Go/No-Go Performance is Related to White Matter Microstructure in a Broad Range of Regions

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CHAPTER 1

INTRODUCTION

Go/No-Go Paradigms

Cognitive control is the ability to initiate appropriate responses as well as to stop or prevent prepotent responses that are currently inconsistent with task demands or goals. This construct is composed of a number of component skills. Response selection is one of these skills and refers to the ability to appropriately select between a series of motor responses. A related skill is response inhibition, which is the ability to inhibit a prepotent motor response. Go/no-go paradigms are among the most frequently used tasks to measure these constructs. In a simple variation of this task, individuals are presented with visual stimuli, and must make a response when certain stimuli are presented and withhold their response when other stimuli are presented. In a common challenging variation of this task, a series of visual stimuli are presented, and individuals must make a button press if the current stimulus is different from the preceding one (go trial), and withhold their response if the stimulus is the same (no-go trial) (Garavan, Ross, & Stein, 1999). This task is challenging because the same stimulus can represent a go or no-go trial depending upon the previous trial, and thus the proper response contingency has to be updated and referenced in working memory on a trial-by-trial basis. Successful completion of this task requires being able to balance both response selection and response inhibition, and the difficulty is magnified when the need to respond quickly is emphasized.

In the go/no-go task, false alarm rate (frequency of responding to no-go trials) is generally conceptualized as a measure of response inhibition. Accuracy on go trials (hit rate) captures the ability to perform the multiple processes necessary for response selection. Though successful performance on both the simple and complex version of the go/no-go task requires both response selection and inhibition, the complex version has a higher load on additional skills. In order to make a correct response one has to engage in a number of tasks including perception and discrimination of the target, comparing the target to

the representation in working memory, and motor initiation. Further, one must rapidly coordinate all of these processes. In many variations of this task each stimulus is presented for only a brief period of time, and therefore the ability to rapidly and efficiently process incoming information in order to make a timely response is critical. Quick processing speed also allows one to rapidly process incoming information in order to make an appropriate response. When examining metrics from the go/no-go task one must be cognizant of the multiple processes that are engaged. A given metric is unlikely to be a pure measure of a single construct, but rather is likely multi-determined.

Given that successful task performance isn't confined solely to response selection and inhibition, but rather how one balances these two processes a more comprehensive measure has been developed. D-prime uses accuracy on go trials and no-go trials to measure the ability to distinguish between target (go) and non-target (no-go) stimuli across trials (Wickens, 2002). As such, d-prime indexes the ability to monitor performance in order to adaptively balance demands to detect and rapidly respond to appropriate stimuli (sensitivity) with the need to inhibit responses to nontargets. It therefore represents the most comprehensive measure of overall task performance. Hit rate, false alarm rate, and d-prime are the most commonly used measures to index performance on go/no-go tasks. However using hit rate, false alarm rate, and d-prime doesn't isolate all of the component processes engaged during these tasks.

Though the go/no-go task is a commonly used measure, it is not the only one that has been used to investigate response selection and inhibition. Another commonly used paradigm is the Stop Signal Task (SST) (Logan, 1994). In this task an individual must make a motor response to a visual stimulus unless another stimulus (known as the stop signal) appears, in which case they must stop their response. There has been some debate as to whether the SST and go/no-go tasks are capturing identical processes. The SST task measures action cancelation, whereas the go/no-go task is measuring action restraint (Eagle, Bari, & Robbins, 2008). Though these are similar processes, there are subtle differences that must be considered when conceptualizing what the tasks are measuring, and studies have suggested that they are engaging slightly different neural processes (Swick, Ashley, & Turken, 2011). Further, an important assumption of the SST is that individuals aren't slowing their go response in order to account for the stop

trials. By contrast, the d-prime metric from the go/no-go task is explicitly measuring how individuals adapt their response on go trials to accommodate the no-go trials. When looking at the findings within the literature it is important to consider that both these tasks are used to measure response inhibition, and are often discussed interchangeably. Though disentangling the differential effects of these two paradigms is not an aim of the current study, understanding these task differences may help explain some of the inconsistencies that exist in the literature.

Psychopathology and Go/No-Go Performance

Go/no-go paradigms have often been used to investigate the etiology of psychopathology. Recently there has been a focus on constructs that cut across different forms of psychopathology (Insel et al., 2010). Studies have examined the response selection and inhibition aspects of the go/no-go task as cross-cutting constructs. Such studies have found that deficits in these skills exist in individuals with impulsive behavior. Given that externalizing disorders are typified by impulsive behavior, a number of studies have focused on examining these skills in specific externalizing disorders. Response inhibition deficits exist in Attention-Deficit Hyperactivity Disorder (ADHD), and these deficits are related to inattentive symptoms (Casey et al., 2007; Nigg & Casey, 2005). Further, studies have shown that siblings of individuals with ADHD demonstrate similar deficits, suggesting that this may represent an endophenotype for ADHD (Slaats-Willemse, Swaab-Barneveld, De Sonneville, Van Der Meulen, & Buitelaar, 2003).

Studies have also shown that individuals with substance misuse disorders exhibit deficits in response inhibition (Monterosso, Aron, Cordova, Xu, & London, 2005; Young et al., 2009). Additionally, impairments exist in antisocial personality disorder and have been shown to correlate with severity of illness (Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009). Thus, these deficits aren't restricted to a single externalizing disorder, but rather are found across a wide range of psychopathology involving impulsive behavior.

Given the relationship of response inhibition to impulsive behavior, it is important to examine whether this applies to impulsive behavior within healthy populations. One such study found that higher degrees of self-reported impulsive behaviors are associated with greater difficulties in response inhibition (Aichert et al., 2012). In sum, studies have found deficits in response selection and inhibition across individuals with a wide range of impulsive behavior.

Fewer studies have focused on other aspects of go/no-go task performance and how these skills might be related to psychopathology. There is some research to suggest that processing speed may also be related to impulsive behavior. For one, individuals with ADHD have been shown to have slower processing speed (Chhabildas, Pennington, & Willcutt, 2001; Nigg, 2001). Further, processing speed is believed to be impacted in individuals with a history of substance abuse (Thoma et al., 2011). Though these studies weren't explicitly looking at processing speed within the context of the go/no-go task, they do suggest that processing speed may be playing a role in the previously observed relationship between go/no-go task performance and psychopathology. It may be the case that poor performance on these tasks in impulsive individuals is due to deficits in response selection and inhibition as well as in processing speed.

