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Indirect association of DAT1 genotype with executive function through white matter volume in orbitofrontal cortex

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Abstract

The dopamine transporter (*DAT1*) gene has been associated with impulsivity and executive functioning. Further, *DAT1* has been associated with brain structural characteristics and resting state connectivity. This study tested an indirect effect model in which *DAT1* genotype (9-repeat carriers vs. 10-repeat homozygotes) is linked to phenotypes representing impulsivity and executive function (planning behavior) through effects on white matter (WM) volumes in prefrontal cortex (PFC), particularly orbitofrontal cortex (OFC). Adolescents (ages 14–18, *n*=38), were recruited from substance use treatment (*n*=22) and the community (*n*=16) to increase phenotype variation. Results indicated that *DAT1* 10/10 genotype was associated with lower WM volume in the PFC, specifically the left OFC. Further, lower WM volume in the left OFC predicted more difficulties in self-reported planning behavior, but not impulsivity. Indirect effect analysis indicated that lower WM volume in the left OFC mediated the association between *DAT1* 10/10 genotype and difficulties in planning behavior. Results suggest a brain structural mechanism, involving lower WM volume in the left OFC, as a link in the association between *DAT1* genotype and a specific aspect of executive function. Genetic effects on regional WM volume that are linked to behavioral outcomes could ultimately inform the development of tailored interventions that address an individual's unique risk factors.

Keywords

DAT1; Impulsivity; Executive function; White matter volume; Adolescent; Substance use

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Contributors

T.C. collaborated on study design, data collection, and data analysis, conducted the statistical analyses, and wrote the draft manuscript. R.F. conducted genotyping and provided feedback on the manuscript. D.C. collaborated on study design and data collection, and provided feedback on the manuscript.

1. Introduction

Neuroimaging measures have been used as an intermediate phenotype to explore neurobiological mechanisms in relationships between genes and behaviors (Hariri and Weinberger, 2003). In this model, genetic influence on a behavioral phenotype may be indirect, or mediated by the neuroimaging intermediate phenotype. Testing an indirect effect model can help to identify links, such as brain structural characteristics (white matter volume), in a pathway that connects the *DAT1* genotype with behavioral phenotypes of impulsivity and executive function. Since single genes are likely to have small effects, which are biased toward one extreme of a continuous phenotype, analytic samples that increase phenotypic variation by including a mix of affected and healthy cases can facilitate detection of genetic effects (Durston et al., 2005). This study tested an indirect effects model in which *DAT1* genotype is linked to behavioral phenotypes (e.g., impulsivity, goal setting and planning) through effects on white matter (WM) volumes in the prefrontal cortex (PFC) using a mixed sample of youth recruited from substance use treatment and the community to increase variation in the behavioral phenotypes of interest.

The dopamine transporter (*DAT1*) gene has a variable number of tandem repeats (VNTR) in its 3′ untranslated region that may influence DAT expression. The 9-repeat (9R) and 10-repeat (10R) alleles are most common. In vitro studies generally suggest lower DAT expression for 9R, relative to 10R, resulting in increased DA signaling for 9R carriers (Mill et al., 2002; Madras et al., 2005). In vivo results, however, have been inconsistent (Heinz et al., 2000; Jacobsen et al., 2000; Krause et al., 2006). Research on the *DAT1* genotype indicates that 10R homozygotes (10/10 genotype), relative to 9R carriers, demonstrated greater impulsive responding (Gizer and Waldman, 2012). Other studies have reported worse executive functioning among 10R homozygotes relative to 9R carriers (Loo et al., 2003; Stollstorff et al., 2010). The 10R allele also has a modest association with attention-deficit/hyperactivity disorder (Yang et al., 2007; Gizer et al., 2009; Hawi et al., 2010), a disorder involving impulsivity and impairment in executive function.

The prefrontal cortex (PFC) plays a key role in the behavioral phenotypes of impulsivity and executive function that have been associated with *DAT1* genotype (Miller and Cohen, 2001). In particular, the orbitofrontal cortex (OFC), as part of the PFC, has been associated in human lesion studies with impulsivity, that is, a preference for smaller but rapid rewards relative to larger but delayed rewards (Bechara et al., 1994). The OFC, together with other PFC regions, is involved in planning and monitoring goal-directed behavior, specifically by encoding the reward value of temporally distant goals (Wallis, 2007). In one model (Wallis, 2007), the OFC serves as a major hub that integrates sensory (e.g., temporal cortex), affective (e.g., amygdala), and motivational (e.g., hypothalamus) inputs to compute the value of possible outcomes and their reward values. Information on outcomes and associated reward values is then transferred from the OFC to other areas of the PFC to prioritize goals and determine action plans (Kringelbach, 2005; Wallis, 2007).

