulsivity.

Neural correlates of behavioral inhibition in children/adolescents.

There are a number of studies that have attempted to compare brain activation patterns between children or adolescents and adults in an attempt to map changes in activation patterns between groups onto differences in inhibitory

control between groups. That is, development of the prefrontal cortex continues through adolescence, and the development of inhibitory control is believed to correlate with maturation of these frontal areas; also, this is supported by age-related changes in behavioral inhibition (Goldman-Rakic, 1987; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). Unfortunately, studies that have attempted to compare brain activation patterns between children or adolescents and adults have been largely inconsistent in their methods (including the age range of children or adolescents, tasks used, and data analysis techniques) and results.

However, one study specifically designed to address these issues provides clear support for age-related increases in functional activation of task-specific prefrontal, striatal, and parietal brain regions that was related to increased cognitive control functions (Rubia et al., 2006). Specifically, these authors examined performance and neural activation during performance of Go/NoGo (behavioral inhibition), Simon (interference inhibition), and Switch (cognitive set shifting) tasks in a group of adolescents (ages 10-17) and adults (ages 20-43). By carefully controlling for performance differences and including only correct trials in their analyses, the authors were able to conclude that there is a progressive linear increase in task-specific functional activation from adolescence to adulthood that underlies both behavioral and cognitive inhibition. Interestingly, they were also able to demonstrate that adolescents recruit a number of posterior brain regions, which may be compensating for reduced activation in prefrontal and striatal regions that are still maturing.

These results are supported by another study comparing neural activation between adolescents (ages 11-17) and adults (ages 18-37) during performance of a Go/NoGo task (Stevens, Kiehl, Pearlson, & Calhoun, 2007). Results from this study provide clear support for a difference in degree of engagement of regions underlying response inhibition in adolescents as compared to adults, as well as a difference in the degree of connectivity between these regions in adolescents as compared to adults. It should be noted that this study used a slightly different approach to data analysis (independent component analyses) than other studies looking at age effects on neural activation during inhibitory control (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Casey et al., 1997; Rubia et al., 2000; Tamm, Menon, & Reiss, 2002), but it may be that in using this approach the authors were best able to demonstrate the differences between adolescents and adults.

Despite critical methodological differences between preliminary studies comparing performance and neural activation in children and adolescents to adults, more recent studies have begun to converge on a picture in which increasing age correlates with task-specific functional activation in key frontostriatal regions underlying behavioral inhibition. In addition, these studies have illustrated that samples characterized by underdeveloped inhibitory control may show increased activation in more diffuse areas as a form of compensation for underdeveloped key frontostriatal regions.

Neural correlates of behavioral inhibition in clinically-relevant samples.

An additional area of research of interest concerns neuroimaging studies of samples characterized by elevated impulsivity or deficits in inhibitory control. These include studies comparing neural activation during response inhibition paradigms in individuals diagnosed with ADHD, PDs, Bipolar Disorder, or substance abuse to activation seen in healthy controls. Despite disease-specific confounds and methodological differences, these studies converge on support for impaired recruitment of a frontostriatal circuit in samples characterized by impairments in inhibitory control. ADHD children and adolescents, compared to healthy controls, display an abnormal pattern of frontostriatal activation during inhibition ((Durston et al., 2003; Rubia, Smith, Oksannen, Overmeyer, & Newman., 2001; Schulz et al., 2004; Tamm, Menon, Ringel, & Reiss, 2004). Personality disordered (De La Fuente et al., 1997; Goethals et al., 2005; Soloff et al., 2003; Soloff, Meltzer, Greer, Constantine, & Kelly, 2000; Vollm, 2004), bipolar (Altshuler et al., 2005), and substance abusing (Kaufman, Ross, Stein, & Garavan, 2003) samples also display an abnormal pattern of frontostriatal activation, particularly hypoactivation or hypometabolism in frontal regions, during inhibition or at rest.

Data from samples characterized by impaired inhibitory control therefore reveals that these samples show hypo-activation, or impaired recruitment, of these key regions when required to inhibit a prepotent motor response. This may reflect a relationship between altered neural activation and impaired inhibitory control, or this may be confounded by disease-specific symptomatology. Therefore, it's necessary to turn to studies examining how individual differences in activation within this frontostriatal circuit are related to individual differences in self-reported trait impulsivity, as well.

Individual differences in impulsivity and functional activation.

The first report of an individual differences approach to impulsivity consisted of a correlation between activation elicited by a Go/NoGo task with absentmindedness, a personality trait measured by the Cognitive Failures Questionnaire, which positively correlates with self-report measures of impulsivity (including the BIS-11) (Garavan, Ross, Murphy, Roche, & Stein, 2002). Activation of the right lFG was associated with successful response inhibition in the entire sample. Other brain regions, on the other hand, showed significant individual differences in activation that correlated with the personality trait of absentmindedness, leading the authors to conclude that individuals who scored high or low in absentmindedness used distinct cortical systems when engaging in inhibitory control. However, given that absentmindedness is not a direct measure of impulsivity and is confounded with cognitive failure, it is difficult to draw conclusions based on this data.

Neural activation elicited by a Go/NoGo task was associated with specific measures of impulsivity, as assessed by Eysenck's impulsiveness scale and the BIS-11 (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003). For the group as a whole, the authors reported significant right-hemisphere activation, including the

right IFG, during inhibition. Impulsivity, as measured with Eysenck's impulsiveness scale, correlated positively with activation in the right IFG during inhibition. Impulsivity, as measured with BIS-11, correlated positively with activation in the left superior temporal gyrus during inhibition. Thus, two self-report instruments, that are each designed to assess trait impulsivity and that were administered to the same subjects, were associated with two distinct sets of brain regions. However, both self-report instruments conceptualize impulsivity differently and are related to different executive inhibitory processes. This discrepancy between the Eysenck and BIS-11 instruments illustrates the difficulty in mapping individual differences based on different self-report measures onto neural circuits.

An added difficulty of mapping individual differences based on different self-report measures onto neural circuits is the divergent use of subscales or paradigms. Horn et al. (2003) reported only on the BIS-11 total score, whereas analyses of the subscales yield different results (Asahi, Okamoto, Okada, Yamawaki, & Yokota, 2004). In fact, Asahi et al. (2004) report a negative correlation between BIS-11 Motor Impulsivity subscale scores and activation in the right medial frontal gyrus during inhibition. In addition, while Horn et al. (2001) reported on the association between BIS-11 total scores and activation elicited by a Go/NoGo task, the association between BIS-11 total scores and activation elicited by a different task yields different results (Valdes et al., 2006). Specifically, while the BIS-11 correlated with individual differences in activation in the left superior temporal gyrus during inhibition in the Go/NoGo task (Horn et al., 2003), BIS-11 total, as well as Motor subscale, scores were associated with activation in the bilateral dorsolateral prefrontal cortex (DLPFC) during performance of the Immediate and Delayed Memory Task (IMT/DMT) (Valdes et al., 2006), which is proposed to assess both impulsivity and aspects of working memory. Thus, an interaction between choice of self-report measures, subscales of that measure, and impulsivity-related task paradigms further complicates the interpretation of available data.

Finally, Brown and colleagues correlated BIS-11 scores in the same subjects while they were scanned using two different tasks (Brown, Manuck, Flory, & Hariri, 2006). Using an emotional face matching paradigm, they reported positive correlations in the ventral amygdala and parahippocampal gyrus, and negative correlations in the dorsal amygdala and ventral prefrontal cortex. Using a Go/NoGo paradigm, they reported a positive correlation in the caudate nucleus and anterior cingulate cortex. Of course, it should not come as a surprise that different task paradigms will activate different neural circuits which may or may not be associated with self-reported impulsivity, but it highlights the importance of matching impulsivity constructs with appropriate task paradigms, when attempting to map self-reported impulsivity onto neural circuits.

In summary, we are limited in the conclusions that we can draw across studies looking at individual differences in activation and self-reported impulsivity because of the divergent tasks and self-report measures used. However, with the exception of the results from Asahi et al., it does appear that across tasks, the

neural response seen (according to the task used) positively correlates with self-reported trait impulsivity (according to the measure used). That is, individuals who reported higher levels of impulsivity (characterized by difficulties in self-control) tended to show greater activation in largely frontal cortical areas during executive inhibitory control processes.

Individual differences in impulsivity and structural brain features.

The individual differences approach can be extended to structural brain features. Several studies have examined the structural features of the frontostriatal pathway, and investigated their association with individual differences in impulsivity. In particular, two sets of studies have quantified white matter microstructure and myelination and gray matter volume and density in relation to impulsivity.

Studies of white matter have used diffusion tensor imaging (DTI) and investigated fractional anisotropy (FA, a measure of axonal and/or myelin fiber integrity) and found it reduced in clinical samples characterized by elevated impulsivity as compared to controls, particularly in frontal cortical regions (de Win, 2006; Hoptman et al., 2004; Moeller et al., 2005). For example, white matter integrity in the corpus callosum was found to be reduced in cocaine-dependent individuals, compared to controls, which implicates degeneration of the prefrontal cortex (Moeller et al., 2005). In addition, impulsivity (as measured by either self-report or task performance) was negatively correlated with FA in these regions (de Win, 2006; Hoptman et al., 2004; Moeller et al., 2005). This relationship is not limited to clinical samples, however. White matter myelination of the right frontostriatal network has been shown to vary considerably between healthy adults, and is correlated with individual differences in behavioral inhibition, as measured by reaction time during performance of the Go/NoGo task (Liston, 2006). Elevated impulsivity is therefore associated with poor axonal and/or myelin fiber integrity, and individual differences in white matter microstructure appear to predict behavioral inhibition in healthy adults.

Studies of gray matter have used high-resolution structural MRI and reported a reduction in gray matter volume in clinical samples characterized by elevated impulsivity (particularly ADHD), compared to controls (Carmona et al., 2005). For example, a significant correlation between age and right caudate volume was reported for healthy controls, but not for ADHD boys (Casey et al., 1997). Self-reported impulsivity has also been correlated with gray matter volume in samples characterized by elevated impulsivity, although the direction of relationship varies across clinical samples (Antonucci et al., 2006; Hazlett et al., 2005). In healthy boys, volumetric measures of the right prefrontal region and basal ganglia structures have been positively correlated with performance on several tasks of inhibitory control (Casey et al., 1997); however, there continue to be drastic changes in gray matter throughout adolescence, making it difficult to draw any conclusions from this data about the relationship between impulsivity and gray matter volume in adults. Elevated impulsivity is therefore associated

with reduced gray matter density, and individual differences in gray matter volume appear to correlate with behavioral inhibition (at least in healthy boys).

To summarize, we are limited in the conclusions that we can draw across studies looking at individual differences in functional activation and self-reported impulsivity because of the divergent tasks and self-report measures used. However, it appears that there is a positive correlation between the amount of neural activation during inhibitory control paradigms and self-reported impulsivity. In contrast, results from studies looking at individual differences in structure and self-reported impulsivity appear to be more consistent. That is, elevated impulsivity is associated with poor axonal and/or myelin fiber integrity, as well as reduced gray matter density, and individual differences in white matter microstructure, as well as gray matter volume, appear to correlate with behavioral inhibition in healthy individuals. It may be, then, that the relationship between neural activation and self-report measures of impulsivity is moderated by individual differences in structural brain features, such as white matter microstructure and myelination or gray matter volume. Alternatively (or in addition), it may be that the relationship between neural activation and self-report measures of impulsivity is moderated by other variables, such as dopaminergic gene polymorphisms.

Summary of neural correlates of behavioral inhibition.

While the use of divergent measures, tasks, samples, and even data analysis techniques limits the extent of conclusions that can be drawn from these studies, the bulk of the data, along with the elegantly designed series of studies by Aron and Poldrack (2006, 2007), suggest that a right-lateralized frontostriatal circuit underlies behavioral inhibition. Specifically, data from neuroimaging and lesion studies converge on the critical role that the right IFC, pre-SMA, and structures of the basal ganglia play in the suppression of a motor response that has already been initiated. As reviewed above, the IFC is believed to play a central role in initiating behavioral inhibition (as opposed to motor planning or response selection). The STN plays a central role in the stopping of a motor response (via the GP), and its position within this frontostriatal circuit is particularly well-suited for braking ongoing motor commands that are in the later stages of being processed by the brain (Frank, 2006). Finally, additional support for the central role of both the IFC and STN in behavioral inhibition comes from the finding that activation in these two structures is positively correlated (Aron & Poldrack, 2006), suggesting that recruitment of both these areas together is required for successful inhibition.

Genetic Basis of Impulsivity

Although impulsivity is a multidimensional construct, there is a support for a significant genetic component of impulsivity. Familial transmission of impulsivity has been demonstrated both outside of DSM categories of mental disorders (defined as commission errors on a task designed to measure impulsive responding) (Dougherty et al., 2003) and within DSM categories (defined as

impulsive personality disorder traits assessed with interviews) (Silverman et al., 1991). Data from twin studies specifically support a genetic component of impulsivity. A twin study using the Control scale of Tellegen's MPQ reports that approximately 45% of the variance in this trait, reflecting impulsivity in this model, was accounted for by genetic factors (Hur & Bouchard, 1997). Remarkably similar estimates were reported in a twin study using the Karolinska Scales of Personality to assess the trait of impulsivity, which reported a heritability estimate of 0.45 (Pedersen, Plomin, McClearn, & Friberg, 1988), and a twin study that assessed impulsivity using the BIS-11 self-report measure, which reported a heritability estimate of 0.44 (Seroczynski, 1999). Converging evidence, therefore, suggests that around 45% of the variance in self-reported impulsivity is accounted for by non-additive genetic factors.

Neuromodulatory Role of Dopamine

The genetic contributions to impulsivity may be mediated through many channels, including genetic mediation of neurotransmitter systems such as serotonin and dopamine (Evenden, 1999; Robbins, 2005). Historically, serotonin has been the main neurotransmitter of interest regarding impulsivity (Carver & Miller, 2006; Evenden, 1999; Soubrie, 1986). However, there is emerging evidence that serotonin is not involved in impulsive behavior, or at least not behavioral inhibition.

For example, participants were given a selective norepinephrine reuptake inhibitor (SNRI), a selective serotonin reuptake inhibitor (SSRI), or placebo in a double-blind parallel-groups design (Chamberlain et al., 2006). The SNRI used in this study (atomexetine) is suggested to alter prefrontal dopamine levels. The SSRI group did not differ in behavioral inhibition from placebo, while the SNRI group did; in contrast, the SNRI group did not differ in probabilistic learning from placebo, while the SSRI group did. Along similar lines, depletion of central serotonin (by acute tryptophan depletion) in healthy adults had no effect on behavioral inhibition (Clark et al., 2005). Furthermore, there was no effect of trait impulsivity on performance-related change as a result of serotonin depletion. Studies such as these provide evidence against the role of serotonin in influencing impulsivity, in particular behavioral inhibition.

Furthermore, reports of a relationship between indices of serotonin turnover and impulsive violence (Linnoila, 1983; Moffitt et al., 1998; Soderstrom, 2001; Virkkunen, 1995) , as well as emerging reports of differences in neural activation as a function of *MAOA* genotype (which regulates serotonin and norepinephrine, but likely not dopamine) in affect-related and impulse control paradigms (Meyer-Lindenberg et al., 2006; Passamonti et al., 2006), suggests that the serotonergic system may be mediating inhibitory control under situations of increased arousal or negative affect (Reif et al., 2007; Vigil-Colet & Codorniu-Raga, 2004), or in interaction with early life stressors (Caspi et al., 2002).

In addition to these studies, there is substantial data to suggest that dopamine influences impulsivity. For example, psychostimulant drugs that target the dopaminergic system are effective in treating symptoms of ADHD (Volkow,

Wang, Fowler, & Ding, 2005). Additional evidence for a role of dopamine in impulsivity comes from pharmacological studies in humans (de Wit, Enggasser, & Richards, 2002; Friedel, 2004), and from pharmacological, metabolite, lesion and knockout studies in animals (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001; Dellu-Hagedorn, 2006; Dulawa, Grandy, Low, Paulus, & Geyer, 1999; Puumala, 1998; Rubinstein et al., 1997; Winstanley, Theobald, Cardinal, & Robbins, 2004; Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006). Therefore, the focus of the present study is on dopamine system-related gene polymorphisms.

Dopamine, or more generally monoamines, have been shown to suppress spontaneous background neuronal firing while enhancing task-specific firing (Foote, Freedman, & Oliver 1975). In this way, dopamine is said to enhance the signal-to-noise ratio. An additional property of dopamine is that there is an optimal range of dopamine stimulation, largely D1 receptor stimulation in the prefrontal cortex, for the performance of functions in which it is involved (Williams & Goldman-Rakic, 1995). In this way, it is said that there is an inverted U-shaped response function of dopamine, such that too little or too much dopamine is disruptive and impairs the functioning of the system, although both situations lead to quite different behaviors (Arnsten & Goldman-Rakic, 1998). These two properties are neatly incorporated into what is known as a tonic-phasic model of dopamine (Bilder, Volavka, Lachman, & Grace, 2004; Grace, 1991). It is useful to frame a discussion of the neuromodulatory role of dopamine on neural networks in terms of a tonic-phasic model of dopamine because this model accounts for a wide variety of existing data, but also because this model allows us to make specific predictions about the influence of dopaminergic variation.

Dopamine System-Related Gene Polymorphisms

Within the dopaminergic system, there are certain gene polymorphisms which may influence impulsivity. Two gene polymorphisms, in particular, have received considerable interest: these include polymorphisms of the genes coding for the dopamine transporter (DAT) and the catechol-O-methyltransferase (COMT) enzyme. A brief description of each of these will be followed by a review of evidence relating the gene variant to impulsivity or impulsive-related measures. It is worth noting at the outset that the significance of these gene variations is that they appear to confer individual differences in impulse-related behaviors *and* are differentially distributed across the frontostriatal network underlying behavioral inhibition.

Dopamine transporter (DAT).

The DAT is a protein that plays a critical role in dopamine neurotransmission because it is responsible for removing dopamine from the extracellular space (Bannon, Michelhaugh, Wang, & Sacchetti, 2001). DAT is expressed and acts primarily throughout the midbrain, with a relative lack of DAT in the frontal cortex (Lewis, 2001; Moron, Brockington, Wise, Rocha, & Hope, 2002; Sesack, Hawrylak, Matus, Guido, & Levey, 1998). The gene coding for the

DAT protein contains a highly variable number of tandem repeats (VNTR) polymorphism, resulting in variants that range from 3- to 13-repeats, with 9- and 10-repeats occurring most commonly (Vandenbergh, 1992). Although the polymorphism is located in a sequence that does not directly code for the DAT protein (3'-UTR), the polymorphism is believed to produce variants that are functionally different in that it may influence mRNA transcription, which in turn can affect mRNA stability and translational efficiency (Conne, Stutz, & Vassalli, 2000; Nakamura, Koyama, & Matsushima, 1998).

Evidence to suggest that the polymorphism in the gene coding for the DAT protein produces variants that are functionally different comes from a number of studies looking at gene expression in brain samples or imaging studies that have examined differences in DAT binding levels between genotype groups. While some studies suggest that the 10-repeat variant is associated with 54% increased expression of the DAT (VanNess, Owens, & Kilts, 2005), and individuals with the 10/10 genotype have been characterized as having excessive amounts of the transporter (Fuke et al., 2001; Heinz et al., 2000; Mill, Asherson, Browes, D'Souza, & Craig, 2002; Swanson, 2000), there are also studies to suggest increased expression is associated with the 9-repeat variant (Jacobsen et al., 2000; Michelhaugh, Fiskerstrand, Lovejoy, Bannon, & Quinn, 2001) or that carriers of the 9-repeat variants have increased DAT protein availability (van Dyck, 2005). In addition, there are also studies to suggest no functional significance of the VNTR (Martinez, 2001; Mill, Asherson, Craig, & D'Souza, 2005). Such studies assessing the effects of the *DAT* polymorphism have used reporter gene assays and transfection in cell cultures, and there have been crucial differences in cloning strategies across studies, which may account for the discrepant results (Brookes, 2007).

In an attempt to address these critical methodological differences and discrepant results, Brookes et al. (2007) conducted an analysis of DAT gene expression in human post-mortem brain tissue and report increased expression of DAT mRNA in human post-mortem midbrain tissue in carriers of the 10-repeat allele as compared to the 9-repeat allele. These data, from the most well-controlled study to date, are consistent with previous findings of increased expression in 10-repeat alleles as compared to 9-repeat alleles in the cerebellum, temporal lobe, and lymphocytes (Mill et al., 2002) and in transfected cells (Fuke et al., 2001; VanNess et al., 2005).

This finding, taken in conjunction with additional reports of increased expression associated with the 10-repeat allele, suggest not only a functional difference between variants, but one in which the 10-repeat allele results in excessive amounts of DAT production. Excessive amounts of the DAT could lead to an overly efficient reuptake of dopamine, reducing intrasynaptic and extracellular dopamine below optimal levels. In brain regions where an optimal range of dopamine is necessary for the performance of functions in which it is involved, *DAT* variation may task-specifically alter dopamine availability and function. In other words, if subcortical regions rely on an optimal range of dopamine for behavioral inhibition (Aron & Poldrack, 2006; Brown et al., 2006),

then individuals with the 10-variant (based on evidence suggesting an increase in expression of the DAT in individuals with the 10-repeat variant) may demonstrate impaired inhibitory control, relative to individuals with the 9-repeat variant.

A review of association studies looking at the *DAT* reveals that the *DAT* has most consistently been associated with ADHD or ADHD-related variables, although results suggest that the association between the 10-repeat allele of the *DAT* and a diagnosis of ADHD is tenuous, showing only a small but significant main effect of *DAT* on ADHD (Faraone et al., 2005). However, the 10-repeat allele (or 10/10 genotype) has been associated with more specific phenotypes, including symptom response, as well as cortical inhibitory activity, after medication treatment in ADHD children (Bellgrove, Hawi, Kirley, Fitzgerald, Gill, & Robertson, 2005; Gilbert et al., 2006; Kirley et al., 2003), greater neuropsychological impairment (Bellgrove, Hawi, Kirley, Gil, & Robertson., 2005), impulsive responding on a continuous performance task (Loo et al., 2003), and severity of hyperactivity/impulsivity symptoms (Waldman et al., 1998).

Other data suggest that the effect of *DAT* on ADHD may be moderated through interaction with other variables, such as subject demographics (Cornish et al., 2005) or other gene polymorphisms, including *DRD4*. For example, increased hyperactive-impulsive scores were reported in ADHD children with at least one 7-allele of the *DRD4* and both 10-repeat alleles for the *DAT* (Roman et al., 2001) and an increased rate of having at least one 7-allele of the *DRD4* and both 10-repeat alleles for the *DAT* was reported in a separate sample of ADHD children (Carrasco et al., 2006). Furthermore, our group has demonstrated an interaction of *DAT* and *DRD4* on behavioral inhibition, as measured with the Stop-signal task, in a sample of healthy adults (Congdon, Lesch, & Canli, 2008). That is, individuals with the *DAT* 10/10 genotype and at least one *DRD4* 7-repeat allele had significantly longer SSRT (indicating poorer inhibitory control) than all other groups.

Our conclusions about genetic variation in the *DAT* polymorphism and its effects on impulsivity are tenuous, however, because ours is the only study to directly asses the influence of *DAT*, in interaction with *DRD4*, on behavioral inhibition outside of clinical samples. Yet insofar as impulsivity is a prominent characteristic of ADHD, I suggest that genetic variation of the *DAT* polymorphism taps into this common dimension, and therefore suggest that reports of an association between the 10-repeat allele of the *DAT* and ADHD symptomatology provide motivation for the current study investigating the influence of *DAT* on neural activation elicited during behavioral inhibition. Specifically, I predict that *DAT* influences dopaminergic transmission such that in a region where the DAT is crucial to neural function, different variants potentially influence the amount of dopamine availability and functioning of that region.

Catechol-O-methyltransferase (COMT).

The COMT enzyme is also central to dopaminergic functioning, has a known functional polymorphism, and has been studied in relation to individual differences in cognition and emotion. COMT degrades catecholamines

(dopamine, epinephrine, and norepinephrine) and is widely distributed throughout the brain (Hong, Shu-Leong, Tao, & Lap-Ping, 1998). The role of COMT in regulating dopamine in the frontal cortex is particularly important, because of the relative lack of DAT (Chen et al., 2004). The COMT gene contains a single nucleotide polymorphism (SNP), which results in the substitution of the amino acid methionine (met) for valine (val). Studies support a functional effect of the SNP, with the met enzyme having one third to one half of the activity of the val enzyme (Lotta, Vidgren, Tilgmann, Ulmanen, Melen, Julkunen, & Taskinen, 1995). As the function of the COMT enzyme is to break down dopamine, the met variant (associated with low enzymatic activity) results in *high* levels of extrasynaptic dopamine, whereas the val variant (associated with high enzymatic activity) results in *low* levels of extrasynaptic dopamine (Chen et al., 2004; Lotta et al., 1995; Mannisto & Kaakkola, 1999).