Neural Underpinnings of the Go/No-Go Task

In order to better understand the sources of individual differences in performance on the go/no-go task, it is important to examine the neural underpinnings. Functional neuroimaging studies have generally focused on the response inhibition components of the task and have identified a number of regions that are involved in successful task performance (Chambers, Garavan, & Bellgrove, 2009). The Inferior Frontal Gyrus (IFG) appears to play a critical role. This has been confirmed by a variety of neuroimaging studies as well as by a meta-analysis of fMRI studies using go/no-go tasks (Aron & Poldrack, 2006; Hughes, Fulham, Johnston, & Michie, 2012; Roberts et al., 2013; Simmonds, Pekar, & Mostofsky, 2008; Swick, Ashley, & Turken, 2008; Swick et al., 2011). The role of this region is further supported by lesion studies demonstrating that damage to the IFG is associated with impaired performance on response

selection and inhibition tasks (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Swick et al., 2008). Likewise, using transcranial magnetic stimulation (TMS) to inhibit IFG functioning leads to impaired task performance (Chambers et al., 2007).

The supplementary/pre supplementary motor area (preSMA) also plays a critical role in response selection and inhibition. A meta-analysis looking at go/no-go fMRI studies indicated that the preSMA is engaged across different versions of the task (Simmonds et al., 2008). Further, damage to this region is associated with impaired performance on response inhibition tasks (Floden & Stuss, 2006). It is hypothesized that this region is specifically involved in the motor planning (Chambers et al., 2009). However, there is conflicting evidence about whether the left or right preSMA plays a more critical role.

Studies have also implicated the basal ganglia (Rieger, Gauggel, & Burmeister, 2003). Lesions in this region can lead to impaired performance on response inhibition tasks. Within the basal ganglia, the subthalamic nucleus (STN) may be especially critical. This is confirmed by fMRI studies looking at activity in this region during response inhibition tasks (Aron & Poldrack, 2006; Li, Yan, Sinha, & Lee, 2008). It is hypothesized that the STN helps put the breaks on the go processes in order to inhibit prepotent responses (Chambers et al., 2009). The important role it plays in inhibition is confirmed by studies of individuals with Parkinson's disease. These individuals have deficits in response inhibition which are mitigated when the STN is electrically stimulated (van den Wildenberg et al., 2006). These studies together implicate the basal ganglia, and especially the STN in stopping a prepotent motor response.

The IFG, preSMA, and STN all appear to play a critical role in response selection and inhibition. Further, evidence suggests that these regions interact with one another and form a functional neural circuit (Chambers et al., 2009). There are a number of direct and indirect pathways through which these regions communicate (Aron & Poldrack, 2006). The quality of this communication impacts whether or not an individual can appropriately select and inhibit responses. In particular, different pathways may relate to selection and inhibition, and the relative speed of communication within these pathways determines whether an individual is able to successfully inhibit or make a response. Thus, a more comprehensive

understanding of the pathways through which these regions communicate will likely enhance our understanding of these constructs.

White Matter Microstructure and Go/No-Go Task Performance

Given that a defined neural circuit is implicated in response selection and inhibition, it naturally follows that structural connectivity between these regions plays an important role in go/no-go performance. Diffusion Tensor Imaging (DTI) allows noninvasive measurement of structural connectivity in vivo. This technique produces a number of metrics that summarize the properties of white matter microstructure (Basser & Pierpaoli, 1996; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). Fractional Anisotropy (FA) is a metric derived from DTI that captures the degree to which water diffusion is restricted in a given region. Restricted water flow can arise from a multitude of factors such as more tightly packed axons or a higher degree of myelination, which may indicate a more efficient tract structure. FA is particularly sensitive to the orientation of white matter as well as its integrity. Another metric produced by DTI is Mean Diffusivity (MD). This measures the degree of diffusion within a given region and is sensitive to both the integrity and size of the cells. Lower MD indicates more restricted diffusion within white matter, and thus may indicate a more efficient tract structure.

A number of studies have examined the relationship between white matter microstructure and response selection and inhibition. These studies have generally focused on the white matter tracts that connect the IFG, preSMA, and STN and have included both healthy individuals and those with specific externalizing disorders. One such study examined go/no-go performance in parent-child dyads with ADHD and found that there was a positive correlation between FA in prefrontal regions and d-prime in both parents and children (Casey et al., 2007). Another study focused on healthy individuals and looked at the relationship between SST performance and FA in tracts connecting IFG, preSMA, and STN. Portions of these tracts demonstrated a positive correlation between FA and SST performance. Overall these findings suggest that white matter microstructure in circuits connecting the IFG, preSMA, and STN is related to measures of response inhibition (Casey et al., 2007; King et al., 2012; Liston et al., 2006). In

particular, that increased integrity within these tracts is associated with better performance on response inhibition tasks.

Studies looking at DTI and go/no-go task performance have generally focused on the response selection and inhibition aspects of the task. No studies have explicitly examined the role of other involved processes such as processing speed. Outside of the context of go/no-go tasks studies have examined the relationship of white matter microstructure and these other processes. For one, processing speed has recently received some attention. In particular, one study found that processing speed was related to white matter microstructure across a number of tracts in the brain (Penke et al., 2010). Further, that this mapped onto a general factor of white matter microstructure that was related to processing speed. This study focused on processing speed outside of the context of go/no-go tasks, and thus it remains to be seen if the general factor of white matter applies to performance on these tasks. However, given the multitude of processes engaged in complex versions of the go/no-go tasks, it wouldn't be a stretch to conjecture that a general factor might play a role in this task.

Pervious Limitations and Current Study

Though there have been a number of studies examining the go/no-go task and white matter microstructure, there are a number of limitations to these studies. For one these studies used a restricted sample. The predominant approach to studying psychopathological correlates has been through the use of case-control designs, in which healthy individuals, often those without a hint of psychopathology symptoms who fall into the class of "super normals", are compared to individuals with a single diagnosis without comorbidity (Kendler, 1990). This approach is problematic because the use of extreme groups may lead to findings that don't apply to the full spectrum of behavior found in the population. In addition, studies often depend on convenience samples such as college students or outpatient clinic samples. The use of such sampling technique ignores the dimensional nature of psychopathology, as it does not reflect the spectrum represented in the population. Given that poor performance on the go/no-go task may arise

from a multitude of factors, it is unclear to what extent prior findings generalize to more heterogeneous samples.

The Research Domain Criteria (RDoC) is a recent initiative to examine psychopathology using a dimensional perspective (Insel et al., 2010). The Tennessee Twin Study (TTS) provides a sample that is in accordance with the sampling principles of RDoC. The TTS is a community sample that has been studied in two waves. The first wave was conducted in 2001 and the follow-up is ongoing (Lahey et al., 2008). The adult twin pairs in the second wave were selected with oversampling for psychopathology risk from the wave 1 sample based on data from clinical interviews. Thus, the wave 2 sample contains individuals with a wide range of psychopathology.

An additional limitation of previous studies is their emphasis on the response selection and inhibition aspects of go/no-go tasks. Although these are critical components of the task, they don't comprehensively capture all the requisite skills such as processing speed. Therefore, it remains to be seen which white matter microstructure tracts are implicated when multiple aspects of task performance are taken into account. The current study used data from the TTS to examine white matter microstructure and multiple aspects of go/no-go task performance in a community sample with a wide range of psychopathology (Lahey et al., 2008).