The OFC's role as a key information-processing hub that is highly connected, functionally and anatomically (Ongur and Price, 2000; Kringelbach, 2005; Kahnt et al., 2012), with other brain regions suggests the importance of efficient communication between relevant brain

regions, as well as within the OFC. In this regard, integrity of white matter (WM) tissue facilitates efficient communication within and across brain regions (Fields, 2008; Filley, 2010). As a classic index of WM tissue integrity (Salat et al., 2005), WM volume reflects, for example, number of axons and degree of myelination (Paus, 2010). Regional WM volume has been associated with, for example, processing speed (Ferrer et al., 2013) and cognitive control as indicated by reduced interference on the Stroop task (Takeuchi et al., 2012). Total brain WM volume has been found to be positively associated with working memory performance (Posthuma et al., 2003). Of particular interest for the current study, WM volume in the area of the OFC adjacent to Brodmann's area 11 was positively correlated with executive functioning involved in everyday events in healthy adults (Takeuchi et al., 2013). Results from these studies suggest a role for the OFC in executive functioning and impulsive behavior, and that WM volume in OFC may be associated with aspects of executive functioning.

Emerging research suggests associations of the *DAT1* genotype with regional brain structure. Specifically, youth with the 10/10 genotype had smaller caudate gray matter volumes than 9R carriers, a result which was tentatively interpreted as related to reduced *DAT1* expression (Durston et al., 2005). Little is known regarding *DAT1* genotype and regional WM integrity, particularly WM integrity within specific regions of interest such as the PFC and the OFC. Although *DAT1* may be expressed more in striatum than in prefrontal areas (Madras et al., 2005), due to the functional and anatomical connectivity of these areas (e.g., fronto-striatal circuit), dopamine signaling that originates in the striatum may have effects in the PFC as part of a network of brain regions, in which striatum gates and updates information in the PFC (Hazy et al., 2007; Braskie et al., 2011). For example, high midbrain dopamine D3 receptor availability was associated with lower resting state functional connectivity between the OFC and networks involved in cognitive control and reward in healthy males (Cole et al., 2012). As another example, a recent study found that resting state connectivity of a striato-frontal circuit mediated the association of DAT1 with working memory and impulsivity in healthy adults (Gordon et al., 2015). These studies suggest effects of midbrain dopamine signaling on the OFC and other cortical areas through network connectivity, although connectivity within a given region (e.g., the OFC) is also important to understanding circuit dynamics (Sporns et al., 2005; Filley, 2010).

The finding reported by Gordon and colleagues (2015) that adults with 10/10 *DAT1* genotype, relative to 9R carriers, had weaker striato-frontal connectivity, which, in turn, was associated with worse executive functioning (working memory) and marginally associated with higher trait impulsivity, suggests that a *DAT1* effect on functional connectivity might occur through genetic association with WM integrity, indexed by regional WM volume. Although inter-region anatomical connectivity may be of interest, we focus here on connectivity within *a priori* selected regions (PFC and OFC) that have been associated with executive functioning and impulsivity (Kringelbach, 2005; Wallis, 2007). In support of a possible association of brain dopamine and WM characteristics, in vitro work indicates an association between levels of brain dopamine and brain myelination (e.g., Karadottir and Attwell, 2007). Further, psychotropic medication effects on dopamine neurotransmission involve complex signaling pathways that can affect myelination (Bartzokis, 2012), which

suggests an association between dopaminergic activity and WM characteristics, such as WM volume (e.g., Bartzokis et al., 2011).

Based on research suggesting effects of the *DAT1* genotype on regional brain structure and striatal-frontal connectivity (Durston et al., 2005; Gordon et al., 2015), we hypothesized that the 10/10 genotype would be associated with lower prefrontal WM volume. We focus on regional WM volumes illuminate the role of selected regions of interest (PFC and OFC) in relation to specific behavioral phenotypes, and WM volume as an indicator of WM integrity within these specific regions of interest. We predicted that lower prefrontal WM volume, particularly in the OFC (due to its role in planning goal-directed behavior and its implication in impulsivity), would be associated with phenotypes representing trait impulsivity and difficulties in executive function related to planning goal-directed behavior. This study of youth from substance use treatment and the community tested a model of gene-to-brain-to-behavior relations (see Fig. 1) in which *DAT1* genotype (10/10) has an indirect effect on phenotypes of higher trait impulsivity and difficulties in planning goal-directed behavior through lower prefrontal WM volume.