As a result of its critical role in cortical regions and the significant difference in function between variants, the *COMT* polymorphism is hypothesized to directly affect cognitive functioning, based on the differential effects of the met and val variants on dopamine availability and function. Briefly, the val variant is thought to facilitate transitions between states or enhance flexibility, though this may disrupt inhibitory control and predispose to impulsivity. On the other hand, the met variant is thought to reduce cortical noise and enhance stability, thereby facilitating inhibitory control (Bilder et al., 2004).

A review of association studies looking at the *COMT* polymorphism reveals that it has been associated with self-reported levels of suicidal and aggressive behavior, (Jones et al., 2001; Rujescu, Giegling, Gietl, Hartmann, & Moller, 2003; Strous et al., 2003) with novelty seeking (in interaction with other polymorphisms) (Benjamin et al., 2000), and with ADHD (Eisenberg et al., 1999). However, the *COMT* polymorphism has been most consistently associated with performance differences in tasks of executive functioning (Bruder et al., 2005; Diamond, Briand, Fossella, & Gehlbach, 2004; Egan et al., 2001; Fossella et al., 2002; Malhotra et al., 2002; Nolan, Bilder, Lachman, & Volavka, 2004; Rosa et al., 2004). An analysis of *COMT* association studies, especially those directly addressing the effects of these variants on dopaminergic tone, reveals that inhibition and conflict may be central to the effects of *COMT* (Nolan et al., 2004). Processes including the maintenance, reordering, manipulation of information in prefrontal neural networks, as well as behavioral inhibition and the switching of task sets, are proposed to be most sensitive to the effects of *COMT* genotype (Bruder et al., 2005).

Support that inhibitory processes are most sensitive to the effects of *COMT* genotype comes from an EEG study assessing neurophysiological markers of performance monitoring (Kramer et al., 2007). Using a standard flanker task with an embedded stop-signal task allowed these authors to test for the influence of *COMT* on error detection and correction, as well as behavioral inhibition. Indeed, they found that inhibition-related prefrontal activity differed between *COMT* genotype groups, whereas error-related prefrontal activity differed between *DRD4* SNP-521 genotype groups. Specifically, the carriers of

the *COMT* val-allele, as compared to the met-allele, exhibited reduced amplitude of an inhibition-related stop N2, which is suggested to represent the stop signal in the prefrontal cortex that triggers inhibitory processes, and enhanced inhibition-related central positivity (P3a), which is suggested to represent monitoring of inhibitory processes. Therefore, the central role that *COMT* has in regulating dopamine neurotransmission in the prefrontal cortex, and the evidence implicating specific frontal areas in behavioral inhibition, motivates the current investigation into the possible role of *COMT* in behavioral inhibition.

Predictions About Dopaminergic Variation and Cognition

In relation to cognition, the tonic-phasic model of dopamine proposes that dopamine acts to expand or contract the breadth of information held in neural networks. In other words, dopamine influences the stability and flexibility of neural networks through the interacting effects of tonic and phasic dopamine in brain regions, thereby allowing for the successful performance of prefrontally-mediated behaviors (Bilder et al, 2004; Cohen et al., 2002; Seamans & Yang, 2004; Robbins, 2005; Grace, 1991). Dopamine's actions on the cortical system are the result of a balance between maintaining and updating, and are achieved by varying the signal-to-noise ratio. That is, dopamine enhances evoked activity in response to a stimulus (the signal) and suppresses spontaneous background activity (noise) (Johnson, 1983). One implication of this model is that there is an optimal level of dopamine availability for the successful performance of a function in which it is involved.

The usefulness of this model is that allows us to make specific predictions about the influence of dopaminergic variation. That is, if there is an inverted U-shaped dose-response curve of dopamine activity and function, then we can test whether deficient and excessive amounts of dopamine activity impair cognitive functions mediated by the prefrontal cortex. There have been several relevant studies to date which have assessed the influence of dopamine system-related gene polymorphisms with imaging measures. Although each has focused on a different behavioral paradigm and/or gene polymorphism, there is support for the increased power and effectiveness of this approach.

Previous imaging genetics studies.

There are reports of differences in brain volume and activation as a function of *DAT* and *DRD4* polymorphisms, in both ADHD boys and their siblings. Using anatomical MRI scans to measure brain volume, Durston and colleagues reported that ADHD boys with the *DAT* 10/10 genotype had smaller caudate volumes than those without the 10/10 genotype, while there was an effect of *DRD4* genotype on their unaffected siblings (Durston et al, 2005). Using fMRI to measure neural activation during performance of a Go/NoGo task in ADHD boys, their siblings, and controls, Durston and colleagues subsequently reported 1) an interaction between *DAT* genotype and group on striatal activation in the inhibition condition, such that activation in the striatum in carriers of the 9-repeat allele was greater than in carriers of the 10/10 genotype, but only in ADHD boys

and their unaffected siblings (there was no difference between genotype groups in controls); and 2) an effect of genotype on activation in the cerebellum, such that activation in the vermis of individuals homozygous of the 10-repeat allele was greater than in carriers of the 9-repeat allele, across all groups (Durston et al., 2008).

Furthermore, an interaction between *DAT* and *DRD4* polymorphisms was reported in a single photon emission computed tomography (SPECT) study, in which higher perfusion (an indicator of metabolism) in the right middle temporal gyrus was reported in ADHD children who had the 10/10 *DAT* genotype and at least one *DRD4* 7-repeat allele, as compared to all other groups (Szobot, Roman, Cunha, Acton, Hutz, & Rohde, 2005). Although these results provide evidence specific to the moderating influence of *DAT* on brain structure and function in individuals at familial risk of ADHD, the results do not exclude the moderating influence of *DAT* on frontostriatal structure and function in healthy individuals. This is because 1) of the relatively small samples used; 2) the age range of controls (ages 11-20); and 3) of the criticism against using the Go/NoGo task in healthy controls, which is relatively easier than the tracking Stop-signal, and therefore may not engage inhibitory control processes to the extent that it may in samples characterized by inhibitory control deficits. In summary, there is evidence for a moderating influence of *DAT* on frontostriatal structure and function, at least in ADHD children or individuals at familial risk of ADHD.

There have been considerably more studies reporting differences in brain activation as a function of *COMT*, based largely on the critical role that the COMT enzyme plays in the catabolism of dopamine in the prefrontal areas (Bilder et al., 2004), as well as consistent reports of a dose-dependent effect of *COMT* genotype on measures of executive function, particularly the WCST. There are several studies reporting differences in prefrontal activation as a function of *COMT* genotype (Mattay et al., 2003; Smolka et al., 2005; Tan et al., 2007), some of which provide indirect support for the influence of *COMT* on neural activation during inhibition. In addition, *COMT* genotype has also been associated with differential regional Cerebral Blood Flow (rCBF) and presynaptic dopaminergic function during a working memory (N-back) task in prefrontal cortex (Meyer-Lindenberg et al., 2005).

Although there is not yet a published report of an interaction of *DAT* and *COMT* on neural activation during a behavioral inhibition task, there are reports of an interaction between *DAT* and *COMT* polymorphisms on neural activation across a number of other tasks (Bertolino et al., 2006; Schott et al., 2006; Yacubian et al., 2007). For example, Caldu and colleagues reported an interaction between *COMT* and *DAT* genotypes on prefrontal function (Caldu et al., 2007). Specifically, the authors assessed WCST and CPT performance in healthy adults genotyped for both *COMT* and *DAT*; in addition, participants performed an N-back task while undergoing fMRI. Similar to previous results, the number of val-alleles was related to the number of perseverative errors in the WCST. Interestingly, while individuals homozygous for the 10-repeat allele of the *DAT* had significantly faster reaction times on the CPT than carriers of the 9-

repeat allele, there was a significant interaction between *COMT* and *DAT* genotypes on commission errors on the CPT, with carriers of the *COMT* val/val and *DAT* 10/10 genotypes having the highest number of commission errors (an index of impulsivity). These results suggest that reduced dopamine availability, as seen in carriers of the val/val and 10/10 genotypes, is associated with increased impulsivity in healthy adults.

Furthermore, Caldu et al. (2007) reported an additive effect of *COMT* and *DAT* genotypes on neural activation seen during performance of the 2-back task, such that there was a linear increase in activation in the left middle frontal gyrus, with *DAT*9/9—*COMT* val/val individuals showing the greatest response and *DAT* 10/10—*COMT* met/met individuals showing the lowest response. These results are in line with some previous reports of increased prefrontal activation in val-allele and 9-repeat allele carriers when performing working memory tasks. These results also suggest that alterations in prefrontal dopamine availability, as predicted by *DAT* and *COMT*, is associated with differences in performance and cortical response, perhaps due to a variations in signal-to-noise ratio (Caldu et al., 2007).

Present Study: The Neurogenetic Correlates of Behavioral Inhibition

As discussed above, neuroimaging studies of behavioral inhibition have reported activation within a right-lateralized frontostriatal network during inhibition of a prepotent response. Furthermore, several studies have linked individual differences in impulsivity to both functional and structural variation within this network. Despite evidence outlining a right-lateralized frontostriatal circuit that underlies behavioral inhibition, and the role of dopamine in influencing behaviors relevant to impulsivity and inhibitory control, we currently have a limited understanding of the neurogenetic correlates of behavioral inhibition. As reviewed above, our understanding is limited by 1) an over-reliance on heterogeneous, DSM-defined groups; 2) an over-reliance on self-report measures of trait impulsivity or related higher-order personality traits; and 3) widespread methodological differences across studies. These issues are primarily problematic because they create noise, thereby obscuring any relationship between a genotype and phenotype of interest, especially when the effect size is small.

The current study therefore aimed to overcome many of these limitations by applying an intermediate phenotype approach to impulsivity (see Figure 1). It is proposed that dopamine system-related gene polymorphisms have a functional role in modulating this network, by altering neural response during behavioral inhibition. In other words, that dopaminergic gene variation may influence the functional response of this frontostriatal circuit to generate individual differences in behavioral inhibition.

Based on the evidence reviewed above, the current study was designed to test the influence of *DAT* and *COMT* genotypes on neural activation during behavioral inhibition in a sample of healthy adults. The specific aims were threefold. The first specific aim was to examine the pattern of neural activation

during performance of a behavioral inhibition task and to test for individual differences in activation. Specifically, I predicted that there would be significant activation in the right-lateralized behavioral inhibition network, particularly in the right IFC, STN, pre-SMA, and GP. I also predicted that there would be a negative correlation between neural activation in these regions during successful inhibition and inhibitory control.

The second specific aim was to test the influence of dopaminergic genetic polymorphisms on brain activation during behavioral inhibition. I predicted that variants of two candidate genes *(DAT* and *COMT*) would differentially influence activation seen in a right-lateralized behavioral inhibition network during inhibition (see Table 2). I hypothesized that if there is an optimal range of dopamine availability for the performance of this task, and the *DAT* and *COMT* polymorphisms modify dopamine availability, then we would see differences in performance and/or activation in key regions during behavioral inhibition between genotype groups. Specifically, if the *DAT* 10/10 genotype results in an overly efficient reuptake mechanism, thereby reducing dopamine availability, then we would see better performance and/or increased activation in key stopping regions during inhibition in the 9-repeat allele carriers as compared to carriers of the 10/10 genotype. Similarly, if the val-allele results in an overly active enzyme, thereby reducing dopamine availability, then we would see better performance and/or increased activation in key stopping regions during inhibition in the met/met group as compared to the val/val group, with intermediate performance in the val/met group.

Finally, the third specific aim was to test for a potential additive effect of these two polymorphisms on brain activation during a behavioral inhibition task. Again, I hypothesized that if there is an optimal range of dopamine availability for the performance of this task, and the *DAT* and *COMT* polymorphisms modify dopamine availability, then those combinations of variants predicted to result in more or less dopamine availability would differentially influence performance and/or activation in key regions during behavioral inhibition. Based on data regarding the functional effects of each polymorphism, I predicted to see an additive effect rather than a true interaction effect. That is, if both the *DAT* 10-repeat allele, and the *COMT* val-allele, result in lower levels of dopamine levels than the *DAT* 9-repeat allele, and the *COMT* met-allele, respectively, then I predicted that we would see poorer performance and/or decreased activation in key stopping regions during inhibition in carriers of both 10-repeat and val-alleles, as compared to carriers of both 9-repeat and met-alleles. I therefore aimed to test for an additive effect of *DAT* and *COMT* genotypes on performance and neural activation during behavioral inhibition in a sample of healthy adults.

Methods

Participants

68 healthy adults (mean age 23.22 (SEM = 0.51), range 18-44; 42 females) were recruited from New Haven and surrounding areas. Exclusion criteria included the following: history of psychopathology, counter-indications for MRI; any mood-altering medication; children under 18; adults over 30; history of severe head trauma, left-handedness. Participants also completed three self-report measures of mental health (K-6, IPDS, and Adult ADHD Self-Report Scale) in order to ensure that the sample included only healthy participants. The K-6 is a brief (6-item) self-report measure that provides a screen for DSM-IV mood and anxiety disorders. It has been shown to outperform other similar screens (Furukawa, Kessler, Slade & Andrews, 2003) and has good psychometric properties (Kessler et al., 2002; Kessler et al., 2003). The Iowa Personality Disorder Screen (IPDS) is an 11-item self-report screening measure based on interview items that provides a screen for DSM personality disorders (Langbehn et al., 1999). Results suggest that the IPDS is an effective screen for personality disorder in clinical (Langbehn et al., 1999) nonclinical populations (Trull, 2001). The ADHD Self-Report Scale is an 18-item self-report questionnaire used to screen for ADHD symptoms in adults that has been validated in community and clinical samples (Kessler et al., 2005; Kessler et al., 2006)

Of the 68 participants screened, 55 participated in the fMRI portion, while the remaining 13 participants were unable, or were not asked, to return for the imaging portion of the experiment. Of the 55 participants that were scanned, one participant was excluded because he lied about his age at initial screening and exceeded the age cut-off for the current study; he also failed to perform the task as instructed. Six participants were excluded for failing to perform the task as instructed, and two participants were excluded due to excessive head motion (exceeding 3 mm in any direction) in the scanner. Forty-six participants were therefore included in the final analyses (mean age 22.85 years (SEM = 0.49), range 18-30; 26 females). All volunteers gave informed consent according to procedures approved by the Yale University School of Medicine Institutional Review Board.

Procedure

All participants were recruited from the New Haven area through postings and advertisements. Each person that responded was first pre-screened via e-mail with an MRI counter-indications form. If no initial exclusion criteria were met, participants were invited to participate in either a preliminary session (in which DNA was collected and a subset of questionnaires was completed) or a complete scanning session (in which DNA was collected, all questionnaires were completed, and scanning was conducted). Before the scan session, participants were given verbal instructions on the task and completed a practice session (of 36 trials) in order to ensure that they understood the requirements of the task before entering the scanner. Participants who completed only the preliminary session had the opportunity to come back for the scanning portion at a later date.

Consent was obtained at the beginning of each session, and participants were debriefed and compensated at the end of each session.

Candidate Genotyping

DNA samples were collected with cheek cell swabs (Epicentre Biotechnologies MasterAmp^{TM} Buccal Swab Kits, Madison, WI). Participants were provided with a bottle of water and a new toothbrush, and instructed to clean their mouth before swabbing in order to ensure a clean sample. Swabs were air dried for approximately 10 minutes, before capping and transporting them to Stony Brook University, where DNA extraction and analysis was performed within one week.

The genotypes for *DAT* and *COMT* were obtained following previously published protocols (Egan et al., 2001; Hunnerkopf, Strobel, Gutknecht, Brocke, & Lesch, 2007). Briefly, for *DAT*, the polymorphic region was amplified by polymerase chain reaction (PCR) with oligonucleotide primers: forward-5'TGTGGTGTAGGGAACGGCCTGAG3'; reverse-5'CTTCCTGGAGGTCACGGCTCAAGG3'. PCR was performed using NovaTaq (Novagen, Madison, WI). PCR started with an initial denaturation at 95° C for 3 minutes, followed by 45 seconds at 95° C, 45 seconds at 67.5° C, 45 seconds at 72° C for 38 cycles, and a final extension at 72° C for 3 minutes. PCR products were separated on a 3% agarose gel containing ethidium bromide, and bands were visualized under UV light. For the *DAT* genotype, the resulting fragments consist of 316 bp when they contain six repeats, 356 bp when they contain seven repeats, 396 bp when they contain eight repeats, 436 bp when they contain nine repeats, 476 bp when they contain ten repeats, 516 bp when they contain eleven repeats, and 596 bp when they contain thirteen repeats.

For *COMT*, the polymorphic region was first amplified by PCR with the oligonucleotide primers: forward-5' GGG GCC TAC TGT GGC TAC TC3'; reverse-5' TTT TTC CAG GTC TGA CAA CG3'. PCR started with an initial denaturation at 94° C for 5 minutes, followed by 45 seconds at 94° C, 45 seconds at 58.4° C, 45 seconds at 72°C for 35 cycles, and a final extension at 72°C for 5 minutes. The resulting 169 bp fragment was incubated for three hours with the restriction enzyme NlaIII (New England Biolabs, Ipswich, MA). The resulting digested fragments consisted of 96 and 13 bp for the A/A genotype, 114 bp alone for the G/G genotype, and 114, 96, and 13 bp for the G/A genotype. PCR products were separated on a 4% agarose gel containing ethidium bromide, and bands were visualized under UV light.

Each participant was genotyped for both *DAT* and *COMT*. Participants were classified by *DAT* and *COMT* genotype as follows. For *DAT*, dichotomization was based on reports of differences between the 9- and 10-repeat alleles of the *DAT*, which are the most common variants (Heinz et al., 2000; Jacobsen et al., 2000; Mill et al., 2002; van Dyck et al., 2005); also, the 9- and 10-repeat alleles were the only alleles present in the current sample. Therefore, for *DAT*, 10-repeat allele homozygotes were grouped into the 10/10 group and carriers of at least one 9-repeat allele were grouped into the 9+ group.

For *COMT*, grouping is based on the fact that the alleles are co-dominant, meaning that val/val subjects have the highest activity of COMT, met/met subjects have the lowest activity of COMT, and val/met subjects have intermediate levels of COMT enzyme activity (Lotta et al., 1995). Therefore, for *COMT*, met-allele homozygotes were grouped into the met/met group, val/met heterozygotes were grouped into the val/met group, and val/val homozygotes were grouped into the val/val group. For both *DAT* and *COMT* groups, genotype groups were matched on age, sex, ethnicity, and education.

Questionnaires

Demographics were assessed with a self-report measure which asked participants to provide information about their age, sex, ethnicity, education, and handedness. Trait impulsivity was assessed with the BIS-11 (Patton et al., 1995), which is a 30-item self-report questionnaire with Cognitive, Motor and Nonplanning subscales. The BIS-11 conceptualizes impulsivity to contain three main components: a Nonplanning component, a Motor component, and a Cognitive component. Typical items on the BIS-11 scale include the following: "I am more interested in the present than the future" (Nonplanning impulsivity); "I 'squirm' at plays or lectures" (Motor impulsivity); and "I act on the spur of the moment" (Cognitive impulsivity). The BIS-11 is a widely used questionnaire that has been validated in impulsive and normal populations, and has high internal consistency (α coefficients = 0.79-0.83) (Patton et al., 1995).

fMRI Task

While being scanned, participants completed three sessions of a tracking Stop-signal task. The Stop-signal task is designed to measure a race between go and stop processes, which allows for the computation of an individual's inhibitory function (Logan, 1994). The tracking Stop-signal task tracks each subject's responses on inhibition trials and modifies the timing parameters on subsequent inhibition trials accordingly (see Figure 2). This tracking procedure ensures that subjects successfully inhibit on 50% of inhibition trials, and fail to inhibit on 50% of inhibition trials. Thus, difficulty level is individualized across subjects and both behavioral performance and trial numbers are equated across subjects.

This study included a rapid event-related design that was derived from previous imaging studies (Aron & Poldrack, 2006; Rubia et al., 2003). Participants viewed black arrows on an off-white background pointing either to the left or right for 500 ms each in a random order at jittered rates, followed by a 1500 ms delay period during which a fixation point (black plus sign) was presented and responses could still be recorded, although participants were encouraged to not wait until this time to respond. Trials were separated by a variable inter-trial interval (ITI) of 500-4000 milliseconds (with an average ITI of 1750 milliseconds). Participants also viewed a black fixation cross during this ITI, but the fixation cross was bold to indicate that the next trial was about to begin and to provide for a separation from the delay period. This jittering technique allows for rapid presentation rates that exceed the hemodynamic response

function usually used to deconvolve the BOLD response (Burock, Buckner, Woldorff, Rosen, & Dale, 1998).

Participants were instructed to press a right or left button (using a keypad button-box) in response to a right- or leftwards pointing arrow, respectively. On a subset of trials (25%), a right- or leftwards pointing arrow was replaced by an upwards pointing arrow (the stop-signal)(Rubia et al., 2003). Subjects were instructed to inhibit responses on trials in which the stop-signal appears, and that correctly responding and inhibiting were equally important. The onset of the stop-signal on the first inhibition trial was 250 ms, but the delay between onset of a right or left arrow and onset of a stop-signal (stop signal delay, SSD) increased or decreased by 50 ms on each successive trial, depending on the subject's performance on the previous inhibition trial. The SSD became 50 ms longer after the subject was able to inhibit successfully on the previous inhibition trial, and the SSD became 50 ms shorter after the subject failed to inhibit on the previous inhibition trial. Stop-signal reaction time (SSRT) can be estimated by subtracting the average SSD (at which the participant successfully inhibits 50% of the time) from the average reaction time on Go trials and it was computed based on each subject's data (Band et al., 2003). SSRT is the main dependent variable of the stop-signal task, and provides an estimate of each subject's stopping time, or inhibitory function (Logan, 1994).

The task consisted of 144 total trials, 108 of which were response trials, and 36 of which were inhibition trials (with equal numbers of trials with left and right arrows across the task) and therefore lasted 9 minutes and 21 seconds. Participants completed three sessions of the task, yielding 1128 total scans (including the twelve and three dummy scans during the instructions and goodbye screens, respectively). Participants completed all three sessions in a row in the scanner, with a brief rest in-between each session. The use of multiple runs is an appropriate means to minimize subject burn-out and does not necessarily lead to high inter-run variability (Todd et al., 2005), which in any case was addressed with appropriate first-level preprocessing, time-series statistics, and registration analysis methodologies (Todd et al., 2005).

Stimulus presentation, the timing of all stimuli, and the recording of participants' responses were achieved through using ePrime (Psychology Software Tools, Inc., Pittsburgh, PA). Visual stimuli were presented on a back-projector which participants could see via a mirror located on the head frame in the scanner. The computer running the ePrime program was synchronized with the scanner throughout the session to ensure accuracy of event timing, and participants' responses were recorded using a fiber optic button box.

Behavioral Analyses

All data collected was reviewed for completeness shortly after collection. Data analysis began with an assessment of the integrity of the data to check for any outliers, unusual data points, or distributions. The self-report and behavioral data were screened for violations of assumptions underlying the statistical tests

to be used. Genotype groups were compared on demographics to ensure that they were matched in the final sample.

Behavioral data, and values extracted from the imaging data, were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL). Pearson's product correlations, independent samples t-tests, and one-way ANOVAs were used to test for associations with, or differences between, demographic variables. Independent samples t-tests and one-way ANOVAs were used to test for differences in the dependent variables between *DAT* and *COMT* genotype groups, respectively. Pearson's product correlations were used to test for associations between the dependent variables.

Image Acquisition and Analysis

fMRI data were obtained using a Siemens 3T Trio scanner at the Yale Magnetic Resonance Research Center. Each fMRI session began with a 3-plane localizer (20 seconds) to localize the brain within the scanner. Sagittal localizer was an inversion recovery T1-weighted scan (TI/TE/TR = 800/11/1800, 256x192x2nex), 3mm thick, skip 0.5mm, FOV=22cm, 16 slices. This acquisition is used to define the ac-pc line for prescription of the anatomic T1 and functional images in the following series. For fMRI scans of task performance, functional whole-brain images were acquired using a gradient echo T2*-weighted echoplanar imaging (EPI) scan using an axial-oblique orientation and a flip angle of 80°, repetition time (TR) = 1.5 s, echo time (TE) = 35 ms, 24 slices, 5 mm thick with no gap, and a field of view (FOV) = 22 x 22 cm. For each task session, 374 scans were collected, including twelve dummy scans at the beginning (in order to allow time for magnetic saturation) and two dummy scans at the end.