CHAPTER 2

MATERIALS AND METHODS

Participants

Participants were individuals from the second wave of the TTS who had participated in the study as of July 2014. The TTS has been conducted in two waves. The first was conducted in 2001 (2000+ twin pairs) and the follow-up is ongoing (target sample size of 200 pairs) (Lahey et al., 2008). The adult twin pairs in the second wave were selected with oversampling for internalizing and externalizing psychopathology risk from the older portion of the wave 1 sample (ages 12-17 in wave one) based on data from clinical interviews. Thus, the wave 2 sample contains a high rate of individuals with prevalent forms of psychopathology. Individuals were pre-screened for participation. Exclusion criteria included a history of head injury with loss of consciousness, seizures, other neurological diseases, and diagnosis of schizophrenia.

The study was approved by the Vanderbilt University Institutional Review Board (IRB). Written informed consent was obtained from the participants before participation. Over the course of an approximately 7-hour visit the twins completed questionnaires, behavioral tasks, as well as functional and structural imaging. In the current paper we will focus on the go/no-go task, the Stroop task, the Diffusion-Weight Imaging (DWI) scan, and the structured clinical interview. Participants were paid $400 for participation in the study.

The initial sample size included 188 young adults (ages 24-30) who had completed both a DWI scan and the go/no-go task. A total of 27 subjects were excluded for data quality. Eleven subjects were excluded because of poor behavioral performance on the go/no go task (defined as performance poorer than 2 standard deviations from the mean) and 6 subjects were excluded because of a programming error leading to an aberrant ratio of go/no-go trials. In addition, 10 subjects were excluded for poor DWI data

quality (excessive movement, missing data, etc.). The final sample comprised 161 individuals. The sample included 63 twin pairs and 35 individuals without a twin with valid data.

In order to ensure that the results weren't inflated due to the presence of twin pairs within the same sample, a follow-up sample was formed. For this sample one subject from each twin pair was randomly selected to be included in the sample (n=63), and all individuals who weren't part of a twin pair were included (n=35). Thus a total of 63 subjects were excluded due to having a twin pair in the sample. The final analysis included 98 independent subjects.

Tasks and Personality Measures

Go/no-go task

We utilized the XY go/no-go task developed by Garavan and colleagues (Garavan et al., 1999). In this version of the go/no-go task participants view a series of Xs and Ys, and must respond if a letter is different from the previous one, but withhold their response if it is the same. This task was comprised of two 8-minute runs, with a total of 732 go trials and 108 no-go trials (total of 840 trials). Each trial lasted 1 second, with the letter duration randomly selected (between 600-900 ms) and the fixation cross filling the remainder of the time. Prior to completing the task participants were trained on a version of the task that provided feedback on performance.

Stroop color word reading speed

We used the standard Stroop task as a measure of processing speed in order to disentangle its role in the go/no-go task (Golden, 1978). We wanted to use this measure because though the reaction time on go trials within the go/no-go task does measure processing speed, it is also conflated with the other measures from the task. The Stroop task provides a measure of processing speed that is independent from go/no-go task performance.

In the Stroop task individuals must complete separate conditions in which they read a series of color words printed in black ink, then indicate ink colors, and finally read color words printed in incongruent colored ink. In the current study we used the word reading speed condition in which individuals are asked to read as many color words as possible within 45 seconds.

YA-DISC

The structured Young Adult Diagnostic Interview for Children (YA-DISC) was administered by a trained interviewer (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). This computerized structured clinical interview is explicitly designed for individual in the samples' age range and has been used in longitudinal studies of psychopathology to assess symptoms from the major diagnostic categories in the DSM-IV. In contrast to most structured and semi-structured instruments, the YA-DISC does not utilize skip-outs, but rather goes through all 12-month symptoms (as well as externalizing symptoms since age 15) regardless of whether or not someone will meet diagnostic criteria for a given disorder. This allows for the generation of symptom counts regardless of diagnoses. The diagnoses assessed in the TTS included mood disorders (Social Phobia, Specific Phobia, Panic Disorder, Agoraphobia, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Posttraumatic Stress Disorder, Major Depressive Disorder, and Mania/Hypomania) as well as externalizing disorders (Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Antisocial Personality Disorder/Conduct Disorder, Alcohol Use Disorders, Tobacco Use Disorders, Marijuana Use Disorders, and Other Substance Use Disorders).

Urine drug screen

In order to determine if subjects had recently used substances, they completed a urine drug screen during the course of their visit. This drug screen tested for the use of the following substances: Cotinine, Cocaine, Marijuana, Amphetamine, Methamphetamine, Benzodiazepine, Barbiturates, Phencyclidine, Ecstasy, Oxycodone, Methadone, and Propoxyphene.

DWI acquisition

Imaging data were acquired on two 3T Intera-Achiava Phillips MRI scanners using a 32-channel head coil. T1-weighted images were acquired with a 3-D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (TE/TR/TI=4.6/9.0/644(shortest) ms; SENSE=2.0; echo train=131; scan time=4 min 32 s; FOV: 256x256x170 mm, 1 mm isotropic resolution). For diffusion weighted images the scan length was 5 min 2 s. We used a multi-slice Stejskal-Tanner spin echo sequence with an echo planar imaging readout (TE/TR=52/7750 ms, SENSE=2.2, FOV: 240x240 mm, 2.5 mm isotropic, 50 slices, 2.5 mm slice thickness). This was acquired with one image without diffusion weighting ("b_0") and 32 diffusion-weighted images (b=1000 s/mm^2).

Data Analysis

Behavioral analysis

For the go/no-go task three variables of interest were calculated: 1) hit rate (the proportion of trials on which an individual correctly responded to a go trial) 2) false alarm rate (the proportion of no-go trials in which the participant incorrectly made a response) 3) d-prime (z(hit rate)-z(false alarm rate)) (Wickens, 2002). Given that d-prime involves a z transform of both false alarm rate and hit rate, and given that hit rate wasn't normally distributed (see results section), we used a normal transformation of hit rate and false alarm rate in subsequent analyses. For the Stroop task we used the word reading speed score, which was the number of color words that an individual could real aloud within 45 seconds.

Diagnoses and symptom counts

Several variables were created from the YA-DISC. First we looked at the prevalence of each disorder during the past year. We then collapsed these disorders using the 3 factor model of psychopathology, which divides diagnoses into the domains of distress (Major Depression, Dysthymia, and Generalized Anxiety Disorder), fear (Social Phobia, Specific Phobia, and Agoraphobia/Panic), and

externalizing (Antisocial Personality Disorder and Substance Use Disorders) (Krueger, 1999; Lahey et al., 2012).

Given the relationship of response inhibition and selection to externalizing symptoms, we created a externalizing symptoms variable (Aichert et al., 2012; Nigg, 2001). This variable was created by summing the number of externalizing disorder symptoms (other than substance misuse symptoms) experienced in the past year (including Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, and Antisocial Personality Disorder/Conduct Disorders). In addition, given that substance misuse may impact white matter microstructure (Lim, Choi, Pomara, Wolkin, & Rotrosen, 2002; Lin, Wu, Zhu, & Lei, 2013; Monnig et al., 2013), we also calculated the total number of substance misuse symptoms within the last year (Alcohol Use Disorders, Marijuana Use Disorders, Nicotine Use Disorders, and Other Substance Use Disorders).