2. Methods

2.1. Participants

Adolescents ages 14–18 were recruited from community-based intensive outpatient treatment for substance use, and from the community using random digit dialing, to participate in a naturalistic longitudinal study. Inclusion criteria for these analyses were self-reported Caucasian race (only Caucasians were included to minimize differences in minor allele frequency by race), valid neuroimaging data, valid *DAT1* genotype data, and complete data on the dependent variables. Imaging data from six participants were excluded due to excess motion (n=3), faulty cortical segmentation (n=2) or a problem with resampling of diffusion tensor imaging data (n=1). Two cases with valid neuroimaging data were excluded because the DNA sample was not successfully genotyped. One case with valid neuroimaging and genotype data was excluded due to missing data for a dependent variable.

The analysis sample included 38 adolescents (58% male), 22 recruited from substance use treatment (57.9%) and 16 recruited from the community (42.1%). Table 1 reports sample descriptive statistics. Participants were, on average, 16.6 (SD=1.2) years old. The sample represented a full range of socio-economic status (SES; range=1–5) and was, on average, middle-class (Hollingshead, 1975). In the total sample, the mean full scale IQ score was in the average range (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999). The Edinburgh Handedness Inventory (EHI) (Oldfield, 1971) indicated that 34 participants were right handed (score >39), one participant was ambidextrous (score=10), and three participants were left handed (score < −39).

2.2. Procedure

Youth from substance use treatment and the community, enrolled in the longitudinal study (King et al., 2009; Maisto et al., 2011), were invited to participate in an add-on neuroimaging protocol (Thatcher et al., 2010; Chung et al., 2011; Clark et al., 2012; Chung et al., 2013). The University's Institutional Review Board approved the study protocol.

Treated youth attended three 3-h group sessions per week for 6–8 weeks, with content (e.g., relapse prevention, 12-step facilitation) that supported a goal of abstinence from alcohol and illicit drugs. Community youth served as a locally representative comparison to treated youth. Informed consent (from 18 year olds) or assent (from minors, with informed consent for the minor's participation provided by the minor's parent) was obtained before initiating study procedures. For treated youth, baseline assessment was typically completed within 2 weeks of starting treatment. Highly trained research associates, with a bachelor's or master's degree, collected substance use and psychiatric data, and saliva DNA according to protocol.

The neuroimaging protocol was completed shortly after baseline assessment, typically within 2 weeks. Youth were instructed to abstain from alcohol and illicit substance use for at least 24 h before the imaging session. No adolescent included in the analyses reported alcohol or illicit drug use <24 h before the scan. In the total sample, average number of days before the scan was 22.2 (SD=11.3) since last alcohol use, 21.9 days (SD=12.8) for marijuana use, 15.5 (SD=14.3) for tobacco use, and 24.8 (SD=9.3) for other drug use. Before magnetic resonance imaging (MRI), participants were screened for any MRI contraindications. Adolescents received compensation for study participation.

2.3. Measures of substance involvement, psychopathology, and cognitive functioning

The Drug Consumption Questionnaire assessed frequency of alcohol and marijuana use in the past 6 months using a 9-point scale (0=never used, 1=no use in the last 6-months, 2=used less than once per month, 3=used once per month, 4=used 2–3 times per month, 5=used once per week, 6=used 2–3 times per week, 7=used 4–6 times per week, 8=daily use) with satisfactory reliability and validity (Chung et al., 2004). An adapted Structured Clinical Interview for DSM-IV SUDs (SCID: First et al., 2002) assessed lifetime diagnoses of substance use disorder with acceptable reliability and validity (Chung et al., 2004). The Kiddie-Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997) assessed lifetime DSM-IV psychopathology.

The Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) has been shown to reliably assess full-scale IQ. Behavior Rating Inventory of Executive Function-Self-Report Version (BRIEF-SR) (Guy et al., 2004), which has good psychometric properties, was used to assess Planning/Organization ("Planning") with 13 items rated "never," "sometimes," or "often." Planning subscale items assess the ability to develop and apply appropriate steps in carrying out a task or accomplishing a goal (e.g., "I don't plan ahead for future activities", "I have trouble prioritizing my activities"). A normalized T-score was used, with higher scores representing greater difficulties in Planning. The Barratt Impulsivity Scale (Patton et al., 1995) includes 30 items (e.g., "I do things without thinking") rated on a 4-point scale (1=rarely/never to 4=almost always/always); higher scores reflect greater impulsivity.

2.4. DNA collection and genotyping

A mouthwash protocol was used to collect DNA from saliva (King et al., 2002). Samples were subjected to whole genome amplification using multiple displacement amplification (Dean et al., 2002), quantified by the pico green protocol, and diluted to 40 ng/μl for storage. Length polymorphisms were genotyped by polymerase chain reaction using unique

sequence flanking primers and resolution of the amplimers on agarose polyacrylamide gel. Polymerase chain reaction amplification and gel separation were accomplished using published methods (Vandenbergh et al., 1992). For *DAT1*, alleles were categorized as 10R, 9R and other. Participants were categorized as 10R homozygotes or 10/10 (*n*=17) or 9R carriers (*n*=21, which included *n*=19 9R carriers [9R heterozygous] and *n*=2 9R homozygotes). Allele frequencies did not deviate significantly from Hardy-Weinberg equilibrium.

2.5. Neuroimaging protocol

MR images were acquired on a Siemens 3T Allegra Scanner. T1 weighted magnetization-prepared rapid gradient echo (MPRAGE) images were acquired for morphometric analyses (scan parameters: repetition time (TR)=1400ms; echo time (TE)=2.48 ms; field of view (FOV)=256×256; 176 1-mm slices × 2; matrix 256 × 256). In addition, diffusion images were acquired using standard fast echo-planar imaging (TR=6500 ms; TE=88 ms; FOV=205×205; b=1000 s/mm^2; 46 3-mm slices × 12 directions in addition to b=0), with images collected twice to optimize the signal-to-noise ratio.

Image processing has been detailed elsewhere (Clark et al., 2012; Chung et al., 2013). In brief, processing involved the creation of WM regions of interest (ROIs) using Freesurfer (Dale et al., 1999; Fischl et al., 2002, Fischl et al., 2004). To ensure data quality, we visually assessed motion artifacts (i.e., striping), and examined motion parameters graphically, as generated by FSL's eddy correct program (fmrib.ox.ac.uk/fsl) to exclude cases with excess motion. Cortical reconstruction processing and volumetric segmentation were run according to standard procedures in Freesurfer. Registration to standard space was performed using individual cortical folding patterns to match cortical geometry across subjects. Parcellation of the cerebral cortex into units based on gyral and sulcal structure was done. Next, WM volumes were calculated for each cortical parcellation. Freesurfer measurements and white/gray matter parcellation have been validated against histological and manual measurements (Rosas et al., 2002; Kuperberg et al., 2003; Han et al., 2006). ROIs created by Freesurfer WM parcellation were visually inspected to ensure anatomical accuracy. The ROI approach used here, compared with whole-brain voxel-based approaches (e.g., Tract-Based Spatial Statistics), permits tests of hypotheses involving specific brain regions with greater sensitivity (Niogi et al., 2007).

Prefrontal and orbitofrontal ROIs were created by combining non-overlapping Freesurfer-defined bilateral WM regions, and were adjusted for total intracranial volume. The prefrontal ROI (excluding the OFC) included the frontal pole, frontal superior, frontal caudal middle, frontal rostral middle, pars opercularis, and pars triangularis. Orbitofrontal ROIs included frontal lateral orbital, frontal medial orbital, and pars orbitalis areas. The "prefrontal ROI" variable represented the sum of "prefrontal ROIs (excluding OFC)" and "orbitofrontal ROI".

2.6. Data analysis

Comparisons between substance use treatment and community youth, and *DAT1* 10/10 versus 9R carrier groups, were conducted using chi-square test or *t*-tests. Correlations,

controlling for recruitment source, age, and sex, were examined to determine the utility of testing hypothesized mediation (indirect effect) models (MacKinnon, 2008). Indirect effect analyses used an SPSS macro that ran a bootstrapping procedure (Preacher and Hayes, 2004). The mediation model tested an "A path," which is the path from the independent variable (*DAT1* genotype) to the intervening variable (e.g., regional WM volume); a "B path," which represents the direct effect of the intervening variable (e.g., regional WM volume) on the dependent variable (Planning score); a "C path," which represents the total effect of the independent variable on the dependent variable; and a "C′ path," which represents the direct effect of the independent variable on the dependent variable, after controlling for the intervening variable. A significant indirect effect is indicated when the 95% bias-corrected and accelerated (BCa) confidence interval around the unstandardized coefficient does not include zero (Preacher and Hayes, 2004).