Imaging preprocessing.

Individual fMRI data were preprocessed using a standard protocol (Canli, Congdon, Gutknecht, Constable, & Lesch, 2005; Canli, Omura et al., 2005; Omura, Constable, & Canli, 2005) with SPM2 (Statistical Parametric Mapping, The Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK) running on MATLAB 6.5 (MathWorks, Natick, MA). For each scan, images for each participant were realigned to the first volume in the time series to correct for head motion. Realigned images were spatially normalized into a standard stereotaxic space (Montreal Neurological Institute template) and then smoothed to minimize noise with an 8 mm full width-half maximum isotropic Gaussian filter. For those participants included in the final analyses, movement parameters never exceeded 3 mm in any direction for any participant or scan.

Fixed-effects models (Friston, 1994) were used at the individual subject level of analysis to calculate the contrast images between inhibition and response trials, and random effects models (Holmes & Friston, 1998) were used for group-level analyses. Specifically, four events were modeled after convolution with a canonical hemodynamic response function: Fixation, Go, StopInhibit, and StopRespond. Six movement parameters were included as regressors to control

for additional movement throughout the scan. Events were modeled at the time of stimulus (bold plus sign or arrow) onset. Fixation, or baseline, events were included as a means of comparing events to baseline, and because these Fixation events do not represent a true null period as the fixation point became bold to prepare the participant for the next trial. Therefore, for each participant, across all three sessions, the following predetermined contrasts were created: Go—Fixation, StopInhibit—Fixation, StopRespond—Fixation, StopInhibit—Go, and StopInhibit—StopRespond. Note that Go trials included only Go trials in which the participant correctly responded; StopInhibit included all Stop trials in which the participant did not respond; and StopRespond included at Stop trials in which the participant failed to inhibit a response.

Statistical analyses.

Second-level contrasts were created for the entire group using each participant's contrast images, and these contrasts were analyzed at the whole-brain level with random effects analyses in SPM2 using one-sample t-tests. For whole-brain analyses, the threshold was set to at least $p < 0.05$ Family-wise error corrected, with a cluster threshold of 10 voxels. The search region included 137,514 voxels. Surface renderings of group statistics maps were created using a SPM2 standard single-subject structural template. Anatomical regions were identified using the SPM2 Anatomy toolbox, which combines probabilistic cytoarchitectonic maps with one's functional imaging data (Eickhoff et al., 2005) and manual inspection using the Duvernoy atlas. All coordinates reported here represent Montreal Neurological Institute (MNI) space.

Additional analyses were conducted using regions of interest (ROI), which were partly defined using the automated anatomical labeling (aal) atlas of the WFU PickAtlas Tool (v1.04) in SPM2 (Tzourio-Mazoyer et al., 2002). ROI analyses included four ROIs: 1) the right IFC, which included the pars opercularis, pars triangularis, and pars orbitalis; 2) the right STN, which was defined using Marsbar (MarsBaR AAL ROI package, version 0.1) (Tzourio-Mazoyer et al., 2002) and consisted of a 10 x 10 x 10 mm sized box, centered at MNI coordinates 10, -15, -5; 3) the pre-SMA (where $y > 0$); and 4) the right globus pallidus . For ROI analyses, since analyses were limited to only four regions and based on strong a priori hypotheses, images were thresholded at $p < 0.01$ uncorrected voxel level, and activation was regarded as significant if it survived $p < 0.05$ small volume correction. For further analyses, mean percent signal change was extracted from the ROIs using Marsbar and analyzed in SPSS. Testing mean signal change in SPSS allows us to further examine the relationship between activation and performance variables, and allows us to confirm the direction of genotype group differences.

To assess the effect of each genotype group, I used a multiple regression model with two regressors: *DAT* (presence of 9-repeat allele) and *COMT* (number of met-alleles) genotypes, which allowed for the assessment of the contribution of each genotype to activation, while controlling for the contribution of the other genotype in the Go—Fixation, StopInhibit—Fixation, and

StopInhibit—Go contrasts. A separate regression model was used to assess the influence of a both genotypes together, or an additive effect of *DAT* + *COMT* (in which the genotype groups were combined to form four groups), on activation in the StopInhibit—Fixation contrast. An interaction term (*DAT* x *COMT*, in which the genotype groups were combined to create six groups) was then added to this model to test for any effects of an interaction beyond the additive effect of *DAT* + *COMT*. For ROI analyses of regression models, since analyses were limited to four regions, images were thresholded at $p < 0.01$ uncorrected voxel level, and activation was regarded as significant if it survived $p < 0.05$ small volume correction. For further analyses, mean percent signal change was extracted from the ROIs using Marsbar and analyzed in SPSS.

Results

Allele and Genotype Frequencies

Demographic and genotype information for the final sample is provided in Table 3. Group analyses included the entire final sample when looking at the effect of each genotype on behavioral and imaging data. *DAT* genotype was unavailable in one participant. In the final sample, for *DAT* (N = 45), participants were divided into those with two copies of the 10-repeat allele (10/10) (N = 28) and those with at least one 9-repeat allele (9+) (N = 17). For *COMT* (N = 46), participants were divided into three groups: met/met (N = 6), val/met (N = 28), and val/val (N = 12). The genotype frequencies of both *DAT* and *COMT* from the final sample of participants did not deviate from Hardy-Weinberg equilibrium (all *p*-values > 0.05).

Behavioral Results

BIS-11 scores averaged 56.07 (*SEM* = 1.30) across the final sample of 46 participants and did not differ by age, sex, ethnicity, or education. These values are within a normative range and are consistent with previously published samples (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008; Forbes et al., 2007) There was no significant effect of *DAT* genotype on BIS-11 scores. However, there was a significant effect of *COMT* genotype on BIS-11 scores: for BIS-11 total scores, $F(2, 45) = 5.46$, $p < .01$; for BIS-11 Nonplanning subscale scores, $F(2, 45) = 6.15$, $p < .01$. Follow up analyses reveal a significant difference in BIS-11 total and Nonplanning subscale scores between met/met and val/met individuals, with val/met individuals having the highest self-reported impulsivity scores and met/met individuals having the lowest.

Descriptive statistics of Stop-signal task performance are presented in Table 4. Inspection of the results reveals that the task worked correctly, with the

inhibition rate for the final sample being close to 50% (mean percent inhibition was 52.11 (SEM = 1.55)). The group mean SSRT was 214.55 ms (SEM = 6.78), which is slightly lower than the published norms from a community sample (221 ms) (Logan & Cowan, 1984; Logan et al., 1997), but which is higher than published results from a smaller sample that was scanned (187.4 ms) (Aron & Poldrack, 2006). Overall, average reaction times on Go trials and SSRT in this sample are in line with previously published samples (Aron & Poldrack, 2006; Logan, & Cowan, 1984; Logan et al., 1997).

BIS-11 total and subscale scores were significantly correlated with each other (see Table 5), but not with any Stop-signal behavioral measure, including SSRT. There was no correlation between BIS scores or any behavioral measure and age, and there was no difference in BIS scores or any behavioral measure as a function of sex, ethnicity, or education level. There were no significant independent effects of *DAT* or *COMT* genotypes on SSRT.

As I was interested in testing for an additive effect of *DAT* and *COMT* genotypes (*DAT* + *COMT*), four groups were created by combining *DAT* and *COMT* genotype information. Groups were formed by separating those individuals with the least number of alleles predicted to influence the dependent variables (predictive-alleles), an intermediate number of predictive-alleles, and the most number of predictive-alleles. This resulted in the following four groups: 1) *DAT* 10/10—*COMT* val/val; 2) *DAT* 10/10—*COMT* val/met or *DAT* 9+—*COMT* val/val; 3) *DAT* 10/10—*COMT* met/met or *DAT* 9+—*COMT* val/met; and 4) *DAT* 9+—*COMT* met/met. Descriptive statistics of the main dependent variables for each of these four groups is presented in Table 6. For illustrative purposes, descriptive statistics for each of the *DAT* x *COMT* groups, in which genotype information was combined to create six groups, is presented in Table 7.

When testing for an additive effect of *DAT* and *COMT* (*DAT* + *COMT*) on the dependent variables, one-way analyses of variance revealed significant differences between these groups in age and percent inhibition on Stop trials and a marginally significant difference in reaction time (in ms) on StopRespond trials (see Table 6). Due to the limited sampling of ages (18-30 years of age), and due to the relatively small differences in ages between groups, I did not include age as a covariate in further analyses. An examination of group means revealed that there was a linear decrease in percent inhibition on stop trials with an increase in the number of predictive-alleles, such that the *DAT* 10/10—*COMT* val/val group had the highest percentage inhibition while the *DAT* 9+--*COMT* met/met group had the second lowest percentage inhibition (the *DAT* 10/10—*COMT* met/met; *DAT* 9+--*COMT* val/met group had the lowest percentage inhibition) (see Figure 4). Similarly, the *DAT* 10/10—*COMT* val/val group had the slowest reaction time (in ms) on StopRespond trials while the *DAT* 9+-met/met group had the fastest reaction time (in ms).

fMRI Results

Whole-brain analyses: The go process.

Inspection of activation from the Go—Fixation contrast revealed significant activation throughout posterior regions, including the occipital cortex and cerebellum, the thalamus and basal ganglia (striatum and globus pallidus), the SMA through the pre-SMA, and the motor cortex (see Table 8 and Figure 5). This pattern of activation is what is to be expected given that the Go stimuli were visual and a motor response was produced during these trials. This pattern of activation, or Go network, is also consistent with previous neuroimaging studies of motor responding (Mattay & Weinberger, 1999), as well as studies using the Stop-signal task (Aron & Poldrack, 2006), and supports a model of a frontostriatal pathway underlying a motor response (Frank, 2006; Mink, 1996). Finally, this Go network was largely contralateral, which is to be expected as every participant produced a right-handed response. There was no activation that was greater for Fixation relative to Go trial.

Whole-brain analyses: The stop process.

Inspection of activation from the StopInhibit—Fixation contrast revealed significant activation throughout posterior regions, including the occipital cortex and cerebellum, thalamus and basal ganglia (striatum and globus pallidus), and the SMA through the pre-SMA and cingulate, but also significant activation in bilateral IFC/insula lobes (see Table 8 and Figure 6). This pattern of activation is what is to be expected given that the Stop stimuli were visual and a motor response was successfully inhibited during these trials, and is consistent with previous neuroimaging studies using the Stop-signal task (Aron & Poldrack, 2006). Although there was bilateral IFC and basal ganglia activation, the extent and degree of activation was much greater in the right than left hemisphere. In particular, there was left insula lobe activation, but this activation extended through the IFG (pars opercularis) in the right hemisphere. There was no activation that was greater for Fixation relative to StopInhibit trial.

Whole-brain analyses: Failure of the stop process.

Inspection of activation from the StopRespond—Fixation contrast revealed significant activation throughout posterior regions, including the occipital cortex and cerebellum, which extended through the thalamus (see Table 8 and Figure 7). StopRespond—Fixation also resulted in activation in the ACC extending into the pre-SMA and SMA, bilateral parietal regions, and bilateral IFC/insula cortices. Again, these results are consistent with previous studies using the Stop-signal task (Aron & Poldrack, 2006). There was no activation that was greater for Fixation relative to StopRespond trials.

Whole-brain analyses: StopInhibit—Go.

Examination of the StopInhibit—Go contrast revealed activation that is specific to the stopping process, including activation in the right IFC/insula cortex, right pre-SMA, and right thalamus (see Table 8 and Figure 8). Activation was also seen in the bilateral posterior clusters (occipital and temporal gyri), left insula cortex, right frontal regions, and the ACC. These results are consistent

with previous studies examining response inhibition (see Congdon, & Canli, 2005), including studies using the Stop-signal task (Aron & Poldrack, 2006), and provide further support of a right-lateralized response inhibition network.

Whole-brain analyses: StopInhibit vs. StopRespond,

In order to further examine activation specific to successful and unsuccessful stopping, StopInhibit and StopRespond were contrasted (see Table 8). StopInhibit—Stop Respond revealed only one cluster of significant activation in the paracentral lobule/SMA. On the other hand, there was significantly greater activation in StopRespond—StopInhibit in the cerebellum, left insula lobe, thalamus, and ACC. These are regions which are involved in the motor pathway (cerebellum, thalamus) or are activated in response to a stop-signal (insula lobe, ACC).

ROI Analyses: StopInhibit—Go.

ROI analyses were also conducted on the StopInhibit—Go contrast, as it was predicted that there would be significantly greater activation in the right IFC, STN, pre-SMA, and GP during successful stopping as compared to going (see Table 9). Indeed, there was significant activation in each of the ROIs for StopInhibit—Go, and each of the ROIs survived a $p < 0.05$ small volume correction.

Individual Differences in Stopping Activation

Stopping activation and SSRT.

Values representing mean percent signal change were extracted from the ROIs using Marsbar and entered into SPSS to examine the relationship between activation during inhibition (StopInhibit—Go) and performance. Activation in each of the ROIs (right IFG, STN, pre-SMA, and GP) was significantly correlated with each other (see Table 10 and Figures 9-11). SSRT significantly correlated with activation in the right IFG (pars triangularis) ($r = -.321$, $p < 0.05$) during StopInhibit—Go (see Figure 12), but did not significantly correlate with activation in any of the other ROIs. Extending analyses to include mean signal change during inhibition relative to baseline also revealed a significant negative correlation between activation in the right IFG (pars opercularis) and SSRT ($r = -.377$, $p < 0.05$).

In order to further explore the relationship between activation during stopping and individual differences in SSRT, I conducted a two-sample t-test in SPM2. Fast- and Slow-SSRT groups were divided according to the median of the sample (210.61), resulting in two groups of 23 participants each. I limited the analyses to the four ROIs ($p < 0.01$ uncorrected voxel level). A significant difference in activation in the right IFC ROI was seen between Fast- and Slow-SSRT groups, with the Fast-SSRT group showing greater activation in the right IFC (x 40, y 16, z 12, $t = 2.96$, $k = 10$, $p = 0.74$); however, this cluster did not

survive a $p < 0.05$ small volume correction. There was no greater activation in the Slow-SSRT group than the Fast-SSRT group in any of the ROIs.

These results suggest that activation in key stopping regions was greater in those participants who had lower SSRT scores, or better inhibitory control. These findings are in line with previously published results (Aron & Poldrack, 2006), and support the conclusion that although engagement of the right-lateralized response inhibition network is crucial for successful stopping, there are significant individual differences in this pattern.

Stopping activation and BIS-11 scores.

In contrast to the relationship between activation during stopping and SSRT, the correlation between activation during stopping and self-reported impulsivity scores was positive. Values representing mean percent signal change were extracted from the ROIs from the StopInhibit—Go contrast and correlated with BIS-11 total and subscale scores. Activation in the right STN significantly correlated with BIS-11 total scores ($r = .330$, $p < 0.05$) and BIS Cognitive subscale scores ($r = .431$, $p < 0.01$). Therefore, those subjects who self-reported higher trait impulsivity tended to show greater activation in a key stopping region when required to inhibit a motor response, while those who self-reported lower trait impulsivity tended to show less activation in the right STN during stopping.

Effect of Genotype on Stopping Activation

DAT and COMT.

A multiple regression was conducted in SPM2 to assess the independent influence of *DAT* and *COMT* genotypes on activation during primary contrasts of interest, while controlling for the influence of the other genotype. Significant effects in the ROIs were found for each genotype independently (see Table 11).

For the initial contrast of interest, StopInhibit—Go, there was a significant influence of *DAT* genotype in activation in each of the four ROIs, although only activation in the right STN (x 10, y -12, z -6, $t = 3.03$, $k = 44$, $p = 0.03$) and SMA/pre-SMA (x 6, y -18, z 72, $t = 4.50$, $k = 360$, $p = 0.006$) survived small volume correction. Mean signal was extracted from each of the ROIs to confirm the pattern of group differences in SPSS. Mean signal in the right STN was significantly different between *DAT* genotype groups (t (43) = -2.08, $p < 0.05$), as was mean percent signal in the right pre-SMA (t (43) = -2.18, $p < 0.05$) and right globus pallidus (t (43) = -2.39, $p < 0.05$) (see Figures 13-15). Mean signal in the right IFG (pars triangularis) was marginally significantly different between *DAT* genotype groups (t (43) = -1.80, $p = 0.079$). Examination of group means reveals that activation was greater in the 9+ group than in the 10/10 group in all ROIs (see Table 12).

For StopInhibit—Go, there was a significant influence of *COMT* genotype on only two of the ROIs, the right IFC and pre-SMA, although only activation in the right IFC survived a small volume correction (x 40, y 28, z -2, $t = 4.33$, $k = 669$, $p = 0.001$) (see Table 11). I extracted mean signal from each of these ROIs

to confirm the pattern of group differences in SPSS. There were no significant differences between *COMT* groups in any of these ROIs ($p > 0.05$). Furthermore, inspection of group means revealed an inconsistent pattern of group means across the ROIs; that is, there was not a consistent pattern of differences across the three *COMT* groups, despite regressing *COMT* (number of met-alleles) genotype on StopInhibit—Go activation.

In order to address the inconsistent pattern of group differences on the StopInhibit—Go contrast, two additional multiple regressions were conducted: one on Go—Fixation and a second on StopInhibit—Fixation. Initial analyses were limited to the ROIs for both of these contrasts. Although greater activation in the ROIs in StopInhibit as compared to Go trials was expected, some activation in these regions for a Go—Fixation contrast, based on the whole-brain analyses, was also expected.

For Go-Fixation, there was only an influence of *DAT* genotype on activation in the globus pallidus, but this did not survive small volume correction. In contrast, for the Go—Fixation contrast, there was a significant influence of *COMT* genotype on all four ROIs, and activation in each of these regions survived a small volume correction (see Table 11). Mean signal was extracted from each of these ROIs to confirm the pattern of group differences in SPSS and, for this contrast, a consistent pattern of *COMT* genotype group differences emerged. Mean signal was marginally significantly different between *COMT* genotype groups in the right IFG (pars opercularis) (F (2, 44) = 2.75, p = 0.076) and in the SMA/pre-SMA (F (2, 44) = 2.60, p = 0.087) (see Figures 16-17). Inspection of the group means reveals that in all regions, except for the SMA/pre-SMA, the greatest amount of activation during Go trials as compared to baseline was in the met/met group, the least amount in the val/val group, and an intermediate amount in the val/met group. There was greater activation in the val/met group in the SMA/pre-SMA for Go—Fixation, although the difference between val/met and met/met was small (see Table 12).

To further explore the modulatory influence of *COMT* on activation in Go trials as compared to baseline, a whole-brain analysis was conducted (Family-wise error corrected at $p < 0.05$ and 10 voxel extent). There was a significant influence of *COMT* genotype on a number of regions involved in producing a motor response, including the thalamus and basal ganglia (x 24, y -30, z 2, t = 7.96, k = 1142, $p < 0.001$), cerebellum (x 36, y -78, z 4, t = 9.08, k = 19346, $p < 0.001$), the SMA through the pre-SMA to the middle cingulate (x 2, y 10, z 46, t = 6.59, k = 940, $p < 0.001$), and motor cortex (x -36, y -22, z 50, t = 6.51, k = 468, $p < 0.001$). Mean signal was extracted from the right thalamus/basal ganglia cluster, right SMA/pre-SMA/cingulate cluster, and left postcentral gyrus to confirm the pattern of group differences in SPSS and, for this contrast, the pattern of group differences was consistent with those observed for the ROI analysis.

Mean signal was significantly different between *COMT* genotype groups in the right thalamus/basal ganglia cluster (F (2, 44) = 5.53, $p < 0.01$) and the left postcentral gyrus (F (2, 44) = 3.85, $p < 0.05$). Mean signal was marginally

significantly different between *COMT* genotype groups in the right SMA/pre-SMA/cingulate cluster (F (2, 44) = 2.47, p = 0.096). Examination of group means revealed that for the right thalamus/basal ganglia cluster and the right SMA/pre-SMA/cingulate cluster, the greatest amount of activation during Go trials as compared to baseline was in the met/met group, the least amount in the val/val group, and an intermediate amount in the val/met group. For the left postcentral gyrus, there was greater activation in the val/met group for Go—Fixation, although the difference between val/met and met/met was small.

For StopInhibit—Fixation, there was an influence of *DAT* genotype on activation in each of the ROIs, although these did not survive small volume correction. Mean signal was extracted from each of the ROIs to confirm the pattern of group differences in SPSS and in each ROI, activation was greater in the *DAT* 9+ group than in the 10/10 group. In contrast, for the StopInhibit—Fixation contrast, there was a significant influence of *COMT* genotype on all four ROIs, and activation in each of these regions survived a small volume correction (see Table 11). Mean signal was extracted from each of these ROIs to confirm the pattern of group differences in SPSS and, for this contrast, a consistent pattern of *COMT* genotype group differences emerged. Mean signal was significantly different between *COMT* genotype groups in the right IFG (pars opercularis) (F (2, 44) = 5.43, p < 0.01) (see Figure 18). Inspection of the group means revealed that in this region, the greatest amount of activation during StopInhibit, as compared to baseline, was in the met/met group, the least amount in the val/val group, and an intermediate amount in the val/met group. This same pattern was seen in the globus pallidus. For the right STN and pre-SMA regions, there was greater activation in the val/met group in the SMA/pre-SMA for Go—Fixation, although the difference between val/met and met/met was small (see Table 12).

To further explore the modulatory influence of *COMT* on activation in StopInhibit trials as compared to baseline, a whole-brain analysis was conducted (Family-wise error corrected at p < 0.05 and 10 voxel extent). There was a significant influence of *COMT* genotype on a number of regions seen in the group-level StopInhibit—Fixation contrast, including the right putamen through the insula lobe and IFG (pars opercularis) (x 26, y 14, z 6, t = 7.07, k = 844, p < 0.001), the pre-SMA through the bilateral middle cingulate cortex (x 4, y 20, z 30, t = 7.18, k = 574, p < 0.001), the left insula lobe, putamen and IFG (pars opercularis) (x -28, y 16, z 12, t = 6.99, k = 386, p < 0.001), right superior temporal and supramarginal gyri (x 58, y -40, z 16, t = 7.55, k = 755, p < 0.001), left supramarginal gyrus (x -56, y -24, z 22, t = 7.19, k = 227, p < 0.001), right precentral gyrus (x 46, y 2, z 30, t = 5.85, k = 68, p < 0.001) and left thalamus (x -20, y -26, z 4, t = 6.82, k = 46, p < 0.001). Mean signal was extracted from the right putamen/insula/IFG cluster, the pre-SMA/middle cingulate cluster, and the left insula/putamen/IFG cluster to confirm the patter of group differences in SPSS and, for this contrast, the pattern of group differences was consistent with those observed for the ROI analysis.

Mean signal was marginally significantly different between *COMT* genotype groups in the right putamen/insula/IFG cluster (F (2, 44) = 3.05, p = 0.058), in the pre-SMA/middle cingulate cluster (F (2, 44) = 2.80, p = 0.073), and in the left putamen/insula/IFG cluster (F (2, 44) = 3.12, p = 0.054). Examination of group means revealed that for each of these clusters, the greatest amount of activation during StopInhibit trials as compared to baseline was in the met/met group, the least amount in the val/val group, and an intermediate amount in the val/met group.

DAT + COMT.

In order to test for an influence of *DAT* and *COMT* together on neural activation during stopping, I performed a regression of a *DAT* + *COMT* additive term in SPM2 on StopInhibit—Fixation. I tested an additive effect of *DAT* and *COMT* genotypes by combining groups with the least number of alleles that were predicted to influence neural activity (called predictive-alleles here), an intermediate number of predictive-alleles, and the most number of predictive-alleles. This resulted in the following four groups: 1) *DAT* 10/10—*COMT* val/val; 2) *DAT* 10/10—*COMT* val/met or *DAT* 9+—*COMT* val/val; 3) *DAT* 10/10—*COMT* met/met or *DAT* 9+—*COMT* val/met; and 4) *DAT* 9+—*COMT* met/met (see Table 6).