DWI data pre-processing

The Diffusion Weighted Images (DWI) were first registered to the B_0 volume using FSL FLIRT (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl/; (Jenkinson, Bannister, Brady, & Smith, 2002). The B_0 volume was then masked using BET (Smith, 2002). Eddy current and motion corrections were performed using FSL. The CAMINO software package was then used to fit the diffusion tensor (Cook et al., 2006). Robust tensor fitting using RESTORE was implemented (Chang, Jones, & Pierpaoli, 2005). RESTORE was chosen because this de-weights outliers in the data and gives a better signal to noise ratio. Quality control of the data was completed by consulting a graphical four-page quality assurance report (for more details see (Lauzon et al., 2013)). This report contains details on movement, bias, power, range of FA values, field of view, and vector directions. Subjects who were determined to be outliers within the dataset on the metrics from the quality assurance report were excluded.

FSL was used to compute Tract Based Spatial Statistics (TBSS) following the procedures detailed in Smith and colleagues (2006). In brief, each subject's FA image was aligned to 1x1x1 mm standard space using nonlinear registration to a pre-defined target image. An affine transformation was then

applied to bring the target image into MNI Space. Then each FA image underwent a nonlinear transformation to the target and then an affine transformation to bring it into MNI space. Next, all of these FA images were merged into a file and then an average image was created. This image was then thinned in order to create a mean skeletonized image, which reflects the center points of tracts shared across subjects. A Threshold of FA > .2 was applied to the mean skeleton, and then this was used as a mask to project each subject's FA values onto this average skeleton. The skeletonized images were used for subsequent statistical analyses.

Whole brain regressions and correlational analyses

A number of analyses were conducted examining metrics of behavioral performance and their relationship to white matter microstructure. For the initial whole brain regressions looking at the relationship between white matter microstructure and go/no-go task performance both MD and FA were examined. In subsequent follow-up analyses looking at twin pairs, motion, processing speed, and psychopathology we focused on FA. One reason we focused on FA is because it is highly correlated with MD (r = -.61 in this sample). Additionally, the majority of previous papers looking at response selection and inhibition have highlighted FA, and thus focusing on this metric allows for more direct comparison with previous results (Casey et al., 2007; King et al., 2012).

D-prime, hit rate, and false alarm rate

Voxel-based statistical analyses were conducted using FSL's randomise program, which utilizes a permutation-testing technique for determining statistical significance (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). The first set of analyses was conducted with the full group of 161 subjects. In each analysis a whole brain regression analysis was conducted between a behavioral variable of interest (hit rate, false alarm rate, and d-prime) and a measure of white matter microstructure (FA and MD) with scanner as a covariate. Whole brain regressions were run with 5,000 permutations and Threshold-Free Cluster Enhancement (TFCE) and correction for multiple comparisons were applied. Regions with a corrected $p < .05$ were considered significant. A follow-up whole brain analysis was completed for FA

and d-prime in the group with 98 subjects, in which only one randomly-selected twin per pair was included in the sample. This analysis was conducted in order to insure that the findings weren't driven by the presence of non-independent twin pairs within the sample.

Motion analysis

Recent studies on DTI methodology have suggested that motion during the scan can have a significant impact on the subsequent FA values, and thereby generate spurious findings (Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014). Thus we performed a follow-up analysis to ensure that motion was not driving the findings. Average translation and rotation across the DWI sequence were averaged together in order to create a motion covariate for each subject. The whole brain regression for d-prime and FA was then repeated with motion entered as a covariate.

Processing speed analyses

Given the potential role that processing speed plays in the XY go/no-go task, we investigated the role that it is playing in the findings in the current study. To index processing speed we used the word reading speed from the Stroop. First a separate whole brain regression was conducted between word reading speed on the Stroop and white matter microstructure. For this analysis the 3 subjects who did not complete the Stroop were excluded, making this a sample of 158 subjects. We then used processing speed as a covariate in the regression between FA and d-prime. For the 3 subjects who didn't complete the Stroop we substituted the average score across the sample (99).

Characterizing significant associations

The whole brain regressions provide information about regions where there is a significant relationship between white matter microstructure and go/no-go performance, but don't characterize the degree of association. Thus we completed post-hoc analyses to further characterize the degree of the significant associations. First masks were created of the significant regions (clusters) from each whole brain regression. Average FA and MD values were then extracted for individual subjects from these regions in order to run correlations with behavioral measures. To determine the global nature of these findings, average FA value across the entire white matter skeleton was extracted for each subject and

correlated with task performance. In calculating statistical significance the degrees of freedom for each correlations were adjusted so that each twin pair counted as a single degree of freedom. This conservative approach limits any potential biasing of results due to non-independence of data among the twin pairs.

Psychopathology

Correlations were examined between psychopathology symptom counts and performance on the go/no-go task. We correlated substance misuse symptom count and externalizing symptom count with behavioral performance on the task (hit rate, false alarm rate, and d-prime) as well as with the extracted average FA values across regions identified in the whole brain regressions. The statistical significance thresholds for these correlations were adjusted so that each twin pair counted as a single degree of freedom.

In order to determine if substance misuse symptoms were driving the findings we divided the sample into 1 group with 0 substance misuse symptoms (n = 83) and those with one or more symptoms (n = 78). Correlational analyses between behavioral measures and white matter microstructure were run in each of these two groups determine if findings held in both groups. We also compared go/no-go task performance between individuals who tested positive for one or more drug on the urine drug screen during their visit (n = 40) and those who did not test positive (n = 121).

CHAPTER 3

RESULTS

Participant Demographics

For the complete sample of 161 individuals, the average age of the participants was 27.25 (1.26), the number of males was 85, and the average number of diagnoses in the past year was 1.02 (1.73). Table 1 contains demographic information. Table 2 shows a summary of the frequency of diagnoses within the past year within the domains defined by the 3 factor model of psychopathology, which divides diagnoses into the domains of distress, fear, and externalizing (Krueger, 1999; Lahey et al., 2012). The average number of symptoms across these categories was: 1.43 (2.56) for fear, 2.93 (3.15) for distress, and 3.50 (3.68) for externalizing symptoms (excluding substance misuse). The average number of substance misuse symptoms was 1.96 (3.21).

Behavioral Results

Behavioral performance on the go/no-go task is reported in Table 3. For hit rate the Kolmogorov-Smirnov test was significant ($D(161) = .19$, $p < .001$), suggesting that assumptions of normality were not met for hit rate. For the z transformed hit rate the Kolmogorov-Smirnov test was not significant, indicating that assumptions of normality were met ($p > .1$) after the data transformation. The Kolmogorov-Smirnov test was not significant for d-prime or z transformed false alarm rate ($ps > .1$). Correlations between measures from the go/no-go task are presented in Table 4. Both false alarm rate and hit rate were correlated with d-prime but not with one another. Go trial reaction time was inversely correlated with both hit rate and false alarm rate (indicating that subjects with slower responses had both a lower hit rate and a lower frequency of false alarms). By contrast, go trial reaction time was not significantly related to d-prime.