In this sample, fractional anisotropy (FA) in the PFC (excluding OFC) and OFC were not associated with DAT1 genotype ($r = -0.14$ to 0.08, $p > 0.3$). Further, WM volume and FA in the PFC and OFC ROIs were not significantly correlated ($r = -0.02$ to 0.19; $p > 0.2$). In this regard, WM volume and FA have been shown to be "moderately to weakly related," and reflect different (complementary) aspects of WM integrity (Salat et al., 2005; Fjell et al., 2008; Taki et al., 2013). In further support of a focus on regional WM volume, a study of healthy college students found a significant association between executive functioning and WM volume (but not FA) in the left OFC (Takeuchi et al., 2013). Thus, analyses focus on WM volume in the PFC and OFC as an indicator of regional WM tissue integrity.

Regression analyses controlled for recruitment source (treatment=1, community=0), sex (1=female, 2=male), age, lifetime alcohol diagnosis (0=no, 1=yes), lifetime marijuana diagnosis (0=no, 1=yes), and IQ score. Recruitment source was covaried given differences between treatment and community youth in mental health and substance use. Due to differences in brain development by age and sex (Gogtay et al., 2007), these demographic characteristics were covaried. Alcohol and marijuana diagnosis was covaried due to possible effects of substance use on WM volume (Squeglia et al., 2009); results were similar using frequency of alcohol and marijuana use as covariates. Inclusion of other drug and nicotine use did not change the overall pattern of findings. Other drug and nicotine use were not significant covariates ($p > 0.2$), and so were not included in the model reported. IQ score was covaried due to its potential relationship to planning and organization of behavior (Guy et al., 2004). Handedness was examined in preliminary analyses, but since it was not significantly associated with DAT1 genotype ($p = 0.5$) or WM volumes ($p > 0.6$), handedness was not included as a covariate in the analyses.

3. Results

3.1. Comparison of treatment and community youth

Treatment and community youth did not differ ($p > 0.05$) in sex, age, SES, or *DAT1* genotype (Table 1). However, treated youth, compared with community youth, had lower full scale IQ ($t_{36} = 3.51$, $p < 0.01$), more difficulties in Planning ($t_{36} = -4.53$, $p < 0.001$), and reported greater impulsivity ($t_{36} = -4.79$, $p < 0.001$). Youth in treatment, compared with community youth, also reported more frequent use (6 months before the assessment) of alcohol ($t_{34} = -2.67$,

$p<0.05$), marijuana ($t_{35}= -6.35$, $p<0.001$), and tobacco ($t_{36}= -4.63$, $p<0.001$); and were more likely to meet criteria for a lifetime DSM-IV diagnosis of alcohol (χ^2[df=1]= 12.77, $p<0.001$), marijuana (χ^2[df=1]= 30.48, $p<0.001$), and nicotine (χ^2[df=1]= 6.24, $p<0.05$) use disorder. Treated youth also were more likely than their community counterparts to have lifetime DSM-IV diagnoses of conduct disorder (χ^2[df=1]= 11.26, $p<0.01$), attention deficit hyperactivity disorder (χ^2[df=1]= 5.74, $p<0.05$), and major depression (χ^2[df=1]= 4.65, p<0.05). In addition, youth in treatment had lower WM volume in prefrontal ($t_{36}= 2.04$, $p<0.05$) and prefrontal excluding orbitofrontal ($t_{36}= 2.05$, $p<0.05$) ROIs compared with community youth (Table 1).

3.2. Comparison of DAT1 10/10 and 9c genotypes

DAT1 10/10 and 9R carrier genotypes did not differ ($p>0.05$) on demographic characteristics (sex, age, SES); IQ score; Planning T-score; impulsivity; alcohol, marijuana, or nicotine use disorder diagnosis; or psychiatric conditions that were commonly observed in the treatment sample (Table 2). However, carriers of the 9R carrier genotype, compared with 10/10, had gre*ater* WM volume in prefrontal ($t_{36}= -2.41$, $p<0.05$), prefrontal excluding orbitofrontal ($t_{36}= -2.19$, $p<0.05$), and orbitofrontal left hemisphere ($t_{36}= -2.72$, $p<0.01$) ROIs.