A regression testing for the additive influence of a *DAT* + *COMT* influence in SPM2 on StopInhibit—Fixation revealed significant additive influence in three of the ROIs, the right IFG (pars opercularis) (x 58, y 10, z 28; t = 3.30; k = 31; p = 0.550), pre-SMA (x 2, y 2, z 66; t = 3.20; k = 7; p = 0.448), and globus pallidus (x 20, y -2, z -6; t = 3.25; k = 26; p = 0.165), although these did not survive small volume correction. I extracted mean signal from each of these ROIs to confirm the pattern of group differences in SPSS. Mean signal was significantly different between *DAT* + *COMT* genotype groups in the right IFG (F (3, 44) = 2.85, p < 0.05) and marginally significantly different in the right pre-SMA (F (3, 44) = 2.54, p = 0.07) and right globus pallidus (F (3, 44) = 2.83, p = 0.05) (see Table 13). Examination of the mean signal in each group revealed a linear increase in activation during StopInhibit trials, as compared to baseline, such that there was the least amount of activation in the *DAT* 10/10—*COMT* val/val group and the greatest amount of activation in the *DAT* 9+—*COMT* met/met (see Figures 19-21).

Finally, to test for nonadditivity of the main effects of *DAT* and *COMT*, an interaction term (*DAT* x *COMT*) was entered into this model. When the interaction term was entered into the model, the influence of the additive *DAT* + *COMT* term did not change. Furthermore, there was no significant influence of the interaction term alone on activation in any of the ROIs. Therefore, these results support an additive effect, but not an interactive effect, of *DAT* and *COMT* genotypes on neural activation during inhibition.

Discussion

The Neurogenetic Correlates of Behavioral Inhibition

The purpose of the present study was to examine the pattern of neural activation underlying inhibition of a prepotent response and to test the influence of *DAT* and *COMT* genotypes on this activation in a sample of healthy adults. These participants were prescreened to ensure that this sample included only healthy adults. Therefore, the results of this study are not likely accounted for by mental health status. These results support significant differences in neural activation during performance of a Stop-signal task as a function of *DAT* and *COMT* genotypes, as well as an additive effect of *DAT* and *COMT*. These findings suggest that genetically driven variability in dopamine availability in frontostriatal regions may influence individual differences in inhibitory control.

The results of the present study are in line with other studies showing increased activation in 9-repeat allele or met-allele carriers (Bertolino et al., 2006; Caldu et al., 2007; Yacubian et al., 2007). However, this is the first study to demonstrate such differences in activation as a function of *DAT* and *COMT* genotypes using the Stop-signal task. Beyond that, this study is novel in its attempt to specifically overcome many of the limitations associated with 1) previous fMRI studies of impulsivity or behavioral inhibition and 2) previous association studies testing for the influence of dopaminergic variation on impulsivity or behavioral inhibition. By carefully parsing the construct of interest to focus specifically on behavioral inhibition, by combining models of frontostriatal function and tonic-phasic dopamine, and by increasing power by using an imaging genetics approach, I was able to make specific predictions about, and provide evidence for, the influence of dopaminergic variation on neural activation underlying inhibitory control in healthy adults.

The first specific aim was to examine the pattern of neural activation during performance of the Stop-signal task, which requires participants to alternate between responding and suppressing a response that has already been initiated. Activation during responding was seen in the expected regions, including the motor cortex, thalamus, basal ganglia, and cerebellum. Activation during inhibition was also seen in the expected regions, including the right IFC, STN, pre-SMA, and GP. These results provide further support for the role of a right-lateralized frontostriatal circuit underlying behavioral inhibition, and are consistent with a direct frontostriatal pathway for going, and a hyperdirect pathway for stopping. I also predicted that there would be individual differences in activation, even when the task controlled for difficulty level, and this was supported as there was a significant negative correlation between right IFC activation during inhibition and SSRT. That is, those individuals who had better inhibitory control showed greater neural activation in key regions.

The second specific aim was to test the influence of dopaminergic genetic polymorphisms on brain activation during behavioral inhibition. I predicted that variants of two candidate genes *(DAT* and *COMT*) would differentially influence neural activation during behavioral inhibition, and these predictions were supported. For *DAT*, there is evidence supporting a functional difference between

variants, one in which the 10-repeat allele results in excessive amounts of DAT production. Excessive amounts of the DAT may lead to an overly efficient reuptake of dopamine, reducing intrasynaptic and extracellular dopamine below optimal levels. Specifically, a lack of dopamine (or hypo-dopaminergic state) in target neurons would impair the signal-to-noise ratio during inhibition.

I predicted that, in brain regions where an optimal range of dopamine is necessary for successful behavioral inhibition, *DAT* variation would task-specifically alter dopamine availability and function. Indeed, for neural activation seen during successful inhibition, relative to both going and baseline, there was significantly greater activation in the regions of interest in the 9+ group as compared to the 10/10 group. As greater activation represents better inhibitory control in this sample, these results suggest that the 10/10 group shows an impaired neural response during the suppression of a prepotent response as compared to the 9+group.

For *COMT*, there is evidence supporting a functional difference between its variants, with the val enzyme having greater activity than the met enzyme. Excessive amounts of the COMT enzyme (which is associated with the val variant) is suggested to lead to a higher rate of dopamine catabolism, thereby reducing dopamine levels below optimal levels. Specifically, a lack of dopamine (or hypo-dopaminergic state) in target neurons would impair the signal-to-noise ratio during inhibition.

I predicted that, in brain regions where an optimal range of dopamine is necessary for successful behavioral inhibition, *COMT* variation would task-specifically alter dopamine availability and function. Surprisingly, *COMT* variation modulates not only the neural response during behavioral inhibition, but also the neural response during the go process. For successful inhibition, and successful motor responding, relative to baseline, there was significantly greater activation in the regions of interest in the met/met group than in the val/val group. For the val/met group, there were either intermediate levels of activation or levels of activation close to those of the met/met group. As greater activation represents better inhibitory control in this sample, these results suggest that the val/val group shows an impaired neural response during performance of this task as compared to the met/met and val/met groups.

This finding that *COMT* modulates the neural response during both inhibition and response is surprising, given that I predicted to see an influence of *DAT* and *COMT* on activation during inhibition, but not performance, of a motor response. This finding of an influence of *COMT* on neural activation during responding may be explained in terms of the difference in function and distribution between DAT and COMT. DAT is responsible for removal of dopamine at the synapse, and there is a relative lack of DAT in cortical areas. COMT, on the other hand, is responsible for degrading dopamine in the extrasynaptic space and plays a particularly important role in regulating dopamine transmission in prefrontal cortical areas. Indeed, the influence of *COMT* on modulating prefrontal cognitive function is consistently reported across a number of tasks, including the present task (although it is worth noting that

most previous tasks require a response for the trial-type of interest). It may be, then, that dopaminergic modulation of prefrontal cognitive functions, including both stopping and going, is more sensitive to variation in COMT activity than variation in DAT activity.

Finally, the third specific aim was to test for a potential additive effect of these two polymorphisms on brain activation during a behavioral inhibition task. Based on evidence that there is an optimal range of dopamine availability for the performance of this task, along with evidence that both *DAT* and *COMT* polymorphisms modify dopamine availability, it was predicted that a combination of certain variants would task-specifically alter dopamine availability and function. Specifically, I predicted that the *DAT* 10-repeat alleles and *COMT* val alleles would result in the greatest reduction of dopamine availability, thereby impairing task performance and/or neural response. In contrast, I predicted that the *DAT* 9-repeat alleles and *COMT* met-alleles would result in the greatest amount of dopamine availability, which is thought to reduce cortical noise and enhance stability, thereby facilitating inhibitory control.

To test these predictions, genotype information was combined to create four groups: 1) *DAT* 10/10—*COMT* val/val; 2) *DAT* 10/10-*COMT* val/met or *DAT* 9+—*COMT* val/val; 3) *DAT* 10/10—*COMT* met/met or *DAT* 9+—*COMT* val/met; and 4) *DAT* 9+—*COMT* met/met. These results support an additive effect, but not an interaction, of *DAT* and *COMT* genotypes on neural activation underlying behavioral inhibition. For neural activation seen during successful inhibition, relative to baseline, there was significantly greater activation in the regions of interest in the *DAT* 9+-*COMT* met/met group as compared to the *DAT* 10/10—*COMT* val/val group. Put another way, there was a linear increase in activation according to levels of predicted levels of dopamine availability: those individuals predicted to have the lowest dopamine availability had the least BOLD signal response during inhibition, while those individuals predicted to have the highest dopamine availability had the greatest BOLD signal response during inhibition. Again, as greater activation represents better inhibitory control in this sample, these results suggest that the group with both variants predicted to reduce dopamine availability shows an impaired neural response during the suppression of a prepotent response as compared to the group with both variants predicted to result in increased dopamine availability. Furthermore, these data suggest that the effects of *DAT* and *COMT* are not dependent on each other, but that their independent effects are additive upon each other.

There was no evidence for an additive effect of *DAT* and *COMT* on SSRT, but this may be because of limited gene group sample sizes. Examination of group means (see Table 6) reveals that the *DAT* 10/10—*COMT* val/val group had the second longest SSRT (the *DAT* 10/10—*COMT* met/met or *DAT* 9+—*COMT* val/met group actually had the longest SSRT), while the *DAT* 9+—*COMT* met/met group did have the shortest SSRT (reflecting better inhibitory control). These results are limited by small sample sizes, but suggest that, with an increased number of participants, we may be able to see behavioral differences consistent with differences in neural activation.

The results of the present study are in line with our previously reported interaction between *DRD4* and *DAT* genotypes on SSRT (Congdon et al., 2008). Specifically, we reported that individuals with the *DAT* 10/10 genotype and at least one 7-repeat allele of the *DRD4* had significantly longer SSRT (poorer inhibitory control) than all other *DAT* x *DRD4* groups. In the present study, individuals with the *DAT* 10/10 and *COMT* val/val genotype had significantly less activation in the regions involved in inhibition than those individuals with the *DAT* 9+ and *COMT* met/met genotype. There was not a significant influence of *DAT* and *COMT* genotypes on SSRT in the current study, but this may be a result of a smaller sample size. It's important to note, though, that both of these findings are consistent with the prediction that reduced dopamine availability (which is associated with the *DAT* 10-repeat allele (Brookes et al., 2007), *DRD4* 7-allele (Asghari et al., 1995), and *COMT* val-allele (Lotta et al., 1995)) is disruptive and impairs the functioning of cognitive systems (Arnsten, 1998; Bilder et al., 2004). As will be discussed below, future research is needed to examine the influence of all three dopamine system-related gene polymorphisms on behavioral inhibition in a larger sample.

Dopaminergic Variation and Prefrontal Cognitive Function

It's useful to consider the results of the present study in terms of the predictions stemming from the tonic-phasic model of dopamine. In relation to cognitive functions, this model proposes that dopamine influences the stability and flexibility of neural networks through the interacting effects of tonic and phasic dopamine in brain regions, which interact to influence the signal-to-noise ratio (Bilder et al, 2004; Cohen et al., 2002; Seamans & Yang, 2004; Robbins, 2005; Grace, 1991). Dopamine acts to vary the signal-to-noise ratio by suppressing spontaneous background firing and enhancing the task-specific response. In this way, then, dopamine is said to modulate the response of neural networks. Again, the usefulness of this model is that allows us to make specific predictions about the influence of dopaminergic variation. That is, if there is an optimal range of dopamine availability for the performance of a given function, then we can test whether individual differences in dopamine availability differentially impair or enhance performance. Four studies which test such predictions will be reviewed, in relation to an inverted U-shaped dose-response curve, and their results will be explained in reference to such a curve (see Figures 22-25).

The first example comes from findings that individual differences in attentional performance in rats predicts response to dopaminergic receptor agents (Granon et al., 2000). Granon and colleagues demonstrated that rats with relatively low baseline levels of performance on a five-choice serial reaction time task (5CSRTT) showed improved performance after low doses of a D1 agonist (SKF 38393), whereas rats with relatively higher baseline levels of performance on a 5CSRTT showed deficits in response to a D1 antagonist (SCH 23390). Using Figure 22 to illustrate their results, we see that the rats with relatively low baseline levels of performance presumably 1) had lower dopamine availability

and function at baseline; 2) fall to the left of the inverted U-shaped curve; and 3) therefore had improved performance in response to a D1 agonist, which increases dopamine availability. In contrast, the rats with relatively high baseline levels of performance presumably 1) already had higher dopamine availability and function at baseline; 2) fall to the middle or left of the inverted U-shaped curve; and 3) therefore had impaired performance in response to a D1 antagonist, which blocks D1 receptor stimulation. Similar results have been reported in other studies (Arnsten, Cai, Murphy, & Goldman-Rakic,1994; Feola, Wit, & Richards, 2000; Zahrt, Taylor, Mathew, & Arnsten, 1997), though the effect of dopamine receptor agents varies according to the task used or behavioral process studied, which suggests that there are different optimum levels of dopamine availability and function for different behavioral processes. In summary, their results suggest that individual differences at baseline may affect the neuromodulatory effects of dopamine on behavior.

The second example comes from findings that individual differences in self-reported impulsivity in humans can predict response to a dopaminergic receptor agent (Cools, Sheridan, Jacobs, & D'Esposito, 2007). Cools and colleagues tested whether dopamine modulates the striatum and frontal cortex during flexible updating and stable maintenance of representations, using a delayed match-to-sample task. They manipulated dopamine levels by administering a D2 receptor agonist, bromocriptine, and assessed neural activity in the striatum and frontal cortex with fMRI. The effects of bromocriptine on neural activity, and to a lesser extent, task performance, depended on trait impulsivity (as measured with the BIS-11). Bromocriptine significantly reduced switch cost (improved flexible updating) in the working memory task in high-impulsive, but not low-impulsive, individuals. In parallel to this, bromocriptine significantly increased striatal activity during switching, and lateral prefrontal activity during distraction, in high-impulsive, but not low-impulsive, individuals.

Using Figure 23 to illustrate their results, the individuals with high trait impulsivity, who 1) show poor baseline working memory (Castellanos & Tannock, 2002; Jentsch & Taylor, 1999); and 2) low baseline D2/D3 receptor binding (Dalley et al., 2007), presumably fall to the left of an inverted U-shaped response curve. Therefore, administering a D2 receptor agonist, which increases dopamine availability, presumably resulted in an optimal range of dopamine availability for performance of this task, thereby improving performance and increasing frontostriatal activity in this group. In summary, the dissociable effects of a D2 receptor agonist on frontostriatal regions during a working memory task were dependent on trait impulsivity.

The third example to demonstrate a test of predictions stemming from the tonic-phasic model of dopamine, specifically that dopaminergic variation impacts cognitive functions mediated by the prefrontal cortex, comes from findings that *COMT* genotype predicts response to amphetamine (Mattay et al., 2003). Mattay and colleagues demonstrated an interaction between *COMT* genotype, amphetamine response, and neural activation during performance of an *N*-back task. Administering amphetamine to participants genotyped for *COMT*, who

performed an N-back task, revealed increased efficiency of prefrontal functioning in the N-back task in the val-group at all levels of amphetamine administration, whereas an effect was only seen on the met/met group at higher doses, at which point they were significantly impaired. Amphetamine, a nonspecific monoamine agonist, blocks reuptake of DA and has been shown to enhance the neuromodulatory role of catecholamines, such that dopamine and norepinephrine suppress spontaneous background firing and enhance task-specific focal firing more so after amphetamine administration (Foote et al., 1975; Mattay et al., 1996).

Using Figure 24 to illustrate their results, we see that individuals in the val-group 1) presumably had lower dopamine availability at baseline; 2) fall to the left of the inverted U-shaped curve; and 3) therefore had improved performance in response to amphetamine (which increased dopamine availability). In contrast, individuals in the met/met group 1) presumably had greater dopamine availability at baseline; 2) fall to the middle or left of the inverted U-shaped curve; and 3) therefore were impaired at higher doses only of amphetamine on the working memory task. By pharmacologically manipulating dopamine, they were able to manipulate signal-to-noise ratio in prefrontal regions and shift the response of groups hypothesized to fall on opposite sides of the inverted-U shaped response curve (Mattay et al., 2003). In summary, their results support the idea that there is an inverted U-shaped dose-response curve of dopamine activity and that increased dopamine activity may differentially enhance or impair performance according to *COMT* genotype.

The fourth and final example comes from findings of differences in performance accuracy between *COMT* genotype in adolescence. Based on data showing that adolescence is characterized by increases in basal prefrontal dopamine levels, Wahlstrom and colleagues predicted a rightwards shift of the relative place of *COMT* genotype groups on the inverted U-shaped dose-response curve (Wahlstrom et al., 2007) (see Figure 25). The authors tested this prediction by assessing children and adolescents (ages 9-17) genotyped for *COMT* on measures of working memory, attention, fine motor coordination, and motor speed. Indeed, they found *COMT* genotype group differences in behaviors modulated by prefrontal dopamine, such that the heterozygote group performed better than both homozygote groups in motor coordination and better than the met/met group in attention and working memory, but no differences in behaviors not dependent on prefrontal dopamine (finger tapping).

Using Figure 25 to illustrate their results, we see that adolescents in the val/met group, who are known to have increased dopaminergic tone as a result of their age, had 1) presumably optimal levels of dopamine availability and function as a result of their *COMT* genotype; and therefore 2) had better performance on cognitive tasks dependent on prefrontal function, as compared to both homozygote groups. In summary, their results provide further support of an inverted U-shaped dose-response curve of dopamine activity and function, such that both deficient and excessive amounts of dopamine activity impair cognitive functions mediated by the prefrontal cortex.

The results of the present study are in line with these findings and suggest that differences in dopamine availability, as predicted by both *DAT* and *COMT* genotypes, may differentially enhance or impair performance. It was predicted that two dopamine-system related gene polymorphisms known to alter dopamine availability would influence inhibitory control and neural activation during behavioral inhibition. Using Figure 26 and 27 to illustrate the results of the present study, we see that in a sample of healthy adults, both independently and additively, those individuals in the *DAT* 10/10 group and/or the *COMT* val/val group 1) had presumably reduced levels of dopamine availability; 2) fall to the left of the inverted U-shaped curve; and therefore 2) exhibited an impaired pattern of activation during inhibition. In contrast, those individuals with in the *DAT* 9+ group and/or the *COMT* met/met group 1) had presumably optimal levels of dopamine availability; 2) fall to the middle or left of the inverted U-shaped curve; and therefore 3) exhibited successful engagement of key stopping regions during inhibition.

What these studies, including the results of the present study, illustrate is that for a given task, there is an optimal range of dopamine availability for the performance of this task, and that there is a growing list of factors which influences this range of dopamine, including individual differences in baseline performance of the given task, self-reported impulsivity, and dopaminergic variation. The neuromodulatory role of dopamine on cognition therefore varies by individual and cognitive processes.

Limitations

There are several limitations of this study. First, there is an important caveat regarding the present sample of healthy adults. I intended to randomly sample a group of healthy adults, which would represent a range of impulsivity. An examination of the relationship between self-reported impulsivity and SSRT in the final sample of participants and in the initial sample of scanned participants reveals a striking difference. In the final sample (N = 46), there was no correlation between BIS-11 total scores and SSRT (r = -.042, $p > .05$), although the relationship was somewhat negative (see Figure 28). In contrast, in the initial sample (N = 53), there was a significant correlation between BIS-11 scores and SSRT (r = .417, $p < .01$) (see Figure 29). Examination of the this relationship revealed that the correlation was clearly being driven by outliers, but also that it was the highest scorers on the BIS-11, and those individuals with the poorest inhibitory control, who were excluded from the analyses due to excessive movement in the scanner or a failure to perform the task correctly throughout the scan session. Therefore, an important qualification regarding this sample, and the interpretation of these results, is that it is composed of healthy, relatively low-impulsive adults, and that an examination of high-impulsive adults may lead to quite different results.

Second, I recognize that there are limitations of fMRI. Demonstrating that there is increased activation in the regions of interest during inhibition does not prove that these regions are exclusively responsible for, or involved in, inhibitory

control. However, these results are in line with previously published results (Aron et al., 2007; Aron & Poldrack, 2006) and are in line with lesion (Aron et al., 2003) and TMS (Chambers et al., 2006) data. Together, these lines of research strongly support the role of a right-lateralized frontostriatal network in the inhibition of a response that has already been initiated.

Furthermore, it is recognized that the BOLD signal does not directly index dopamine availability or function. However, there is some data linking these two processes, including an *in vivo* study showing a relationship between striatal DA synthesis (FDOPA PET) and neural activation (BOLD signal) (Siessmeier et al., 2006), as well as a review of evidence which suggests that a BOLD signal increase in the nucleus accumbens (during a relevant task) may predominantly reflect postsynaptic D1 receptor activation (Knutson & Gibbs, 2007). Therefore, the significant influence of *DAT* and *COMT* genotypes, as well as a *DAT* + *COMT* additive effect, on neural activation in this study may be interpreted as differences in neural activation that may result from differences in dopamine availability or function.

A third limitation concerns sample size. Although the final sample consisted of a sufficient number of participants, this sample was limited by the small sample sizes of some *DAT* + *COMT* genotype groups. In particular, there were only two individuals in the *DAT* 9+—*COMT* met/met group, even after participants were pre-selected based on genotype. This limitation demonstrates an inherent difficulty in conducting studies based on genotypes with infrequent alleles, and suggests that future imaging genetics studies will need to oversample these individuals in order to get more balanced distributions.

A fourth limitation concerns specificity. I predicted that, in brain regions where an optimal range of dopamine is necessary for inhibition, certain variants of *DAT* and *COMT* polymorphisms would task-specifically alter dopamine availability and function. Although the present study provides evidence that such variation does influence neural activation, I cannot conclude that it is task-specific, as this investigation only included the Stop-signal task. Furthermore, I did not assess resting activation and cannot rule out differences in baseline activity as a function of *DAT* or *COMT* genotype. Finally, I did not assess structural features and cannot rule out anatomical differences which may underlie functional differences.

Future Directions

Based on the striking difference in relationships between self-reported impulsivity and inhibitory control from the final sample of participants (N = 46) and the larger sample of those scanned (N = 53), additional investigations into the neural and genetic correlates of behavioral inhibition in high-impulsive individuals is warranted. Of course, there appears to be a methodological limitation in requiring participants that have difficulty staying still to remain essentially motionless for 90 minutes. This limitation may help to explain why there are only several published fMRI studies assessing individual differences in impulsivity and why, of these few studies, the self-reported levels of impulsivity

are relatively low. However, there are likely important differences between healthy low-impulsive and healthy high-impulsive individuals that may have significant implications for psychiatric groups characterized by elevated impulsivity.

A second, though related, direction for future research involves varying the information processing demands. The tracking Stop-signal task was designed to ensure comparable difficulty level, which is advantageous in an imaging paradigm, and presumably varies difficulty level within sessions. However, there are reasons to believe that it would be worthwhile to include a separate paradigm in which information processing demands were varied.

First, there is evidence that when information-processing demands are increased, high-impulsive individuals slow down (whereas low-impulsive speed up in response to increased information processing demands)(Keilp, Sackheim, & Mann, 2005). This is helpful in understanding why a long SSRT (reflective of a slower stopping process) is an index of increased impulsivity. Second, there is evidence that impulsivity (or the influence of dopaminergic variation) is only seen when information processing demands are increased (James, Groman, Seu, Jorgensen, Fairbanks, & Jentsch, 2007). For example, in vervet monkeys selected for being high-impulsive, low-impulsive, or carrying the *DRD4* risk allele, these researchers assessed social impulsivity, novelty seeking, and working memory (using a three-choice spatial response task, in which delay intervals were varied in order to increase difficulty level). In monkeys, the *DRD4* risk allele is the DRD4.5 variant, and this group represented an intermediate group in terms of impulsivity. Overall, high-impulsive monkeys performed poorer than low-impulsive monkeys on the working memory task. However, when considering the different delay intervals, there was a group x delay interaction: none of the groups differed at the easiest delay, but the high-impulsivity group performed more poorly than the low-impulsivity group at the middle and long delays, whereas the DRD4.5 group performed significantly more poorly from the low-impulsive group only at the long delays. In other words, impulsivity was negatively related to working memory performance, but this relationship was seen only at the more difficult level of the working memory task.

Therefore, it would be worthwhile to include an inhibitory control paradigm in which information processing demands are varied in a future study. By varying difficulty level, it may be possible 1) to further characterize impairments in inhibitory control in high-impulsive individuals; 2) to test for varieties of impaired inhibitory control in participants that don't necessarily score high on trait measures of impulsivity, but that may be at-risk for impaired inhibitory control when information processing demands are increased; and 3) to extend predictions stemming from the tonic-phasic model of dopamine's influence on prefrontal cognitive function.