Whole Brain Analyses Results

D-prime, hit rate, and false alarm rate

The whole brain regressions demonstrated broad patterns of significant associations for FA and MD with d-prime and hit rate, but not false alarm rate. Table 5 details the number of statistically significant voxels in each analysis and the widespread nature of the implicated regions are shown in representative slices for FA in Figure 1 and MD in Figure 2. The follow-up analysis using the restricted sample of 98 individuals (with only 1 twin per pair included) and looking at FA and d-prime was also significant, but with a modest reduction in the number of voxels implicated (40,310). Overall these findings suggest that the relationship between white matter microstructure and hit rate as well as d-prime isn't limited to a specific tract or set of tracts, but rather to a wide range of tracts.

Motion analysis

The whole brain regression for d-prime with motion entered as covariate remained significant, with only a slight reduction in the number of significant voxels (58,380).

Whole brain FA

Given the widespread nature of the relationship between white matter microstructure metrics and go/no-go task performance, it would appear that the relationship is global in nature. Thus we wanted to determine if the relationship could be accounted for by global FA. A whole brain regression between FA and d-prime was conducted with average FA across the white matter skeleton as a covariate. No voxels were significant.

Processing speed

The whole brain regression for Stroop word reading speed was significant a wide range of tracts. The results are presented in Table 5 and Figure 4. Given the widespread nature of the relationship of

white matter microstructure to processing speed from the Stroop and go/no-go metrics, the Stroop word reading speed was entered in as a covariate for the whole brain regression between d-prime and FA. This whole brain regression remained significant in a wide range of voxels, but the total number of voxels was reduced (41,526). The results of these tests are presented in Table 6 and Figure 4. These results would suggest that processing speed is accounting for part of the relationship identified between FA and go/no-go task performance.

Magnitude of Significant Relationships

Though whole brain regressions identify areas in which white matter microstructure is associated with measures of task performance, these analyses don't provide information about the degree of association. In order to determine the degree of association and therefore better characterize our findings, we completed post-hoc analyses. In these analyses average FA and MD values were extracted from the significant voxels in the whole brain regressions for d-prime and hit rate. As expected, correlation analyses confirmed that FA and MD values were correlated with d-prime and hit rate. As an additional exploratory analysis we examined the correlation between false alarm rate and FA in extracted cluster of voxels with significant associations with d-prime regions. As expected there was a significant correlation. In addition, average FA across the white matter skeleton was correlated with behavioral measures to determine if the findings represented a global phenomenon. Whole brain FA was correlated with hit rate and d-prime but not with false alarm rate. Correlations are presented in Table 5, and the scatter plots in Figures 1-3.

Relationship to Psychopathology

We also conducted an analysis to examine the relationship between psychopathology and task performance as well as white matter microstructure. For this analysis we focused on average FA values extracted from the large significant clusters identified in whole brain analyses. We focused on FA because this is the more commonly used metric, and thus this makes it easier to compare the results with previous

studies. These correlations are presented in Table 7. The number of substance misuse symptoms was inversely related to hit rate as well as average FA values across the regions defined by the d-prime and hit rate whole brain regression. Externalizing symptom count (excluding substance misuse symptoms) was not significantly related to either task performance or white matter microstructure. Within the sample, a total of 40 people tested positive for one or more substance on the urine drug screen during their visit, though we cannot say when they last used the substance. The correlations between white matter microstructure and task performance remained significant in a sample with no substance misuse symptoms (see Table 8). In addition, there were no significant group differences in behavioral performance between individuals who had tested positive for drug use on the urine drug screen and those who had not ($p > .05$)

Table 1. *Participant Demographics.*

Variable	Mean (Standard Deviation)
Age (Years)	27.25 (1.26)
Education (Highest Grade)	13.87 (2.91)

Variable	N (Percentage)
Male	85 (52.80)
Race	
White	119 (73.91)
Black	40 (24.84)
Other	2 (1.24)

Table 2. *Number of Diagnoses Based on the Three-factor Model of Psychopathology.*

Number of Categories	N
Single Category	
Distress	0
Fear	13
Externalizing	37
Two Categories	
Distress & Externalizing	2
Distress & Fear	2
Fear & Externalizing	8
All 3 Categories	
Distress, Fear, & Externalizing	7

Table 3. *Mean (Standard Deviation) of Task Performance and White Matter Microstructure Metrics.*

Variable	Mean (Standard Deviation)
Behavioral Variables	
Hit Rate	.93 (.07)
Z Transform Hit Rate	1.73 (.56)
False Alarm Rate	.59 (.16)
Z Transform False Alarm Rate	.25 (.45)
D-prime	1.48 (.75)
Reaction Time on Go Trials	364.98 (50.14)
Stroop Word Reading Speed	98.54 (16.55)
DWI Variables	
FA D-prime	.45 (.02)
FA Hit Rate	.45 (.02)
FA Whole Brain	.43 (.02)
MD D-prime	$.75 \times 10^{-3}$ ($.21 \times 10^{-4}$)
MD False Alarm Rate	$.75 \times 10^{-3}$ ($.21 \times 10^{-4}$)

Table 4. *Correlation Among Behavioral Measures From the Go/No-Go Task.*

	Hit Rate	False Alarm Rate	D-prime
False Alarm Rate	-.11		
D-prime	.81**	-.68**	
Reaction Time on Go Trials	-.26*	-.57**	.15

Note: * $p < .05$, ** $p < .005$.

Table 5. *Number of Significant Voxels From the Whole Brain Regressions and Correlations Between White Matter Microstructure Metrics and Task Performance.*

	FA		MD		Whole Brain FA
	Voxels	Correlation	Voxels	Correlation	Correlation
Hit Rate	65,414	.44**	78,264	-.40**	.30**
False Alarm Rate	0	-.20*	0	.10	-.09
D-prime	61,775	.43**	61,491	-.36**	.27**
Stroop Word Reading Speed	41,526	.43**	-	-	.23**

Note: * $p < .05$, ** $p < .005$. The whole brain regression for false alarm rate was not significant for MD or FA. The correlations for false alarm rate presented here are based on FA and MD values extracted from regions that were significant in the whole brain regressions with D-prime

Table 6. *Number of Significant Voxels From Whole Brain Regression Between D-prime and FA With Covariates.*

Covariate	Number of Voxels
Stroop Word Reading Speed	41,526
Average FA Across White Matter Skeleton	0

Table 7. *Correlations Between Symptom Counts and Task Performance as Well as FA.*

	D-prime	Hit Rate	False Alarm Rate	D-prime FA	Hit Rate FA
Substance Misuse Symptom Count	-.19[t]	-.20*	.07	-.20*	-.21*
Externalizing Symptom Count	-.06	-.10	-.02	-.06	-.08