3.3. Correlations of DAT1 genotype, white matter volume, and self-report measures

Partial correlations (controlling for recruitment source, sex, and age) indicated significant associations (“moderate” effect size; Cohen, 1988) between the *DAT1* genotype and WM volume in prefrontal and left orbitofrontal ROIs ($p<0.05$; see Table 3). The left orbitofrontal ROI was negatively associated with the Planning T-score ($p<0.05$), indicating that lower WM volume in this region was associated with greater self-report of Planning difficulties. Although the partial correlation of Planning and impulsivity was 0.69 ($p<0.01$; bivariate $r=0.83$, $p<0.001$), the left orbitofrontal ROI was only significantly associated with Planning. The *DAT1* genotype was not significantly associated with either Planning or impulsivity. The pattern of correlations supported the utility of testing an indirect effects model in which the *DAT1* genotype is indirectly associated, through WM volume in the left orbitofrontal ROI, with the Planning T-score (see Fig. 1).

3.4. Indirect effect of DAT1 genotype on Planning T-score through WM volume

Table 4 reports the parameter estimates for the indirect effects regression model. Results indicate that the *DAT1* 9R genotype is associated with greater WM volume in the left orbitofrontal ROI (A path), and that greater WM volume in this ROI is associated with less self-reported difficulties in Planning (B path). The direct association between the *DAT1* genotype and Planning was not significant. A significant indirect effect linking the *DAT1* genotype with the Planning T-score, through WM volume in the left hemisphere orbitofrontal ROI, was detected, point estimate=−3.92 (BCa 95% CI: −10.59, −0.88). Among the covariates, only IQ score was significant, such that higher IQ was associated with fewer difficulties in Planning ($p<0.05$).

4. Discussion

The results provide some support for the hypothesized indirect effects model. As predicted, the *DAT1* 10/10 genotype was associated with lower PFC WM volume, and lower PFC WM volume, specifically in the left OFC, was associated with difficulties in Planning. These associations represent “moderate” effect sizes. Although the *DAT1* genotype was not directly associated with either impulsivity or Planning, an indirect effect of the 10/10 genotype on difficulties in Planning was detected, with lower WM volume in the left OFC serving as a linking mechanism. Although impulsivity and Planning measures were correlated, significant associations were specific to Planning, and to the left OFC, instead of to the PFC more generally.

Regarding the specificity of findings to difficulties in Planning, the BRIEF Planning scale assesses an adolescent’s ability to manage future-oriented demands, such as the ability to anticipate future events, set a goal, and develop a sequence of steps to be accomplished in achieving the goal (Guy et al., 2004). Although there is some overlap in the domains covered by the Planning scale and the Barratt Impulsivity Scale (BIS), such as planning ahead, the BIS provides less coverage of the cognitive aspects of goal setting and planning. The BRIEF Planning scale’s greater focus on cognitive aspects of planning that have been related specifically to the OFC, and more generally to PFC function, may partially explain the specificity of the association between OFC WM volume and the Planning T-score. Given that other studies have observed direct associations of the *DAT1* genotype and risk taking behavior (e.g., Mata et al., 2012) and impulsive responding (Gizer and Waldman, 2012), other aspects of OFC and PFC structure (such as gray matter volume), or functioning, which were not examined here, might be associated with specific facets of impulsivity and executive functioning.

This study’s finding of an association with OFC WM volume and the Planning score is in line with results from a study of healthy young adults, which found that greater left OFC WM volume was associated with better executive functioning in everyday activities (Takeuchi et al., 2013). The localization of findings to the left OFC in adolescent and young adult samples warrants further investigation, particularly since this asymmetry did not appear to be associated with handedness in this adolescent sample, and the *DAT1* effect on resting state striato-frontal connectivity in a study of healthy adults was symmetrical (Gordon et al., 2015). Of note, however, a recent functional MRI study of youth (ages 12–15) found that greater activation in the left lateral OFC in order to achieve correct performance on an antisaccade task (a result which was interpreted as lower efficiency of processing) was associated with self-reported difficulties in flexibly in using problem-solving strategies to adapt to changing circumstances (Zhai et al., in press). The importance of structural and functional deviations specifically in left, versus right, OFC in relation to planning, problem solving, and other executive functions warrants further study.