A third direction for future research involves taking into account potential environmental variables which may mediate the relationship between dopaminergic variation, inhibitory control, and trait impulsivity. In support of this aim, there is evidence from a PET study that life stress and impulsivity interact to

predict a blunted striatal dopamine response after amphetamine administration, which is suggested to reflect a risk factor for drug abuse (Oswald et al., 2007). In particular, these researchers assessed binding potential with a D2/D3 receptor antagonist ([^{11}C]raclopride), before and after amphetamine administration. In high impulsive individuals with low or moderate life events stress, dopamine release after amphetamine administration was blunted, as compared to low impulsive individuals. However, there were no differences between high and low impulsive groups with high levels of life events stress. Similarly, another group reported a significant reduction in striatal dopamine release in a stress vs. resting condition in subjects reporting low parental care, as compared to those reporting high parental care (Pruessner, Champagne, Meaney, & Dagher, 2004). These results not only highlight the role of impulsivity, but also of life stress, in mediating the dopaminergic response to amphetamine.

It was reviewed above how both trait impulsivity and dopamine system-related genotypes predict individual differences in cognitive function and neural activation, in relation to an inverted U-shaped dose-response of dopamine availability and function. These data suggest that another predictive variable, interacting with both impulsivity and dopaminergic variation, may be life stress (chronic and acute). Therefore, future research will need to include additional information on individuals' environments, as well.

A fourth future direction, as discussed above, would be to consider additional dopamine system-related gene polymorphisms. For example, there is evidence implicating an interaction between the *DAT* and the DRD4 receptor gene polymorphism on SSRT (Congdon et al., 2008). There is also evidence suggesting a role for serotonin, specifically the *5HT2A* receptor gene polymorphism, on Go/NoGo commission errors during a punishment condition (Nomura et al., 2006). Future studies which test their influence on specific components of impulsive behavior, both separately and together, will help to tease apart the influence of both dopamine and serotonin neurotransmitter systems on the complex construct of impulsivity.

Finally, future studies which take advantage of advanced neuroimaging techniques and analyses are warranted. It was reviewed above that elevated impulsivity is associated with poor axonal and/or myelin fiber integrity, as well as reduced gray matter density, and that individual differences in these structural measures appear to correlate with behavioral inhibition in healthy individuals. Therefore, it would be worthwhile to conduct DTI and structural analyses to examine whether 1) the relationship between neural activation and inhibitory control is moderated by individual differences in structural brain features; or 2) the influence of dopaminergic variation is also seen on structural brain features.

Similarly, it would be worthwhile to conduct functional connectivity analyses to examine whether the degree of coupling between the regions of interest in the present study varies as a function of *DAT* and *COMT* genotypes. Results of the present study demonstrate that there was greater activation in these key stopping regions during inhibition, and that activation in these regions was significantly correlated, but it would be useful to test for the degree of

coupling between these regions. Furthermore, results of the present study demonstrate that there was an influence of *DAT* and *COMT*, and an additive effect of *DAT* + *COMT*, on activation in these regions. It would also be useful to test for the influence dopaminergic variation on the degree of coupling between these regions. Doing so may help to further test whether dopaminergic modulation of prefrontal cognitive functions, including both stopping and going, is more sensitive to variation in COMT activity than variation in DAT activity.

Conclusion

The purpose of the present study was to apply an intermediate phenotype approach to impulsivity, and these results suggest that the influence of dopaminergic variability on behavioral inhibition may be an appropriate intermediate phenotype. To my knowledge, this is the first report of the effect of both *DAT* and *COMT* on neural activation during performance of a tracking Stop-signal task in healthy adults. In addition to providing additional evidence for the role of right-lateralized frontostriatal network underlying behavioral inhibition, the present study also provides evidence of significant individual differences, such that those individuals who show greater activation in these key stopping regions show better inhibitory control. However, these results are clearly representative of healthy, low-impulsive individuals and therefore may not provide a complete picture of the neural activation as a function of impulsivity. Nonetheless, this data suggest that the neurophysiological response during behavioral inhibition may be a suitable intermediate phenotype as the influence of *DAT* and *COMT* genetic variation was detectable on neural response. This study is a major step towards elucidating the biological correlates of impulsivity, particularly with regard to individual differences in inhibitory control. As impulsivity is of significance for a number of psychiatric disorders, it is likely that this line of research will be of considerable clinical significance in advancing the prediction, diagnosis, and treatment of impulsivity-related forms of mental illness.

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Table 1. Two dopamine (DA) system-related genes with functional polymorphisms

Candidate	Protein Function	Polymorphism	Type	Functional Significance
Dopamine Transporter	Plasma membrane transport protein; reuptake of DA	DAT (DAT1 or SLC6A3)	VNTR; 40-bp repeat; 3-13 times	Noncoding region; affects mRNA transcription; 10 variant has increased expression
COMT	Enzyme degrades catecholamines	COMT or COMTval$^{108/158}$met	G to A mutation	Methionine substituted for valine at codon 158; val variant has increased activity

Note. VNTR, variable number of tandem repeats polymorphism; bp, base-pair; 3'-UTR, 3'-untranslated region; mRNA, messenger RNA

Table 2. Predicted differences between variants of dopamine (DA) system-related gene polymorphisms in neural response during inhibition

Polymorphism	Allele-group	Effect on DA	Brain Region	Neural Response
DAT				
	9+	Increased	Subcortical	Increased
	10/10	Decreased	Subcortical	Reduced
COMT				
	met/met	Increased	Prefrontal	Increased
	val/met	Intermediate	Prefrontal	Intermediate
	val/val	Decreased	Prefrontal	Reduced

Table 3. Sample- and genotype-specific demographics

Genotype	Group	Sex	N	Ethnicity					Mean age +/- SEM
				AA	AS	CS	LA	OT	
DAT	Total		45						22.78 (3.34)
	10/10		28						23.25 (0.68)
		Male	12	2	2	7	0	1	23.00 (1.11)
		Female	16	0	6	8	1	1	23.44 (0.89)
	9+		17						22.00 (0.66)
		Male	7	0	0	7	0	0	22.14 (1.01)
		Female	10	0	2	6	1	1	21.90 (0.92)
COMT	Total		46						22.85 (3.33)
	val/val		12						23.17 (0.95)
		Male	5	1	2	2	0	0	23.20 (1.68)
		Female	7	0	2	3	1	1	23.14 (1.22)
	val/met		28						23.00 (0.67)
		Male	13	1	0	11	0	1	22.54 (1.00)
		Female	15	0	4	9	1	1	23.40 (0.91)
	met/met		6						21.50 (1.03)
		Male	2	0	0	2	0	0	24.00 (1.00)
		Female	4	0	2	2	0	0	20.25 (0.95)

Note. There were no significant differences in age, sex, ethnicity, or education between any of the genotype groups. AA, African-American; AS, Asian; CS, Caucasian; LA, Latino/Hispanic; OT, Self-Identified as Other. N = 45 for DAT; N = 46 for COMT.

Table 4. Behavioral data from the Stop-signal task

Behavioral measure	Mean	SEM	Min	Max
RT-Correct Go trials	484.48	13.74	368.36	760.04
Percent Correct-Go trials	96.39	1.13	51.86	100.00
RT-StopRespond trials	433.95	11.24	313.46	653.88
Percent Inhibition-Stop trials	52.11	1.55	4.63	80.56
SSRT	214.55	6.78	140.05	366.84

Note. SEM, standard error of the mean; Min, minimum; Max, maximum; RT and SSRT are in ms; N = 46.

Table 5. Correlations between BIS-11 scores and Stop-signal reaction time

	Nonplanning	Motor	Cognitive	SSRT
Total	.841***	.806***	.743***	-.042
Nonplanning		.527***	.398***	-.008
Motor			.444**	-.028
Cognitive				-.073

Note. Table shows Pearson' product correlation coefficients. BIS-11, Barratt Impulsiveness Scale; SSRT, Stop-signal reaction time; N = 46.
* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

Table 6. Descriptive statistics of dependent variables according to DAT + COMT genotype groups

Measure	10/10-v/v	10/10-v/m; 9+-v/v	10/10-m/m;9+-v/m	9+-m/m	ANOVA *F*, *p*
Demographics					
Men/Women	5/3	7/13	5/10	2/0	
Age	23.00 (1.09)	24.00 (0.86)	20.87 (0.50)	24.00 (1.00)	2.99, 0.042
Trait impulsivity and performance					
BIS-11 Total	54.50 (2.55)	58.90 (2.40)	53.20 (1.49)	50.50 (0.50)	
Nonplanning	20.38 (1.27)	22.65 (1.17)	20.33 (0.82)	18.50 (2.50)	
Motor	20.62 (0.94)	20.95 (0.94)	19.53 (0.58)	20.00 (3.00)	
Cognitive	13.50 (0.78)	15.30 (0.87)	13.33 (0.68)	12.00 (1.00)	
RT- G trials	549.75 (45.22)	473.78 (18.67)	478.42 (20.67)	398.75 (13.49)	
%Correct-G trials	38.70 (12.40)	60.48 (6.07)	59.71 (6.67)	91.36 (2.47)	
RT-SR trials	497.88 (37.97)	422.68 (15.73)	423.16 (14.47)	382.87 (11.20)	2.63, 0.063
%Inhibition-S trials	62.04 (4.75)	51.76 (1.11)	47.72 (2.18)	49.07 (0.00)	3.89, 0.016
SSRT	221.67 (24.96)	207.61 (8.07)	230.28 (10.17)	173.06 (9.19)	

Note. Mean (+/- SEM) of self-reported impulsivity and task performance are shown for each DAT + COMT additive genotype group. F- and p-values are shown from one-way ANOVAs for significant or marginally significant effects. BIS-11, Barratt Impulsiveness Scale; RT, Reaction time; G trials, Correct Go trials; SR trials, StopRespond trials; S trials, Stop trials; SSRT, Stop-signal reaction time; RT and SSRT are presented in ms; N = 45.

Table 7. Descriptive statistics of dependent variables according to DAT x COMT genotype groups

Measure	10/10-v/v	10/10-v/m	10/10-m/m	9+-v/v	9+-v/m	9+-m/m
Demographics						
Men/Women	5/3	7/9	0/4	0/4	5/6	2/0
Age	23.00 (1.09)	24.12 (0.97)	20.25 (0.95)	23.50 (2.10)	21.09 (0.60)	24.00 (1.00)
Trait impulsivity and performance						
BIS-11 Total	54.50 (2.55)	61.06 (2.36)	47.25 (2.14)	50.25 (6.36)	55.36 (1.42)	50.50 (0.50)
Nonplanning	20.38 (1.27)	23.75 (1.19)	17.00 (0.41)	18.25 (2.69)	21.55 (0.84)	18.50 (2.50)
Motor	20.62 (0.94)	21.69 (1.01)	17.75 (1.49)	18.00 (2.04)	20.18 (0.48)	20.00 (3.00)
Cognitive	13.50 (0.78)	15.62 (0.94)	12.50 (1.32)	14.00 (2.38)	13.64 (0.81)	12.00 (1.00)
RT- G trials	549.75 (45.22)	472.16 (22.85)	532.92 (52.80)	480.25 (24.01)	458.60 (19.08)	398.75 (13.49)
%Correct-G trials	38.70 (12.40)	61.77 (7.31)	41.44 (13.93)	55.32 (9.26)	66.35 (6.87)	91.36 (2.47)
RT-SR trials	497.88 (37.97)	420.93 (19.32)	451.71 (33.24)	429.67 (18.73)	412.78 (15.46)	382.87 (11.20)
%Inhibition-S trials	62.04 (4.75)	51.91 (1.38)	53.70 (1.96)	51.16 (0.88)	45.54 (4.14)	49.07 (0.00)
SSRT	221.67 (24.96)	203.53 (9.25)	234.43 (22.86)	223.96 (15.46)	228.77 (11.81)	173.06 (9.19)

Note. Mean (+/- SEM) of self-reported impulsivity and task performance are shown for each DAT x COMT genotype group. BIS-11, Barratt Impulsiveness Scale; RT, Reaction time; G trials, Correct Go trials; SR trials, StopRespond trials; S trials, Stop trials; SSRT, Stop-signal reaction time; RT and SSRT are presented in ms; N = 45.

Table 8. Neural activation during conditions of Stop-signal task

Contrast		MNI coordinates					
Region	Side	x	y	z	*t*	*P*corr	voxels
Go—Fixation							
Thalamus	L	-14	-14	10	17.03	0.000	21,207
Thalamus	R	14	-16	12	13.93		
Cerebellum	Bi	22	-54	-24	16.76		
Inferior/middle/superior occipital gyri	Bi	4	-84	-2	13.58		
Globus pallidus	L	-26	-6	-4	11.86		
Rolandic operculum	L	-48	-2	-8	11.52		
Putamen	L	-20	12	6	10.52		
Caudate nucleus	L	-12	22	10	7.21		
SMA	Bi	-2	-2	50	11.88	0.000	1,502
Middle cingulate cortex	L	-10	8	38	9.43		
Pre-SMA	R	10	4	6	9.09		
Postcentral gyrus	L	-42	-20	56	10.44	0.000	1,183
Precentral gyrus	L	-28	-18	70	9.54		
Supramarginal gyrus	L	-60	-20	42	7.11		
Inferior parietal lobule	L	-54	-22	20	7.09		
Supramarginal gyrus	L	-56	-22	20	8.52	0.000	325
Rolandic operculum	L	-46	-28	22	7.78		
Intraparietal sulcus	L	-42	-36	30	6.91		
Putamen	R	24	14	10	8.56	0.000	269
Caudate nucleus	R	22	18	12	8.44		

Putamen	R	26	8	6	8.39		
Insula lobe	R	36	12	10	7.81		
Superior temporal gyrus	R	62	-34	22	7.96	0.000	215
Rolandic operculum	R	46	-2	10	8.00	0.000	135
Superior parietal lobule	L	-26	-56	58		0.000	17
StopInhibit—Fixation							
Inferior/middle/superior occipital gyri	Bi	-46	-72	4	15.81	0.000	24,350
Cerebellum	Bi	-32	-50	-24	12.03		
Inferior temporal gyrus	R	42	-52	12	11.07		
Supramarginal gyrus	R	60	-28	24	10.09		
Inferior/superior parietal lobule	Bi	32	-52	46	8.96		
Thalamus	R	12	-20	12	11.35	0.000	3,885
Thalamus	L	-18	-28	4	10.22		
Insula lobe	L	-28	18	10	9.75		
Middle cingulate cortex	R	8	-18	34	9.18		
Rolandic operculum	L	-46	0	8	9.11		
Putamen	L	-20	10	2	8.93		
Globus pallidus	L	-18	-2	0	7.56		
SMA	Bi	12	6	46	12.25	0.000	2,203
Middle cingulate cortex/ACC	Bi	6	22	30	9.63		
Insula lobe/IFG	R	32	16	8	10.43	0.000	2,075
Putamen	R	28	16	6	10.24		
Precentral gyrus	R	52	2	36	8.32		
Rolandic operculum	R	58	2	14	7.83		
Supramarginal gyrus	L	-52	-28	20	8.26	0.000	615
Intraparietal sulcus	L	-42	-36	30	8.21		
Superior temporal gyrus	L	-56	-40	18	8.17		

Precentral gyrus	L	-42	-18	58	8.64	0.000	406
Postcentral gyrus	L	-36	-28	44	7.89		
Inferior/middle/superior frontal gyri	R	32	38	32	8.54	0.000	312
Middle frontal gyrus	L	-28	46	18	7.75	0.000	70
StopRespond—Fixation							
Inferior/middle/superior occipital gyri	Bi	20	-74	-12	16.27	0.000	21,594
Cerebellum	Bi	24	-54	-20	16.02		
Inferior/middle temporal gyri	Bi	46	-66	4	13.99		
Thalamus	L	-14	-18	4	13.85		
Thalamus	R	14	-14	10	12.47		
ACC	Bi	0	26	28	12.80	0.000	3,063
Middle cingulate cortex	Bi	8	14	38	12.00		
Pre-SMA	Bi	12	10	42	10.87		
SMA	Bi	8	-4	70	10.73		
Supramarginal gyrus	L	-50	-26	20	9.75	0.000	2.267
Inferior/superior parietal lobule	L	-52	-28	42	9.49		
Superior temporal gyrus	L	-60	-38	26	9.16		
Intraparietal sulcus	L	-40	-40	42	8.07		
IFG (pars opercularis)/insula lobe	R	50	10	2	12.65	0.000	1,611
Insula lobe/IFG	L	-32	14	4	12.28	0.000	1,503
Supramarginal gyrus	R	58	-40	30	11.84	0.000	1,106
Intraparietal sulcus	R	62	-26	24	11.84		
Superior temporal gyrus	R	64	-38	24	9.29		
Precentral gyrus	R	52	0	44	7.68	0.000	63
Middle frontal gyrus	L	-30	44	24	7.74	0.000	42
Middle frontal gyrus	R	30	48	18	7.72	0.000	21

StopInhibit—Go							
Inferior/middle/superior temporal gyri	R	60	-48	12	11.13	0.000	7,303
inferior/middle/superior occipital gyri	R	44	-74	0	9.82		
inferior/superior parietal lobule	R	34	-46	40	8.78		
Supramarginal gyrus	R	52	-40	42	7.25		
inferior/middle/superior occipital gyri	L	-48	-70	-2	10.89	0.000	4,257
Inferior/middle/superior temporal gyri	L	-54	-62	6	10.12		
Inferior parietal lobule	L	-54	-50	46	7.72		
Supramarginal gyrus	L	-62	-44	30	7.69		
Insula lobe	R	36	18	-2	10.85	0.000	2.557
IFG (pars opercularis)	R	54	12	20	7.84		
Precentral gyrus	R	42	2	40	7.66		
Inferior/middle frontal gyrus	R	44	2	52	6.73		
Insula lobe	L	-34	18	-6	9.57	0.000	754
Middle/superior frontal gyrus	R	24	48	26	6.68	0.000	88
Superior medial gyrus/ACC	L	-4	36	32	5.97	0.000	50
Pre-SMA	R	12	16	58	6.05	0.004	11
Thalamus	R	18	-32	2	6.16	0.004	11
StopInhibit—StopRespond							
Paracentral lobule	Bi	10	-26	66	6.96	0.000	294
SMA	R	6	-26	58	6.16		
StopRespond—StopInhibit							
Cerebellum	Bi	10	-52	-16	6.48	0.000	70
Rolandic operculum	L	-50	6	2	6.14	0.000	66

Insula lobe	L	-46	4	4	5.97		
Brainstem	Bi	0	-20	-16	6.34	0.000	49
Thalamus	L	-14	-18	4	5.89	0.000	30
ACC	L	-6	20	30	5.92	0.002	18

Note. Whole-brain corrected significant clusters of activation for contrasts of interest (thresholded at least at Family-wise corrected, $p < .05$, 10 voxel extent): Go—Fixation, StopInhibit—Fixation, StopRespond—Fixation, StopInhibit—Go, StopInhibit—StopRespond, and StopRespond—StopInhibit. Subclusters of each large cluster are shown for greater precision. x, y, and z coordinates are shown in MNI space. MNI, Montreal Neurological Institute; *P*corr, corrected cluster-level p-value; R, right; L, left; SMA, supplementary motor area; ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; N =46.

Table 9. Neural activation in regions of interest during inhibition

Region	Side	MNI coordinates			*t*	*P*corr	voxels
		x	y	z			
IFG (pars orbitalis)	R	36	22	-8	9.37	0.000	2,402
IFG (pars opercularis)	R	46	16	0	9.04		
IFG (pars orbitalis)	R	40	28	-2	7.89		
STN	R	6	-20	-4	4.41	0.008	129
Pre-SMA	R	12	16	58	6.05	0.001	550
Globus pallidus	R	14	6	2	4.06	0.025	21

Note. Region of interest analyses for StopInhibit—Go contrast, thresholded at $p < 0.01$ uncorrected voxel level and activation was considered significant if it survived a $p < 0.05$ small-volume correction. Subclusters of larger cluster are shown for greater precision. x, y, and z coordinates are shown in MNI space. MNI, Montreal Neurological Institute; *P*corr, corrected cluster-level p-value; IFG, inferior frontal gyrus; STN, subthalamic nucleus; SMA, supplementary motor area; R, right; N =46.

Table 10. Correlations between mean signal in regions of interest during inhibition

	STN	pre-SMA	GP
IFG (pars opercularis)	.539***	.769***	.422**
STN		.718***	.422**
Pre-SMA			.546***

Note. All data are from the right-hemisphere and the StopInhibit—Go contrast. IFG, inferior frontal gyrus; STN, subthalamic nucleus; SMA, supplementary motor area; GP, globus pallidus; N = 46.
* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

Table 11. Influence of DAT and COMT genotypes on neural activation in regions of interest during inhibition

Region		Side	MNI coordinates			*t*	*P*corr	voxels
			x	y	z			
Genotype	Contrast							
DAT	StopInhibit—Go							
IFG (pars triangularis)		R	42	36	26	3.55	0.272	83
IFG (pars opercularis)		R	52	12	34	3.19		
IFG (pars triangularis)		R	38	30	10	3.15		
STN		R	10	-12	-6	3.03	0.031	44
SMA		R	6	-18	72	4.50	0.006	360
Pre-SMA		R	12	4	48	3.36	0.084	116
Globus pallidus		R	20	-6	8	2.43	0.311	2
COMT	StopInhibit—Go							
IFG (pars orbitalis)		R	40	28	-2	4.33	0.001	669
IFG (pars triangularis)		R	46	40	8	3.07		
Pre-SMA		R	14	12	60	3.54	0.155	72
DAT	Go—Fixation							
Globus pallidus		L	-24	-8	-2	2.85	0.243	7
COMT	Go—Fixation							

IFG (pars opercularis)		R	48	10	0	5.16	0.000	952
STN		R	14	-20	-10	4.93	0.007	163
SMA		R	6	-2	62	5.44	0.000	1,301
Globus pallidus		R	26	-18	-4	6.70	0.008	296
Globus pallidus		L	-22	-4	-4	5.90	0.008	306
DAT	StopInhibit—Fixation							
IFG (pars opercularis)		R	32	16	30	2.75	0.766	7
STN		R	8	-10	0	2.43	0.091	1
Pre-SMA		R	16	4	62	2.46	0.569	1
Globus pallidus		L	-24	-8	-2	2.42	0.305	2
COMT	StopInhibit—Fixation							
IFG (pars opercularis)		R	38	8	14	6.17	0.000	1,806
STN		R	14	-20	-2	5.21	0.005	174
Pre-SMA		R	4	8	46	6.20	0.000	1,298
Globus pallidus		L	-12	0	2	5.28	0.006	288

Note. Region of interest analyses thresholded at $p < 0.01$ uncorrected voxel level and activation was considered significant if it survived a $p < 0.05$ small-volume correction. Subclusters of larger cluster are shown for greater precision. x, y, and z coordinates are shown in MNI space. MNI, Montreal Neurological Institute; *P*corr, corrected cluster-level p-value; IFG, inferior frontal gyrus; STN, subthalamic nucleus; SMA, supplementary motor area; R, right; L, left; N =45.

Table 12. Genotype group differences in neural activation during inhibition

Genotype	Contrast	Group (N)		
	Region	Mean %Signal (SEM)		
DAT	StopInhibit—Go	10/10 (28)		9+ (17)
	R IFG (pars triangularis)	1.03 (0.34)		2.01 (0.41)
	R STN	0.45 (0.29)		1.51 (0.46)
	R pre-SMA	0.52 (0.34)		1.82 (0.52)
	R GP	-0.30 (0.25)		0.80 (0.42)
COMT	Go—Fixation	v/v (12)	v/m (27)	m/m (6)
	R IFG (pars opercularis)	-0.15 (-.92)	1.56 (0.39)	2.41 (1.16)
	R SMA	1.16 (0.88)	3.37 (0.39)	3.27 (0.48)
COMT	StopInhibit—Fixation	v/v (12)	v/m (27)	m/m (6)
	R IFG (pars opercularis)	0.63 (1.03)	4.60 (0.65)	5.64 (2.42)

Note. Region of interest analyses thresholded at $p < 0.01$ uncorrected voxel level and mean percent signal extracted. R, right; STN, subthalamic nucleus; SMA, supplementary motor area; GP, globus pallidus; IFG, inferior frontal gyrus N =45.