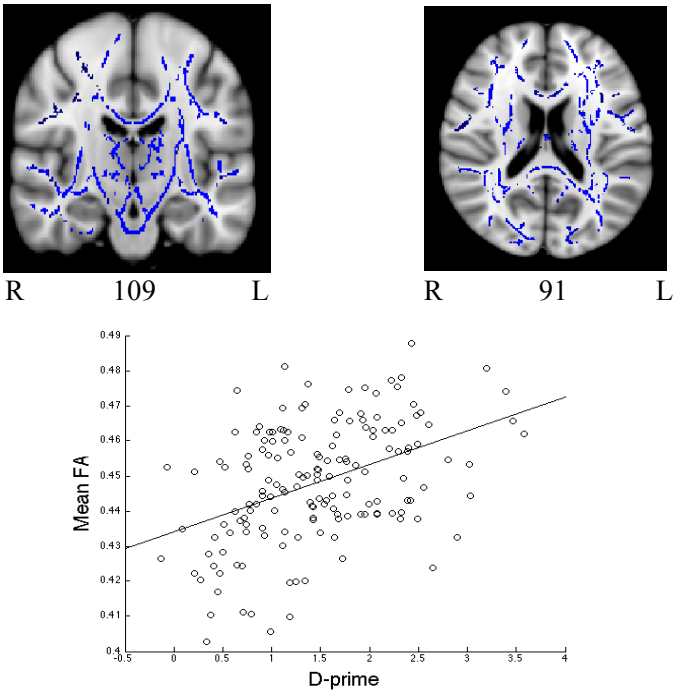
Note: *$p < .0$, [t]$p < .10$.

Table 8. *Substance Misuse Follow-Up Analysis.*

Correlations	Full Sample (n = 161)	No Substance Misuse (n = 83)	1+ Substance Misuse (n = 78)
Hit Rate and FA	.44**	.45**	.40**
D-prime and FA	.43**	.40**	.42**

Note: * $p < .05$, ** $p < .005$.

A)



B)

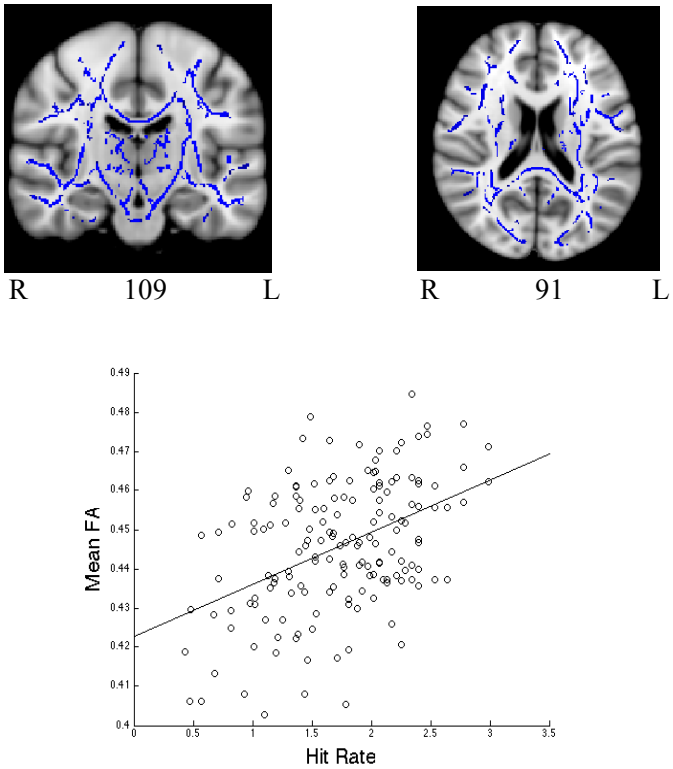
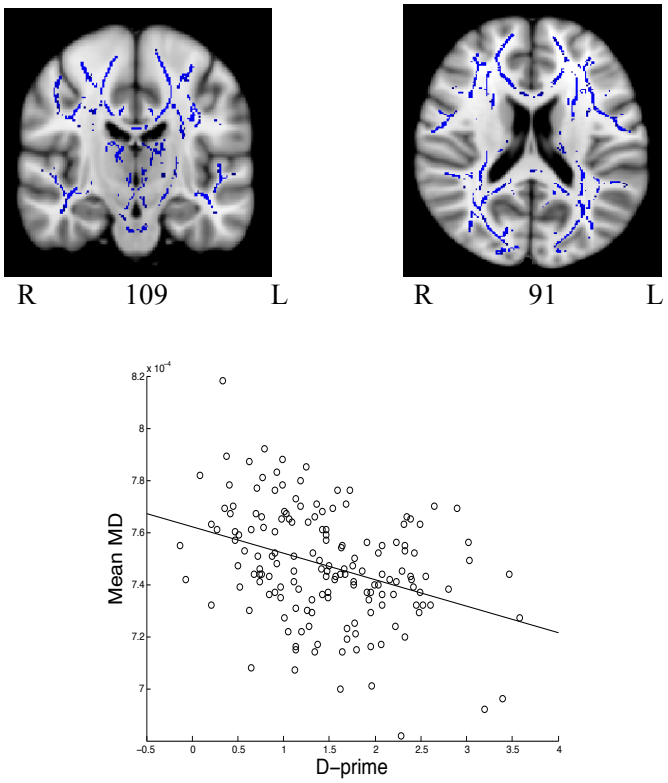


Figure 1. A) Significant regions from whole brain regression between FA and d-prime. Scatter plot of average FA values across significant regions and d-prime. B) Significant regions from whole brain regression between FA and hit rate. Scatter plot of average FA values across significant regions and hit rate.

A)