Table 13. Mean signal during inhibition according to DAT + COMT genotype groups

Region	10/10-v/v	10/10-v/m; 9+-v/v	10/10-m/m;9+-v/m	9+-m/m	ANOVA *F*, *p*
R IFG (pars opercularis)	0.28 (1.03)	3.14 (0.95)	4.70 (1.24)	8.22 (0.80)	2.85, 0.049
R Pre-SMA	1.28 (1.36)	4.31 (0.90)	5.90 (1.48)	9.43 (0.93)	2.54, 0.070
R GP	-0.16 (0.99)	0.87 (0.33)	1.77 (0.57)	3.70 (0.29)	2.83, 0.050

Note. Mean (+/- SEM) of percent signal change from StopInhibit—Fixation contrast are shown for each DAT + COMT additive genotype group. F- and p-values are shown from one-way ANOVAs for significant or marginally significant effects. IFG, inferior frontal gyrus; SMA, supplementary motor areas; GP, globus pallidus; N = 45.

Figure 1. An intermediate phenotype approach applied to impulsivity. ADHD, Attention-Deficit/Hyperactivity Disorder; BPD, Borderline Personality Disorder; ASPD, Antisocial Personality Disorder; SA/SD, substance abuse and dependence; Neurobio, neurobiological; STN, subthalamic nucleus; DRD4, dopamine D4 receptor; DAT, dopamine transporter; COMT, catechol-O-methyltransferase; Environ, environment.

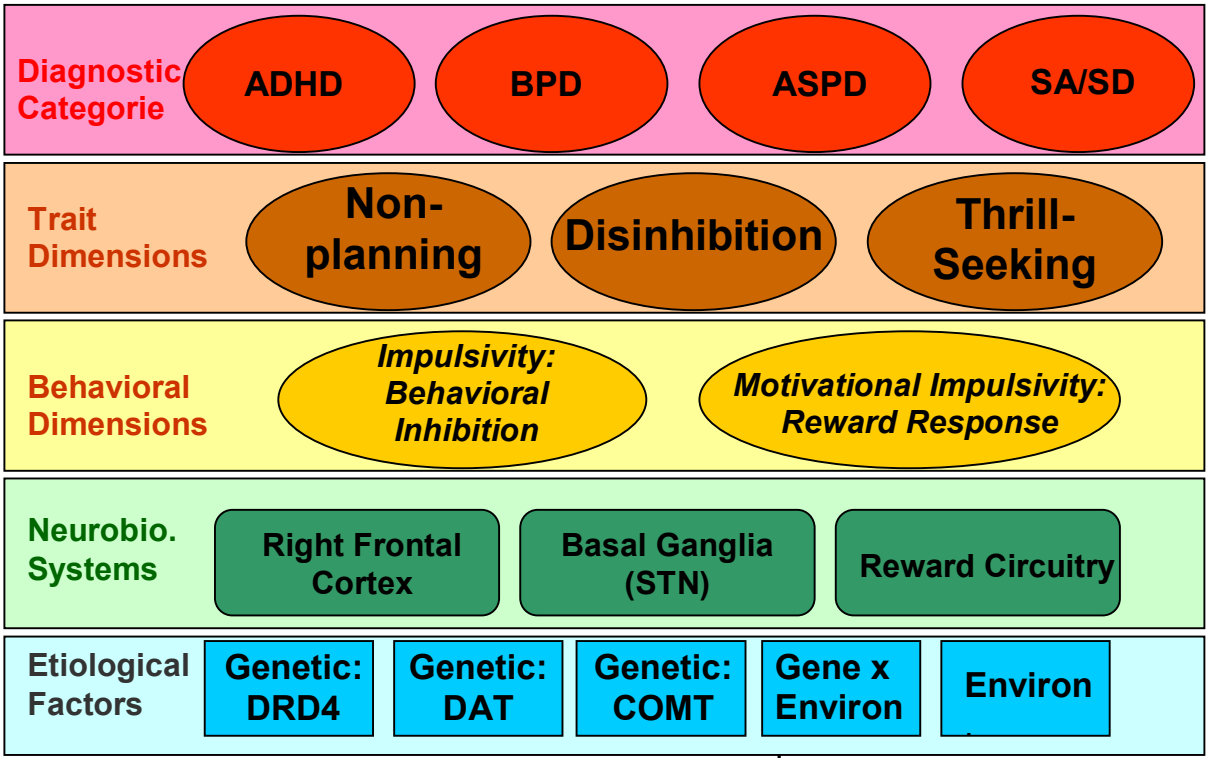

Figure 2. The tracking Stop-signal task. SSD, stop-signal delay.

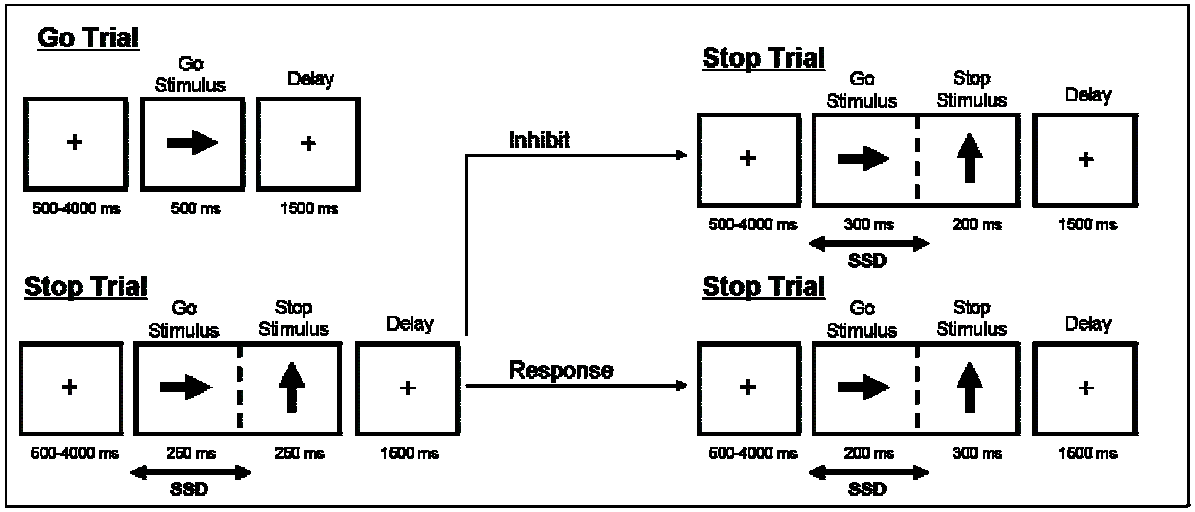

Figure 3. Pathways of the basal ganglia. The hyperdirect pathway (corticothalamic input sent to STN results in direct inhibition of pallidal output) enables rapid termination of already initiated motor response. Red arrows = excitatory; black arrows = inhibitory. GP, globus pallidus; STN, subthalamic nucleus; DA, dopamine.

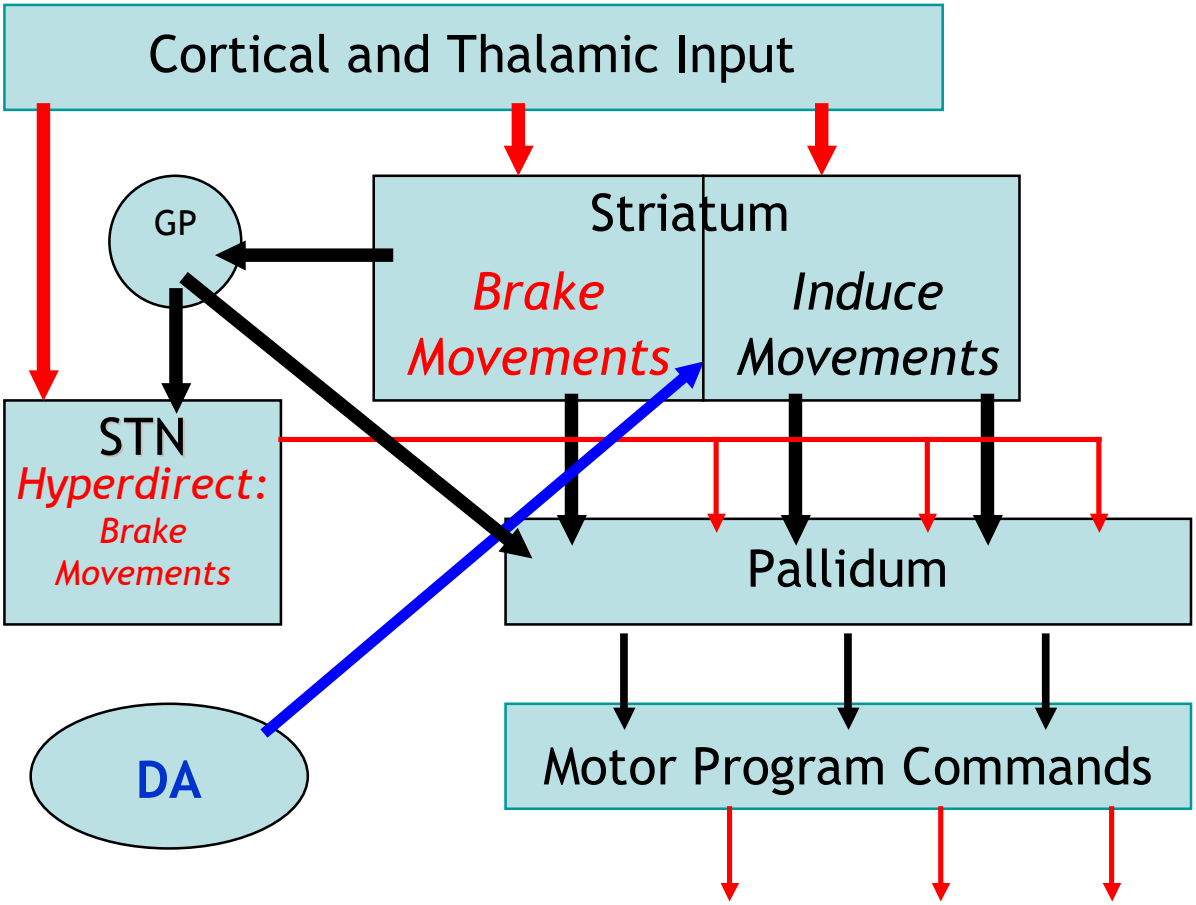

Figure 4. Percent inhibition on Stop trials as a function of DAT + COMT genotype groups.

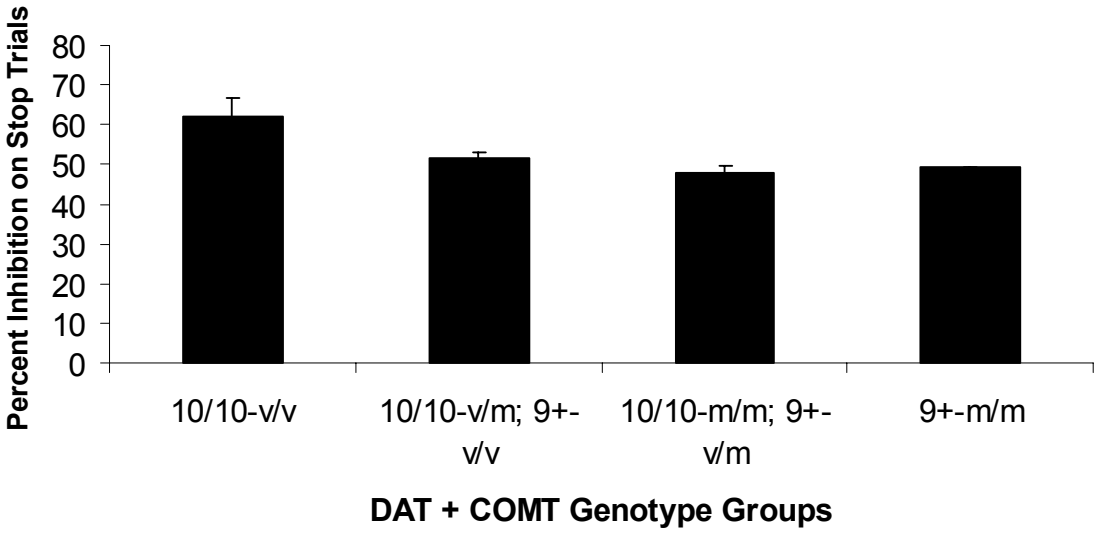

Figure 5. Activation for Going relative to Fixation. For all images, right = right, and activation are overlaid on coronal (top) and saggital (bottom) slices from the SPM2 structural template. Activation map is thresholded at $p < 0.001$, with a 10 voxel extent, corrected for family-wise error (FWE). GP, globus pallidus; SMA, supplementary motor area.

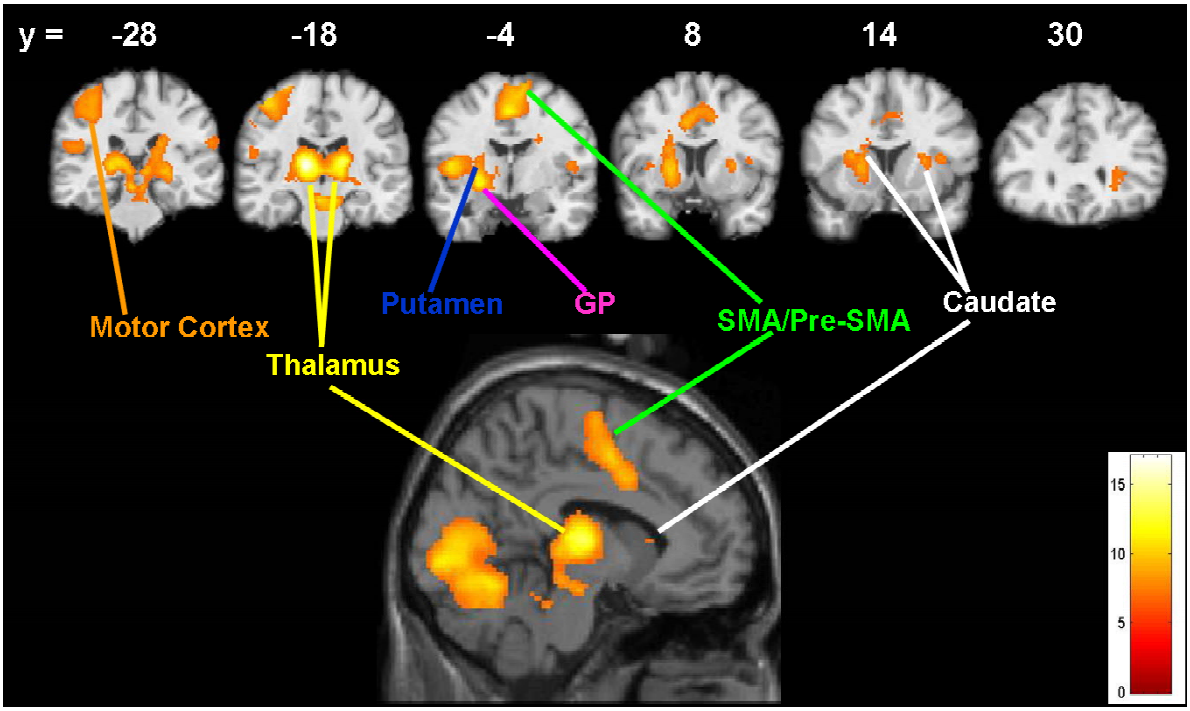

Figure 6. Activation for StopInhibit relative to Fixation. For all images, right = right, and activation are overlaid on coronal (top) and saggital (bottom) slices from the SPM2 structural template. Activation map is thresholded at $p < 0.001$, with a 10 voxel extent, corrected for family-wise error (FWE). GP, globus pallidus; SMA, supplementary motor area; IFC, inferior frontal cortex.

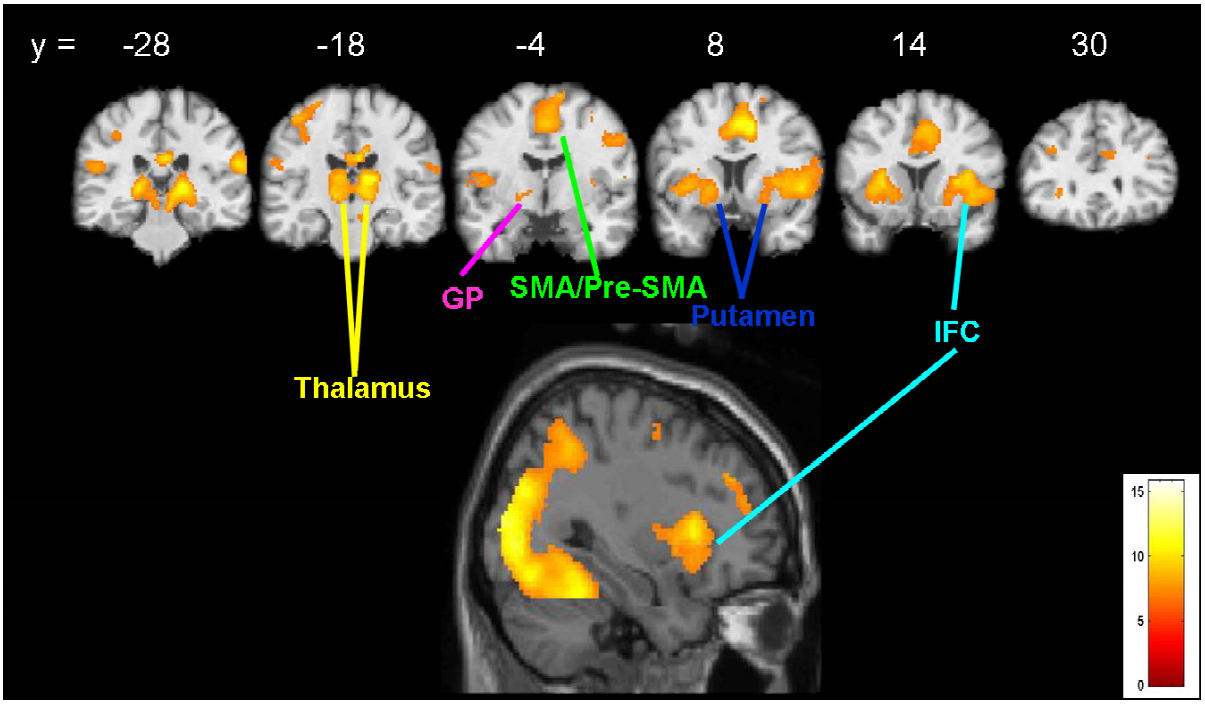

Figure 7. Activation for StopRespond relative to Fixation. For all images, right = right, and activation are overlaid on coronal (top) and saggital (bottom) slices from the SPM2 structural template. Activation map is thresholded at $p < 0.001$, with a 10 voxel extent, corrected for family-wise error (FWE). SMA, supplementary motor area; IFC, inferior frontal cortex; ACC, anterior cingulate cortex.

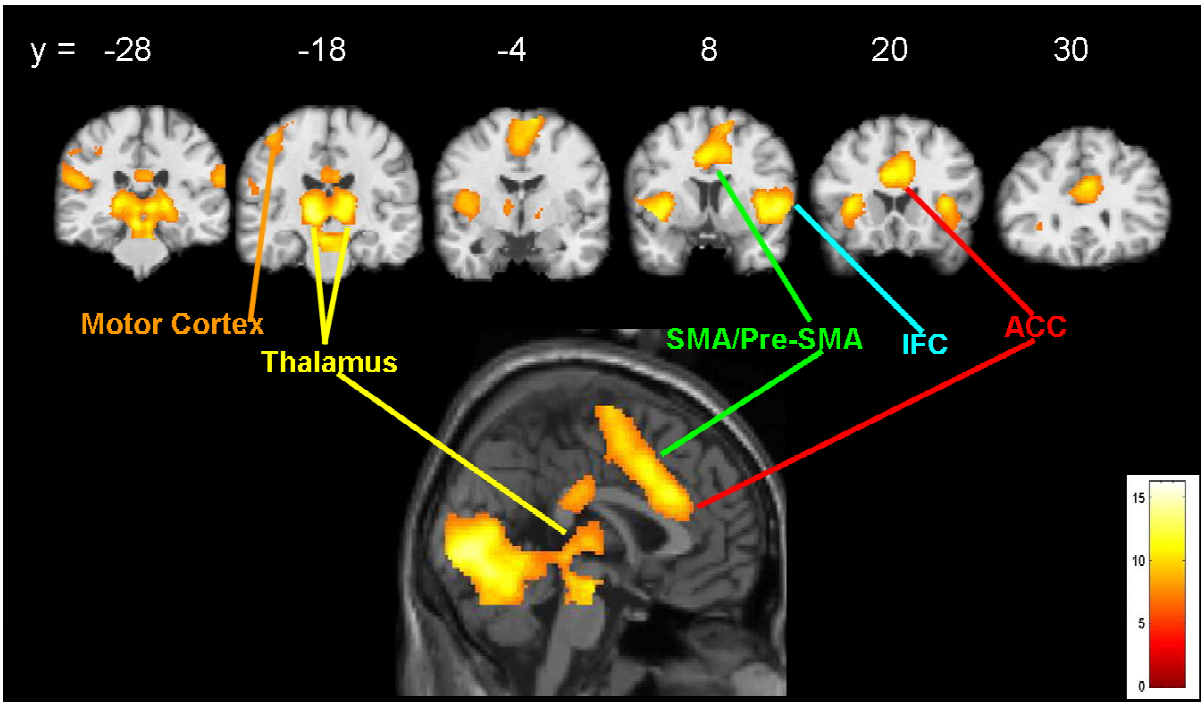

Figure 8. Activation for StopInhibit relative to Going. For all images, right = right, and activation are overlaid on coronal (top) and saggital (bottom) slices from the SPM2 structural template. Activation map is thresholded at $p < 0.05$, with a 10 voxel extent, corrected for family-wise error (FWE). SMA, supplementary motor area; IFC, inferior frontal cortex.

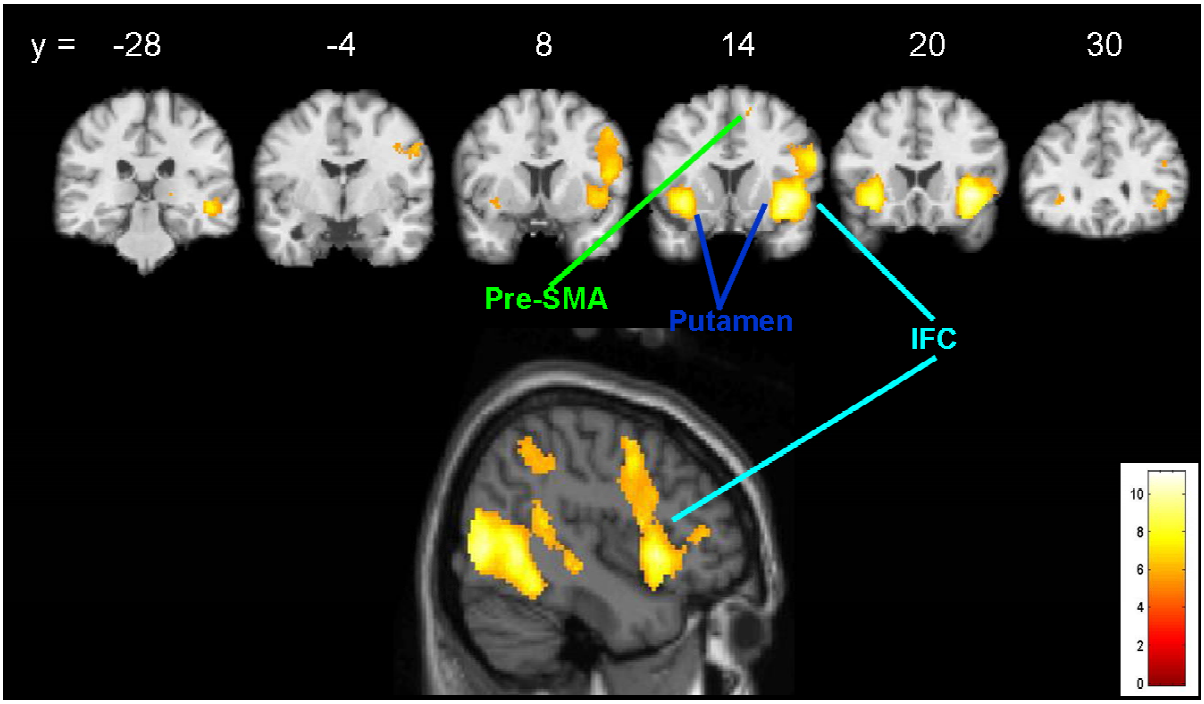

Figure 9. Correlation between mean signal in right inferior frontal gyrus (IFG) (pars opercularis) and right subthalamic nucleus (STN) during inhibition.

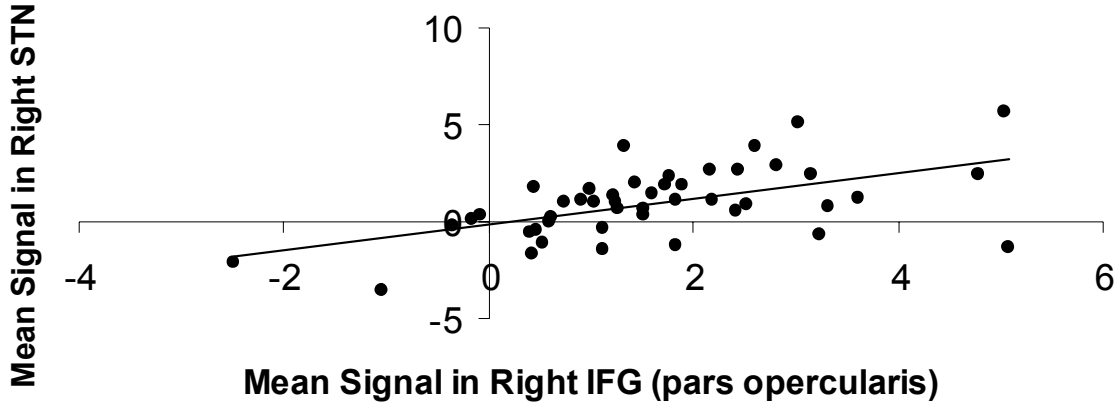

Figure 10. Correlation between mean signal in right inferior frontal gyrus (IFG) (pars opercularis) and pre-supplementary motor area (SMA) during inhibition.

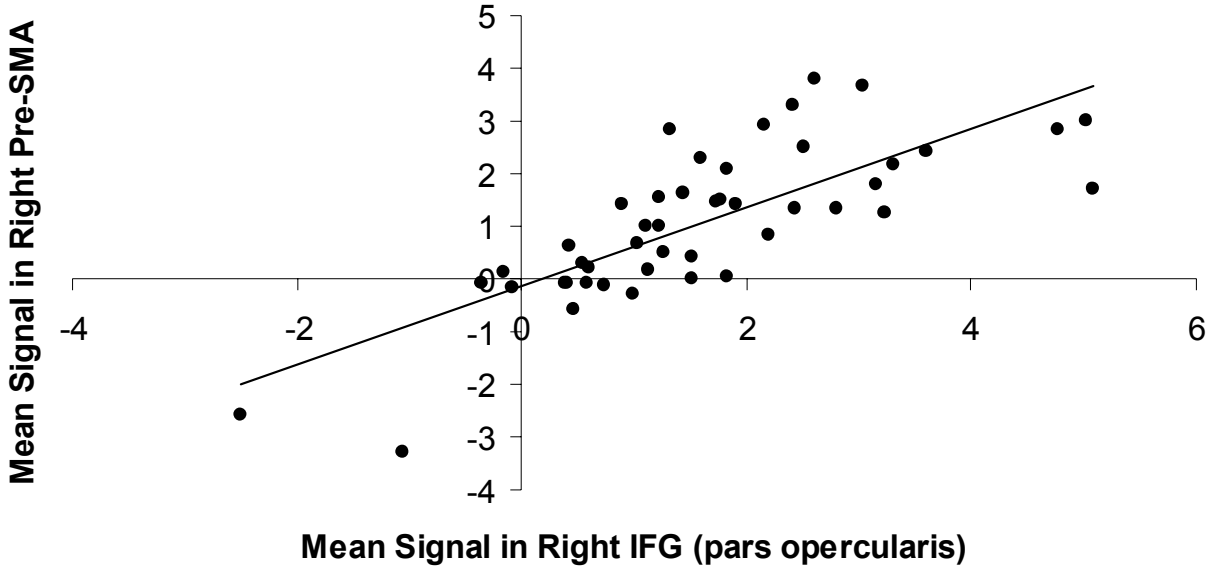

Figure 11. Correlation between mean signal in right inferior frontal gyrus (IFG) (pars opercularis) and globus pallidus (GP) during inhibition.

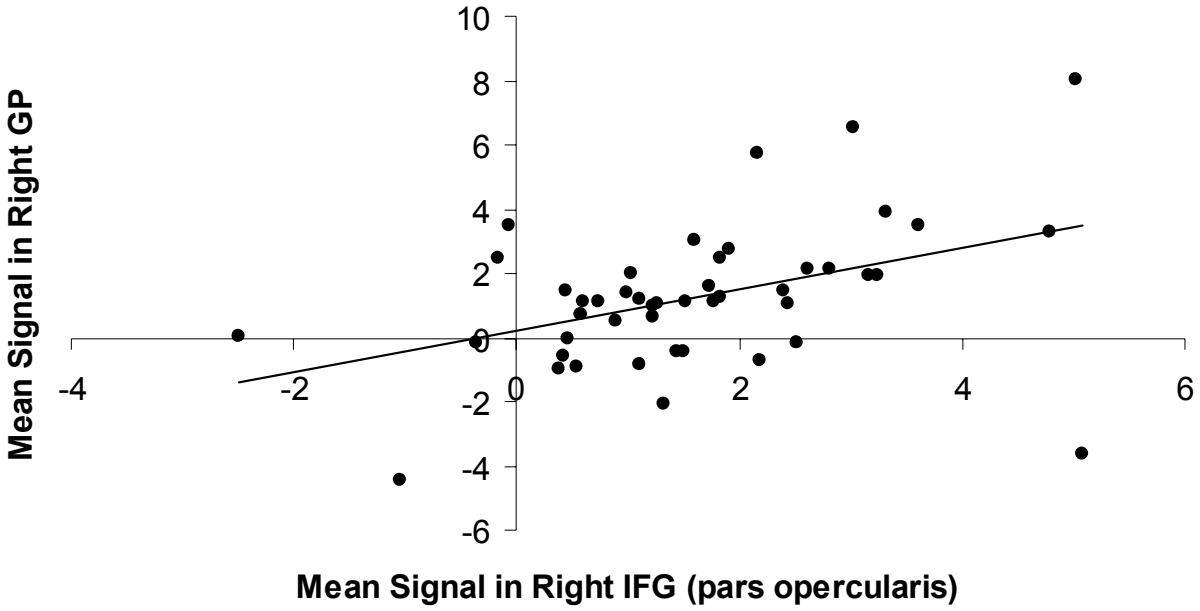

Figure 12. Correlation between Stop-signal reaction time (SSRT, ms) and mean signal in right inferior frontal gyrus (IFG) (pars triangularis) during inhibition. (a) Activation in right IFG during StopInhibit relative to Going overlaid on a coronal section (x 0, y 16, z 0). Activation map is thresholded at $p < 0.01$ uncorrected voxel level. (b) Correlation between inhibition-related activity (mean signal change) and SSRT.

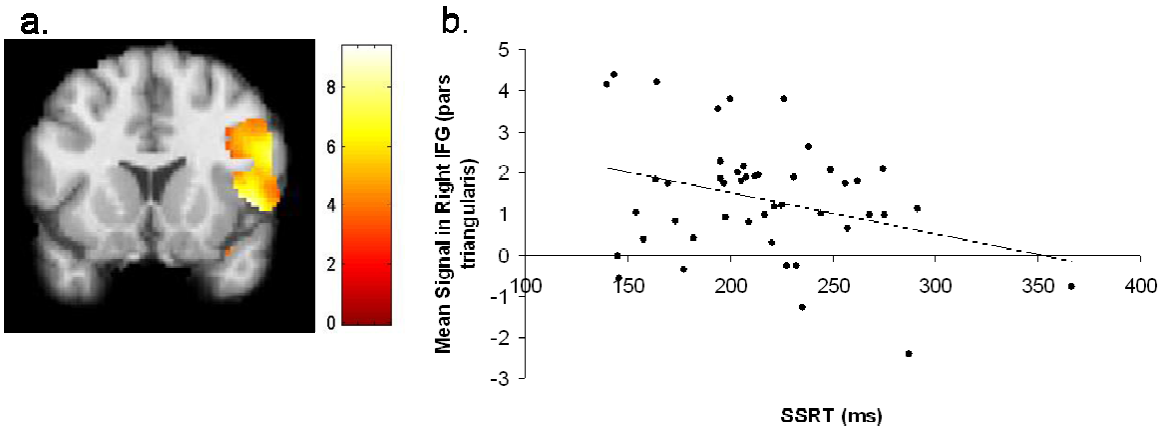

Figure 13. Mean signal in the right subthalamic nucleus (STN) on StopInhibit—Go trials as a function of DAT genotype. (a) Activation in right STN during StopInhibit relative to Going overlaid on a coronal section (x 10, y -12, z -6). Activation map is thresholded at $p < 0.01$ uncorrected voxel level. (b) Mean signal in right STN during inhibition in DAT 10/10 and 9+ groups.

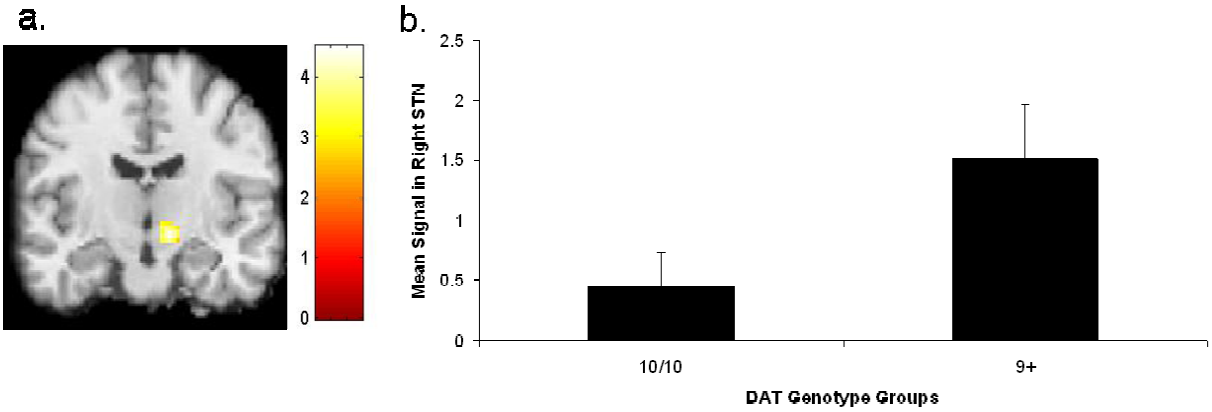

Figure 14. Mean signal in the right pre-supplementary motor area (SMA) on StopInhibit—Go trials as a function of DAT genotype. (a) Activation in right pre-SMA during StopInhibit relative to Going overlaid on a coronal section (x 6, y -18, z 72). Activation map is thresholded at $p < 0.01$ uncorrected voxel level. (b) Mean signal in right pre-SMA during inhibition in DAT 10/10 and 9+ groups.

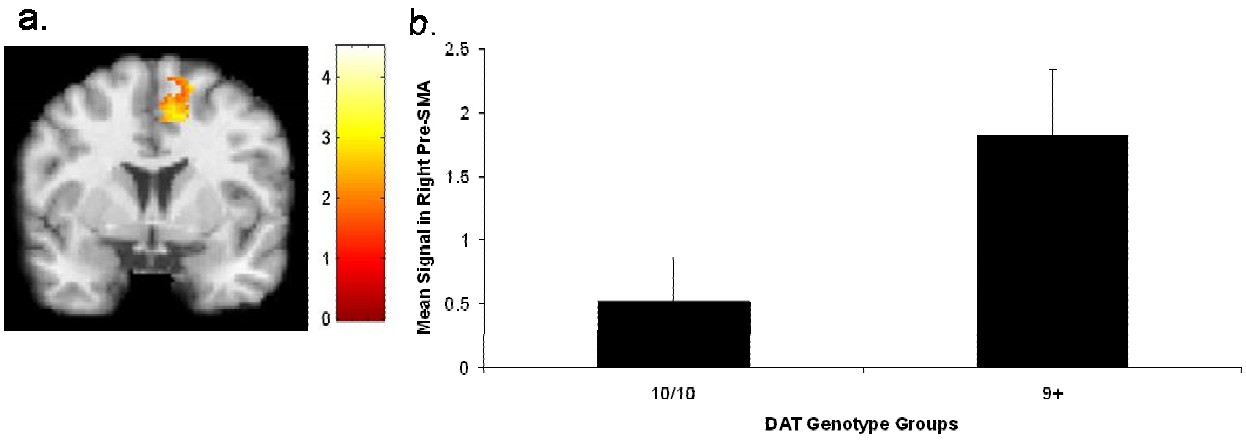

Figure 15. Mean signal in the right globus pallidus (GP) on StopInhibit—Go trials as a function of DAT genotype. (a) Activation in right GP during StopInhibit relative to Going overlaid on a coronal section (x 20, y -6, z 8). Activation map is thresholded at $p < 0.01$ uncorrected voxel level. (b) Mean signal in right GP during inhibition in DAT 10/10 and 9+ groups.

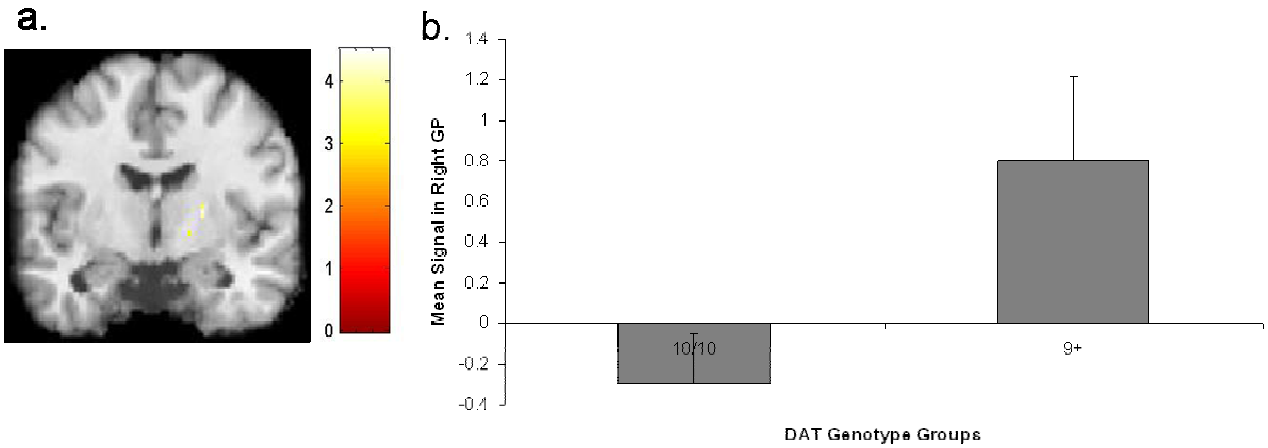

Figure 16. Mean signal in the right inferior frontal gyrus (IFG) (pars opercularis) on Go—Fixation trials as a function of COMT genotype. (a) Activation in right IFG during Go relative to Fixation trials overlaid on a coronal section (x 48, y 10, z 0). Activation map is thresholded at $p < 0.01$ uncorrected voxel level. (b) Mean signal in right IFG during inhibition in COMT val/val, val/met, and met/met groups.

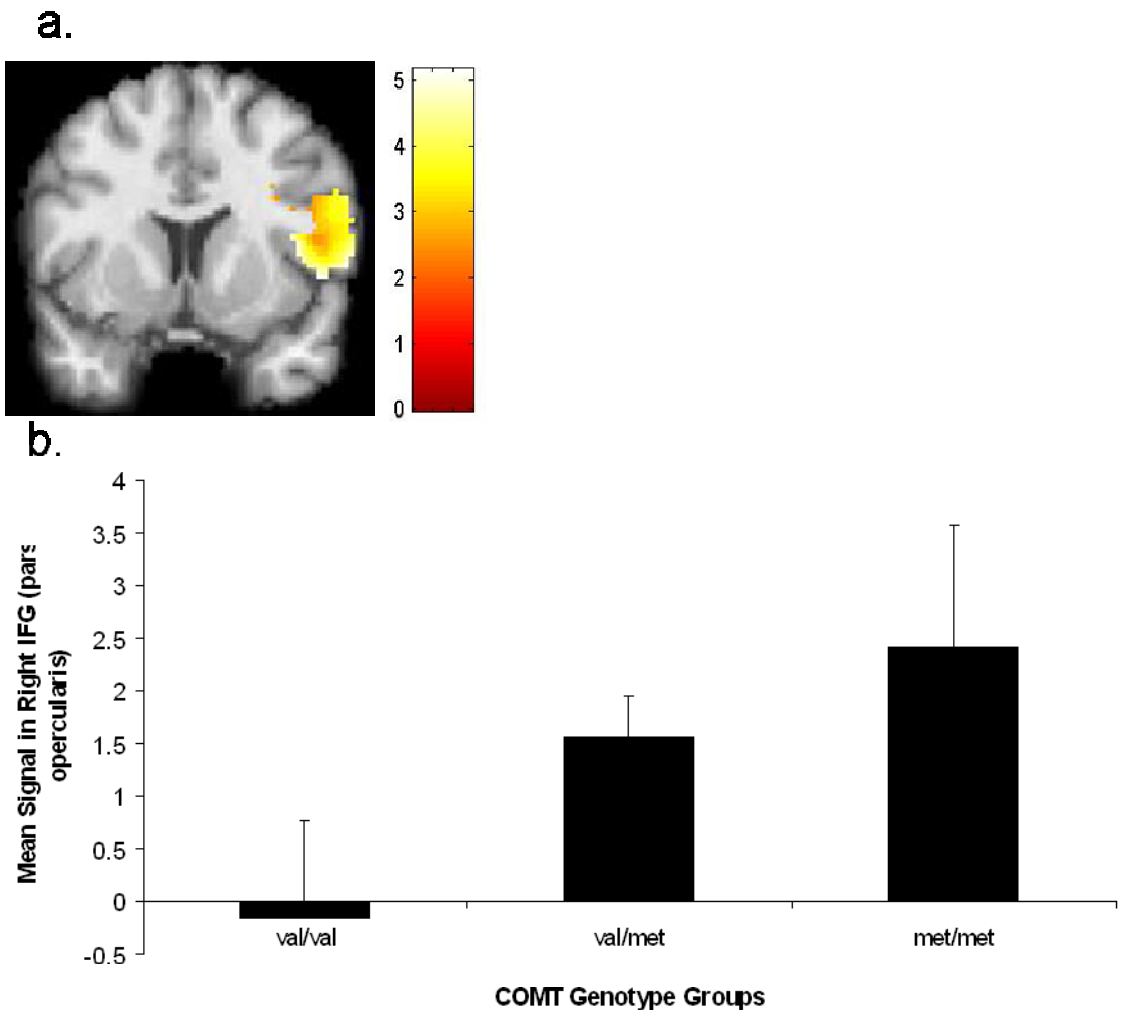

Figure 17. Mean signal in the right supplementary motor area (SMA) on Go—Fixation trials as a function of COMT genotype. (a) Activation in right SMA during Go relative to Fixation trials overlaid on a coronal section (x 6, y -2, z 62). Activation map is thresholded at $p < 0.01$ uncorrected voxel level. (b) Mean signal in right SMA during inhibition in COMT val/val, val/met, and met/met groups.

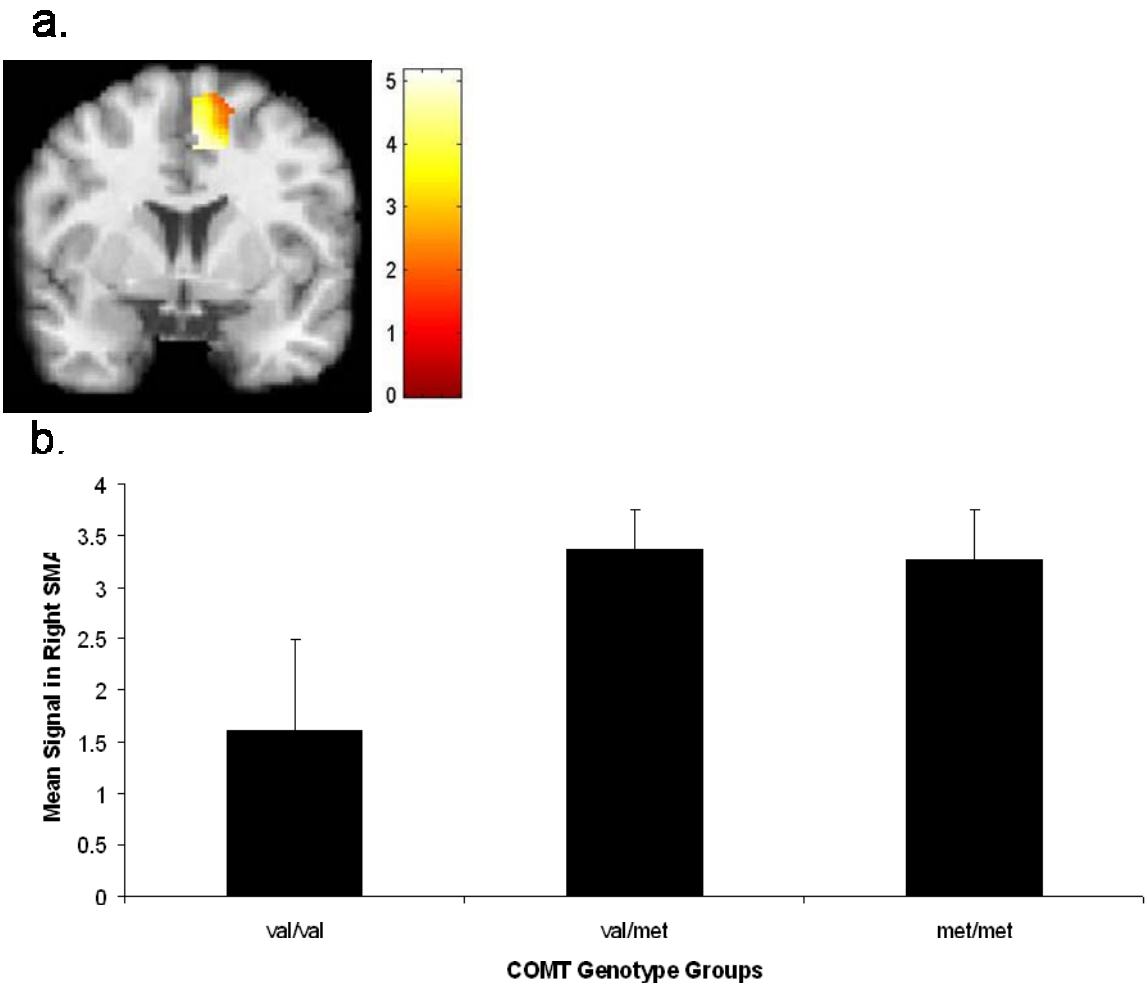

Figure 18. Mean signal in the right inferior frontal gyrus (IFG) (pars opercularis) on StopInhibit—Fixation trials as a function of COMT genotype. (a) Activation in right IFG during StopInhibit relative to Fixation overlaid on a coronal section (x 38, y 8, z 14). Activation map is thresholded at $p < 0.01$ uncorrected voxel level. (b) Mean signal in right IFG during inhibition in COMT val/val, val/met, and met/met groups.