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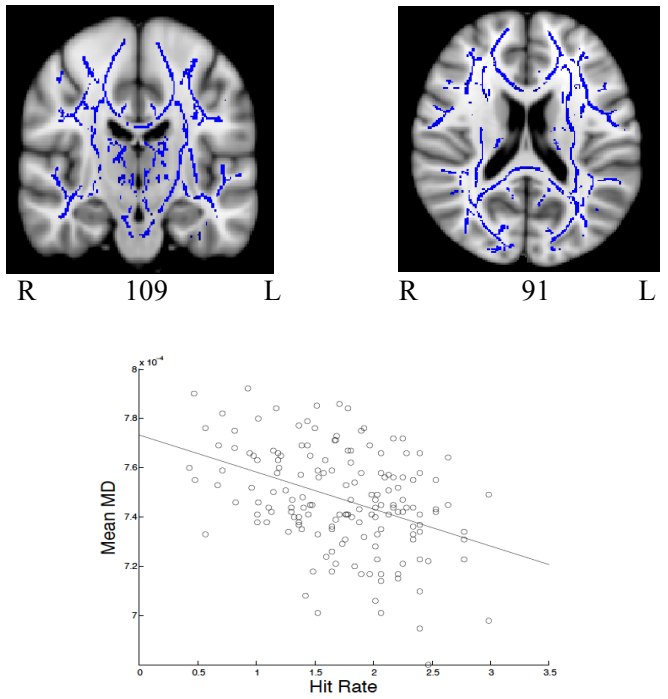
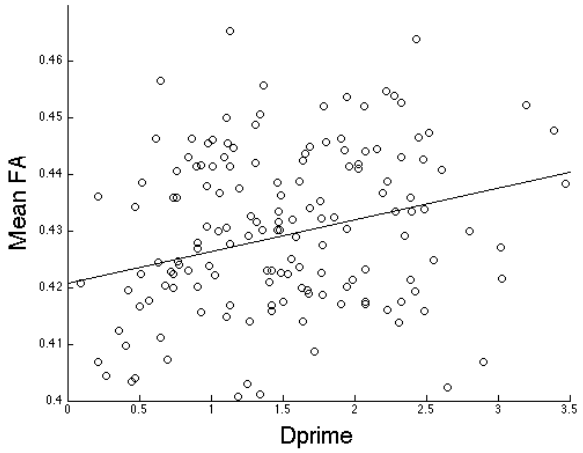


Figure 2. A) Significant regions from whole brain regression between MD and d-prime. Scatter plot of average MD values across significant regions and d-prime. B) Significant regions from whole brain regression between MD and hit rate. Scatter plot of average MD values across significant regions and hit rate.

A)



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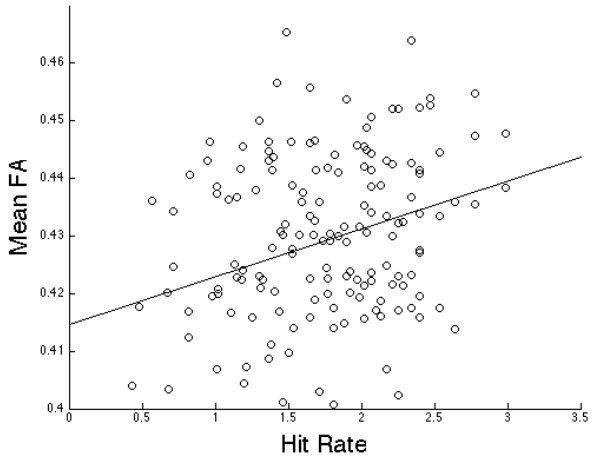
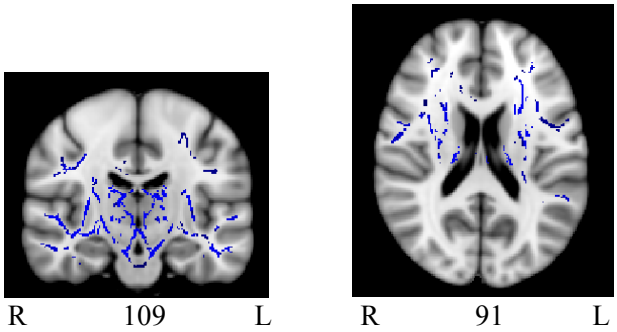
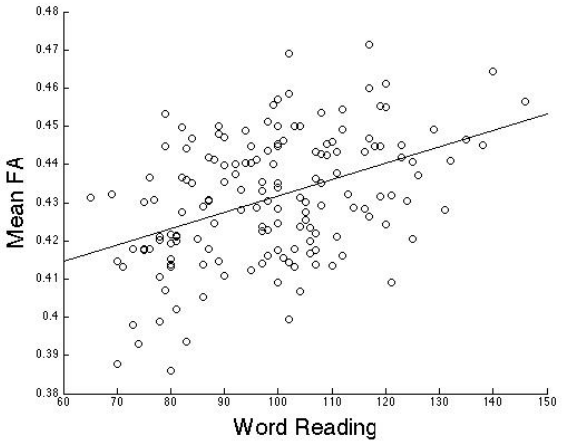


Figure 3. A) Scatter plot of average FA across the white matter skeleton and d-prime B) Scatter plot of average FA across the white matter skeleton and hit rate.

A)



B)



C)

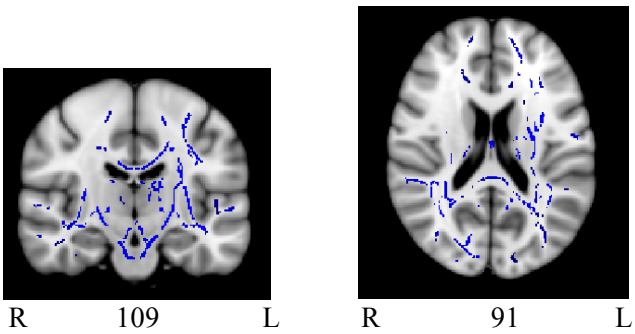


Figure 4. A) Significant regions from whole brain regression between Stroop word reading speed and FA. B) Scatter plot of Stroop word reading speed and FA values across significant regions from whole brain regression. C) Whole brain regression between d-prime and FA covarying for Stroop word reading speed.

CHAPTER 4

DISCUSSION

Overall Findings

In the present study we examined the relationship of white matter microstructure and go/no-go task performance in a large community sample that included a range of prevalent forms of psychopathology and found that d-prime was related to FA and MD in a large number of white matter tracts/brain regions. In these analyses, FA demonstrated a positive correlation with d-prime and hit rate and MD showed a negative correlation. Higher FA values indicate more restricted water flow, which is typically interpreted as arising from a more efficient tract structure (Pierpaoli et al., 1996). MD indicates overall diffusion within a region, with lower MD values possibly indicating more efficient tracts. Therefore, the FA and MD findings are highly consistent, with better performance on the go/no-go task being associated with more restricted diffusion within white matter. This suggests that the ability to successfully select appropriate responses and inhibit inappropriate ones in the go/no-go task is associated with more efficient structure within a number of white matter tracts. This effect was also found in a sample with no twin pairs, suggesting that this effect wasn't unduly influenced by the presence of twin pairs within the same sample. Further, when motion was used as a covariate the results remained largely unchanged, suggesting that motion wasn't driving the findings.

The widespread nature of the relationship between white matter microstructure and hit rate and d-prime differs somewhat from previous studies (King et al., 2012). The majority of previous studies found a relationship between d-prime or false alarm rate and white matter microstructure in a more restricted set of regions (King et al., 2012; Liston et al., 2006). However, these studies generally used a region of interest approach and focused on white matter tracts connecting the IFG, preSMA, and STN. In addition, the variation of the go/no-go task in the current study was a complex one. Many previous studies used a simple version which is less challenging. In such versions go and no-go trials are always represented by

the same stimulus. Therefore, the complex version requires a higher demand on skills such as working memory and processing speed. A prior meta-analysis found that simple and complex versions of the go/no-go task recruit both overlapping and unique regions, with the complex task recruiting a wider range of regions (Simmonds et al., 2008). This is consistent with the broad range of tracts identified in the present study. Thus, the use of a complex version of the go/no-go task as well as a whole brain approach may explain why the results of this study may differ from previous studies.

Contrary to previous studies no significant relationship was found with false alarm rate at a whole brain level (King et al., 2012; Liston et al., 2006). This suggests that response inhibition as indexed by false alarm rate in this task doesn't appear to be significantly related to white matter microstructure on a whole brain level. It could be the case that within the complex version of the go/no-go task used in this study false alarm rate doesn't capture response inhibition, but rather a more heterogeneous set of constructs. This may explain why the results in this study differ from previous ones.

General Factor and Processing Speed

The wide range of implicated tracts in this study is consistent with the concept of a general factor of white matter (Penke et al., 2010). The concept of a general factor was identified in a study that examined the relationship between white matter microstructure and processing speed. This study extracted average FA values across multiple tracts and found that these values loaded onto a single factor, and that this factor was related to a single behavioral factor: information processing speed. Another study found that a general factor of white matter microstructure was related to intelligence (Penke et al., 2012). However, it is important to consider that both these studies focused on older adults and on two specific constructs. Follow-up studies are needed to investigate whether or not this general factor applies across the age range and to a wide variety of processes.

To further investigate the widespread nature of our findings, we completed a whole brain regression between d-prime and FA with average FA across the white matter as a covariate. In this analysis there were no significant voxels. This suggests that average FA across the white matter skeleton

accounts for the significant regions identified in the whole brain regression between d-prime and FA. This confirms that the findings observed here are of a more global nature rather than specific to a particular tract.

Though metrics from the go/no-go task don't explicitly index processing speed, processing speed likely plays an important role. In this task the stimuli are presented rapidly and thus successful performance is impacted by the speed with which participants process the incoming information. The potential role of processing speed can be better understood by examining the role of reaction time within this task. Reaction time on go trials was negatively correlated with both hit rate and false alarm rate. This suggests that individuals who had slower reaction times on go trials were more accurate on no-go trials but less accurate on go trials. The speed with which individuals complete the task does appear to impact performance, though not in a simplistic manner. Regardless, these significant correlations suggest that differential processing speed has an impact on task performance and needs to be investigated to better understanding the findings from this study.

In order to further investigate the role of processing speed in this task, we used a measure that wasn't conflated with task performance. The measure we used was the word reading speed from the Stroop task. A whole brain regression between word reading speed and white matter microstructure was significant in a wide range of tracts. Though the relationship wasn't quite as widespread as the one identified for the metrics from the go/no-go task, the findings still appear to be global in nature. When we covaried for word reading speed in the whole brain regression between FA and d-prime, there was a reduction in the number of significant voxels. These results together suggests that processing speed is likely related to a global factor of white matter, and that processing speed is likely playing a role in the relationship between white matter microstructure and go/no-go task performance.

Overall these findings suggest that go/no-go task performance may be related to a global factor white matter microstructure. This is unsurprising given that successful task performance requires rapidly coordinating a range of processes including response selection, response inhibition, working memory, and performance monitoring to name a few. The ability to coordinate these processes requires quick and

efficient communication between multiple brain regions. The quality of this communication is largely determined by the efficiency of white matter tracts throughout the brain. Thus the integrity of white matter microstructure throughout the brain contributes to successful performance on the go/no-go task.

Relationship to Psychopathology

Previous studies of white matter microstructure and go/no-go performance have focused on the use of case-control designs. By contrast, this study used a community sample with a wider range of psychopathology. Thus, it's important to examine the role that psychopathology might be playing in the findings. In this study, externalizing symptom count was not significantly related to either behavioral performance or to white matter microstructure. This is in contrast with previous findings that individuals with externalizing disorders showed deficits in response selection and inhibition (Casey et al., 2007; Monterosso et al., 2005). One possibility is that this deficit doesn't exist at a dimensional level across a wide range of externalizing behaviors, but rather when categorical comparisons are made between groups with and without externalizing disorders. It could also be the case that go/no-go task performance deficits are related to more specific aspects of externalizing behavior that weren't captured by this broad and heterogeneous metric. In addition, a recent meta-analysis examining performance on response inhibition tasks across disorders found that deficits do exist in externalizing disorders, but the effect size may not be that high (Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). Thus these deficits may not have a large enough effect size to appear in this heterogeneous sample. Finally, it could be that there are differences in how externalizing behaviors relate to performance on simple versus complex versions of the go/no-go task.

By contrast, the relationship between hit rate and substance misuse count was significant, and the relationship with d-prime was trending. This suggests that substance misuse symptoms may be related to response selection. This is consistent with previous studies that found deficits in these skills in individuals with substance misuse disorders (Casey et al., 2007; Monterosso et al., 2005). Though this relationship was identified, the direction of causality remains unclear. Substance misuse may be causing impairment

in performance, or that individuals with slower response selection may be prone to drug misuse. The present study design doesn't allow for conclusions about the direction of this causality.

One important possibility to consider is that participants with high levels of substance misuse symptoms could have been under the influence of substances at the time of the study, which could have impacted their performance. Though participants were asked to abstain from the use of alcohol, drugs, and non-essential medications 12 hours prior to their visit we can't discount the possibility that individuals ignored this request and were under the influence of substances during their visit. Forty participants tested positive for at least one substance on a urine drug screen on the day of their visit. From this screen we cannot identify when a substance was most recently used. To further investigate the possible role of substance use during the study, we compared task performance between individuals who tested positive for drug use on the day of the study and those who did not, and found no significant differences. Thus, it seems unlikely that substance use during the visit is driving the findings seen in this study.

We also identified a significant relationship between substance misuse count and FA values in the regions showing significant associations with hit rate and d-prime. This is in line with previous studies suggesting that substance misuse is associated with decreased integrity in white matter (Lim et al., 2002; Lin et al., 2013; Monnig et al., 2013). Given that the relationships between white matter microstructure and behavioral performance still held true in individuals without substance misuse symptoms the relationship likely can't entirely be explained by differential substance use.

Limitations and Future Directions

There are several limitations in this study. First, our sample included twin pairs, which may have impacted the results given their non-independence. However, we completed a follow-up analysis without twin pairs and adjusted the degrees of freedom when appropriate. In addition the YA-DISC only probes for symptoms within the past year for many of the symptom clusters. Thus, it may not identify individuals with remitted psychopathology or those whose symptoms are well managed by medication. In addition,

given that we used the complex version of the go/no-go task, it isn't possible to fully disentangle which aspects of the task are driving the relationship with white matter microstructure.

Overall, the findings suggest that relationship between white matter microstructure and go/no-go task performance isn't restricted to a single tract but rather is global. Future studies should look at the relationship between white matter microstructure and performance on simple and complex versions of the go/no-go task. Further, studies should strive to disentangle the component processes involved in this task and how they may be differentially related to white matter microstructure. In addition, studies should examine how a general factor of white matter microstructure might relate to response selection and inhibition versus processing speed.

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