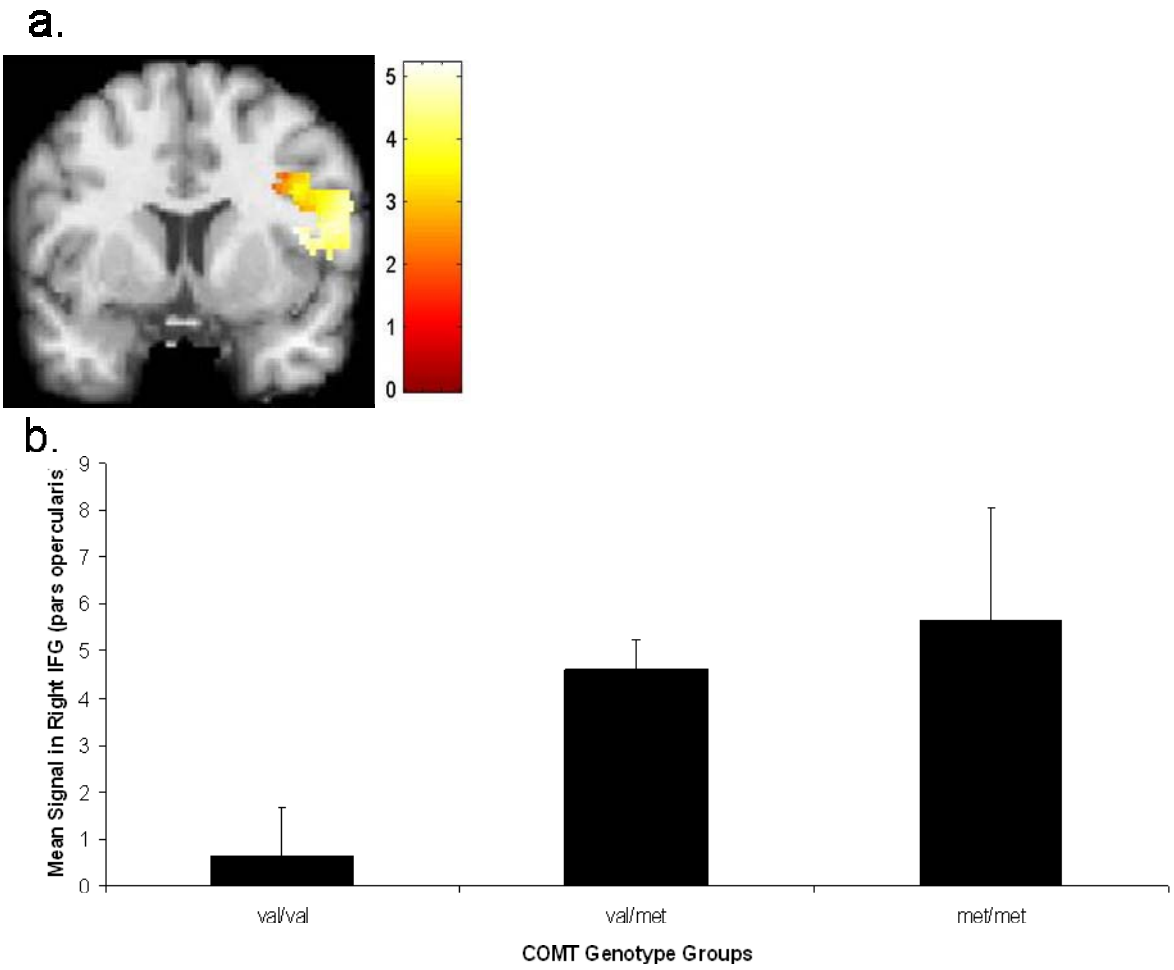

Figure 19. Mean signal in the right inferior frontal gyrus (IFG) (pars opercularis) on StopInhibit trials as a function of DAT + COMT genotype groups.

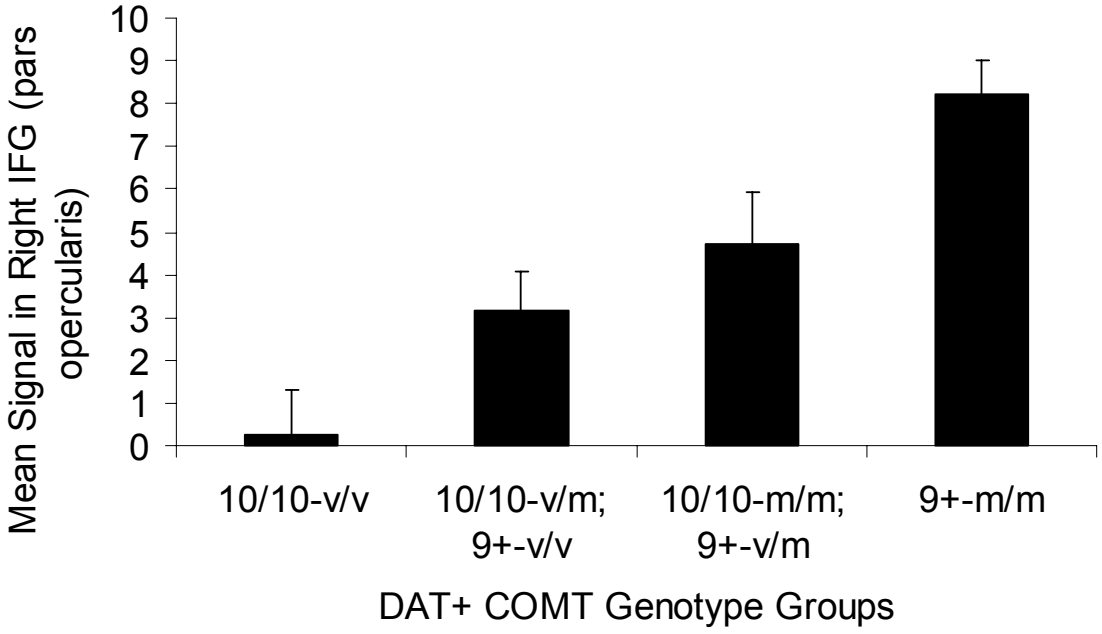

Figure 20. Mean signal in the right pre-supplementary motor area (SMA) on StopInhibit trials as a function of DAT + COMT genotype groups.

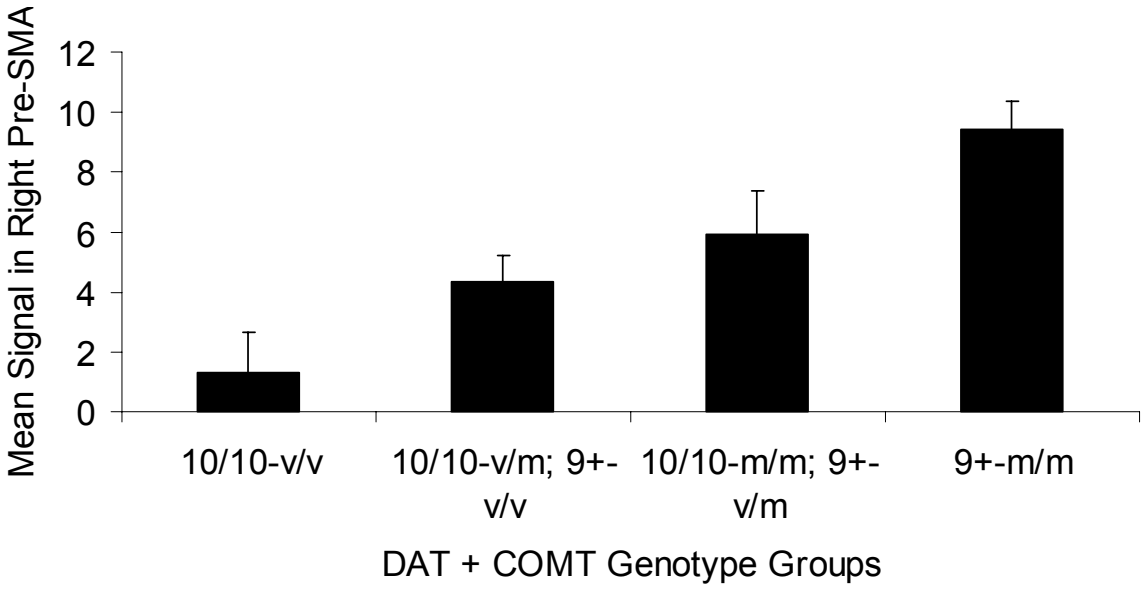

Figure 21. Mean signal in the right globus pallidus (GP) on StopInhibit trials as a function of DAT+ COMT genotype groups.

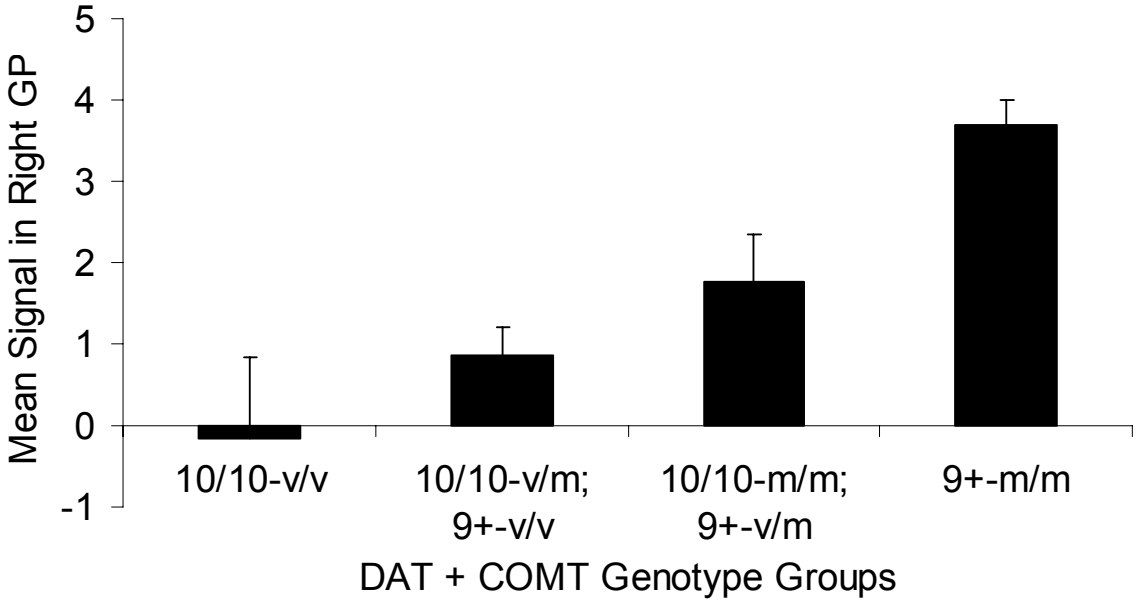

Figure 22. Individual differences in attentional performance in rats predicts the neuromodulatory effects of dopamine on performance. Low Perf, rats with low baseline levels of performance; High Perf, rats with high baseline levels of performance. From Granon et al., 2000.

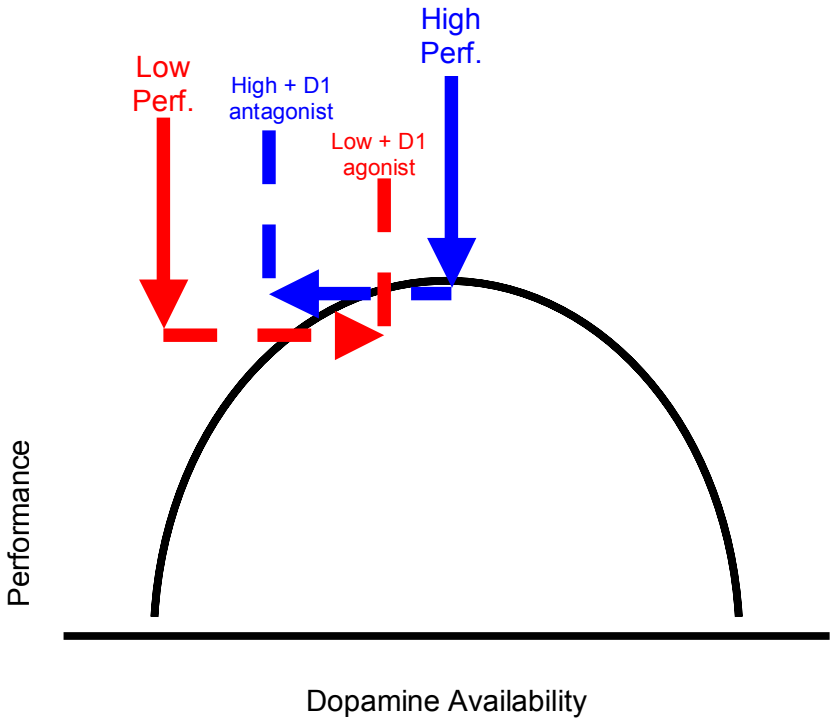

Figure 23. Individual differences in self-reported impulsivity predict the neuromodulatory effects of dopamine on performance and neural activation. High Imp, individuals with high impulsivity; Low Imp, individuals with low impulsivity. Based on data from Cools et al., 2007.

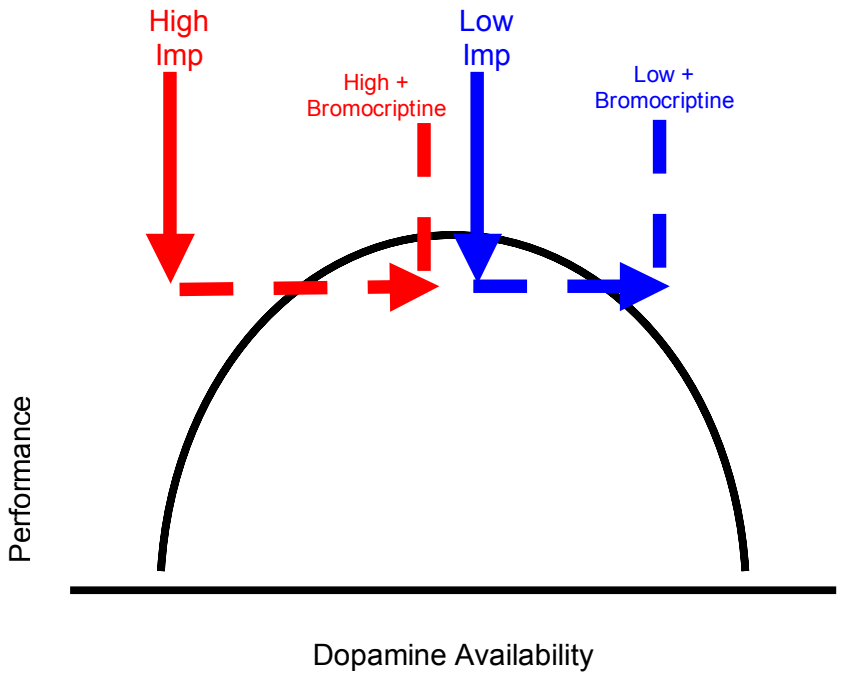

Figure 24. Individual differences in dopamine availability, as predicted by COMT genotype, influence performance and response to dopaminergic manipulation. 2-back and 3-back, versions of the N-back task; Amph, amphetamine. Based on data from Mattay et al., 2003.

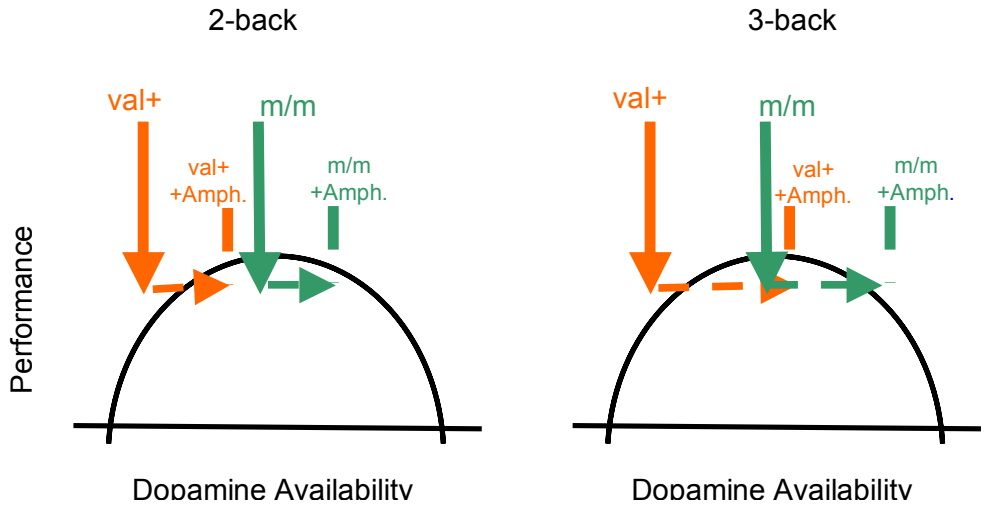

Figure 25. Individual differences in dopamine availability, as predicted by COMT genotype and age, influence performance. Based on data from Whalstrom et al., 2007.

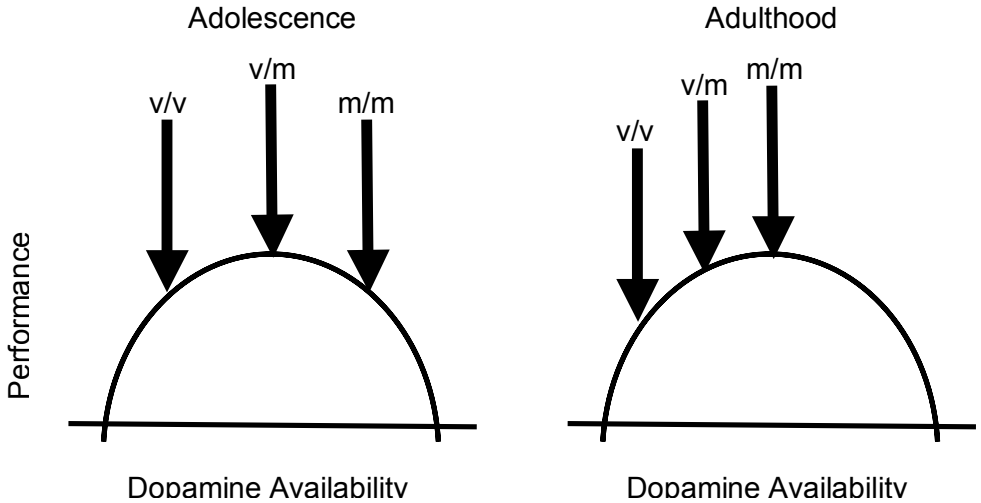

Figure 26. Individual differences in dopamine availability, as predicted by DAT and COMT genotypes, influence performance and neural activation.

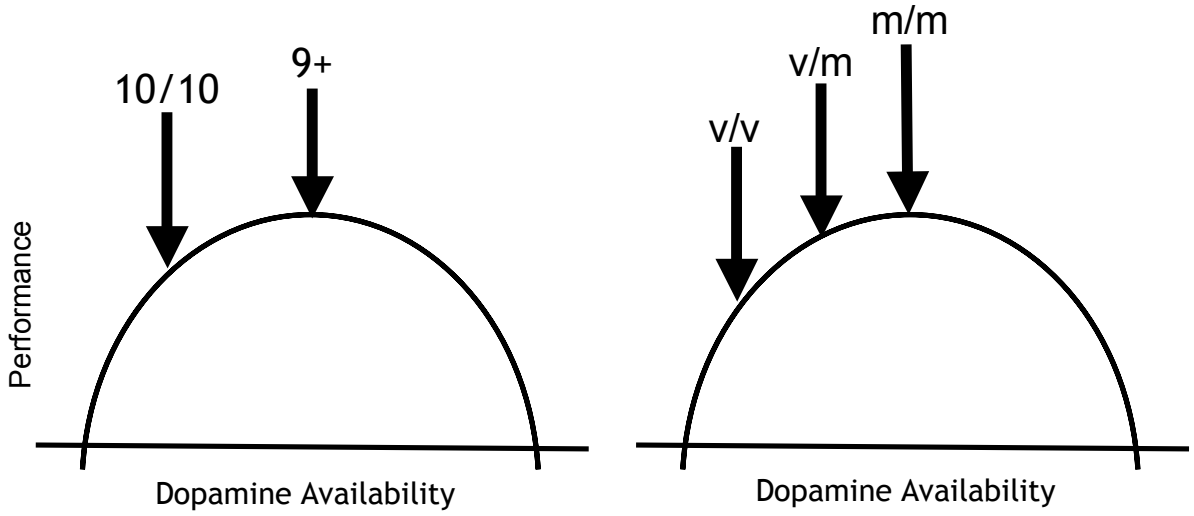

Figure 27. Individual differences in dopamine availability, as predicted by DAT + COMT, influence performance and neural activation.

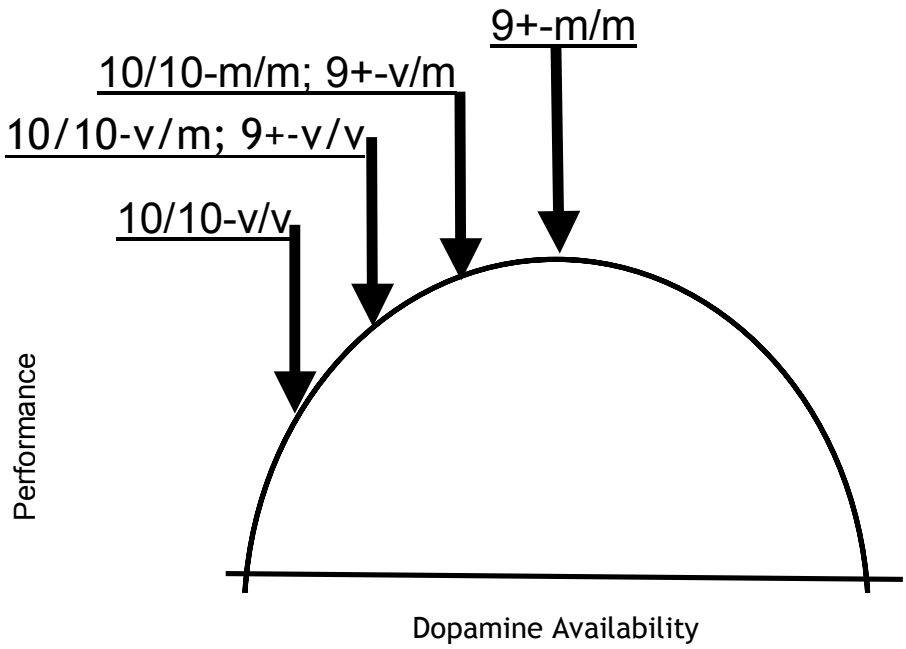

Figure 28. Correlation between Stop-signal reaction time (SSRT, ms) and BIS-11 total scores in final sample of usable participants.

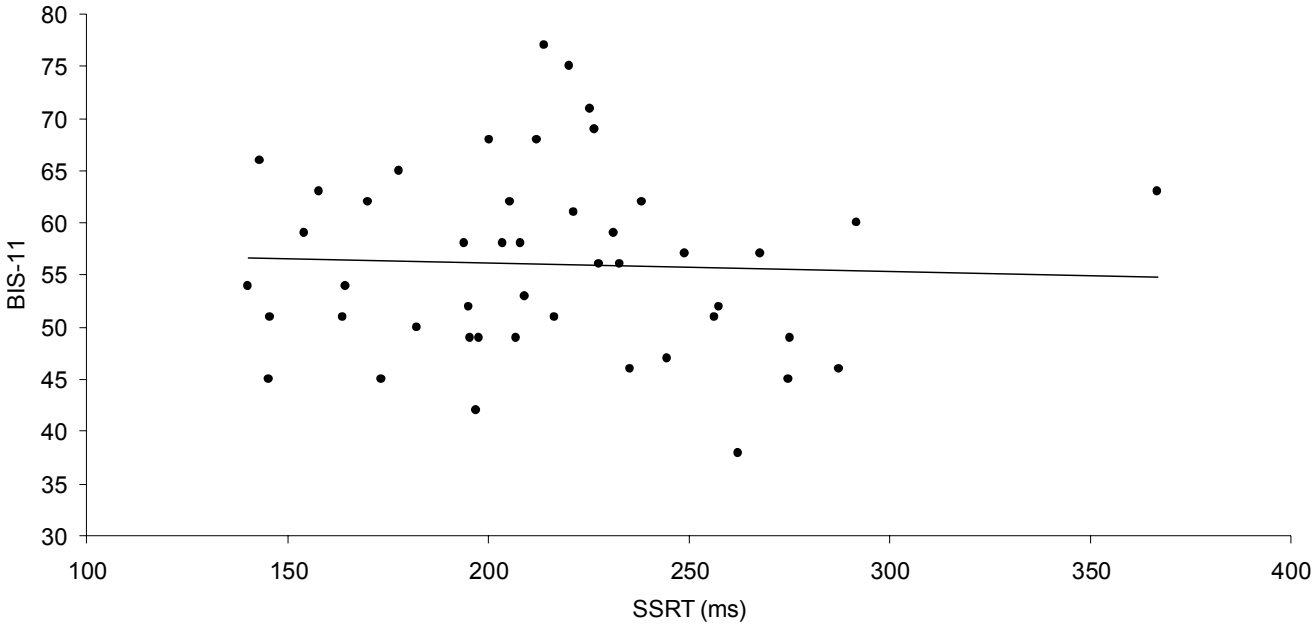

Figure 29. Correlation between Stop-signal reaction time (SSRT, ms) and BIS-11 total scores in total sample of scanned participants.