Study results did not support a direct association of the 10/10 *DAT1* genotype with a deficit in executive function, as found in some studies (Loo et al., 2003; Stollstorff et al., 2010). In this adolescent sample, the *DAT1* genotype was only indirectly associated with managing future-oriented goals, through left OFC WM volume. The finding of lower WM volume in

the left OFC among youth with the 10/10 genotype is novel, and suggests possible downstream effects on, for example, weaker striato-frontal connectivity, which was observed among adults with the 10/10 genotype (Gordon et al., 2015). For example, lower regional WM volume may reduce efficiency of communication within, as well as among, brain regions, serving as a mechanism by which the *DAT1* genotype might be associated with more complex behavioral phenotypes involving executive function. Results from earlier work indicating *DAT1* effects on caudate gray matter volume (Durston et al., 2005) suggest multiple potential, and possibly converging, pathways that could contribute to *DAT1* effects on measures of executive function.

The study sample included youth from both substance use treatment and the wider community, which provided a range in severity of the behavioral phenotypes. This phenotypic variation likely increased the ability to detect associations between the *DAT1* genotype and phenotype (Durston et al., 2005). Notably, treatment and community samples did not differ in *DAT1* genotype distribution, despite between-group differences in impulsivity and Planning, level of substance involvement, and co-occurring psychopathology. In addition, treatment and community youth differed in prefrontal WM volume, but not left OFC WM volume. Importantly, the *DAT1* genotype was associated with left OFC WM volume in analyses that controlled for age, sex, and recruitment source. Further, the effect of the *DAT1* 10/10 genotype and lower left OFC WM volume was observed when controlling for recent substance use, supporting a more general *DAT1* genetic effect on left OFC WM volume that was independent of recruitment source. The *DAT1* effect on left OFC WM volume is notable, since greater WM integrity as indicated by regional fractional anisotropy has been associated with better substance use treatment outcome in an overlapping sample of youth (Chung et al., 2013). Since WM volume and FA are only moderately to weakly related, and appear to reflect different aspects of WM integrity (Fjell et al., 2008), further research examining various indicators of WM integrity is needed.

Study limitations warrant comment. Only Caucasian youth, sampled from substance use treatment and the community, were included, which limits generalizability. Although the sample provided a broad range in the behavioral phenotypes of interest, sample size was relatively small. Only one candidate gene was examined, although multiple genes likely contribute to WM volume and complex behavioral phenotypes. Substance use may reduce WM volume in youth (Squeglia et al., 2009), although recent frequency of substance use was not correlated with regional WM volume in this mixed sample of treated and community youth. Only WM volume within selected brain regions (PFC and OFC) was examined, such that directions for future research include the use of other methods to examine WM integrity such as tract-based analyses to examine inter-region connectivity, other measures of regional brain structure (e.g., WM fractional anisotropy, gray matter volume), and more narrowly defined structural regions (e.g., separate analyses of the three component OFC segments that were combined in this study). Measures of functional activation (e.g., resting state or task-related connectivity) also remain to be examined. Self-reports of impulsivity and Planning were used, which could be supplemented by laboratory-based measures in future research. Although we tested a specific gene-to-brain-to-behavior

model, alternative models that could account for the pattern of observed correlations remain to be tested. A relatively large number of statistical tests were conducted. Procedures to minimize Type I error included examining a limited number of ROIs and behavioral measures based on earlier research findings, including relevant covariates, and describing effect sizes for statistically significant associations. Replication of results is needed.

The current study's findings suggest a possible brain structural mechanism, involving lower WM volume in the left OFC, which links the 10/10 *DAT1* genotype to impaired executive functioning, specifically in relation to planning goal-directed behavior. The novel finding that lower WM volume mediated the association between the *DAT1* genotype and an indicator of executive functioning supports the use of neuroimaging measures as an intermediate phenotype, which could ultimately inform the development of interventions that aim to improve executive functioning in youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- *DAT1* 10/10 (vs 9 carrier) was associated with lower orbitofrontal white matter (WM) volume
- Lower left orbitofrontal WM volume predicted difficulties in planning (executive function)
- *DAT1* 10/10 was linked with difficulties in planning through lower left orbitofrontal WM volume

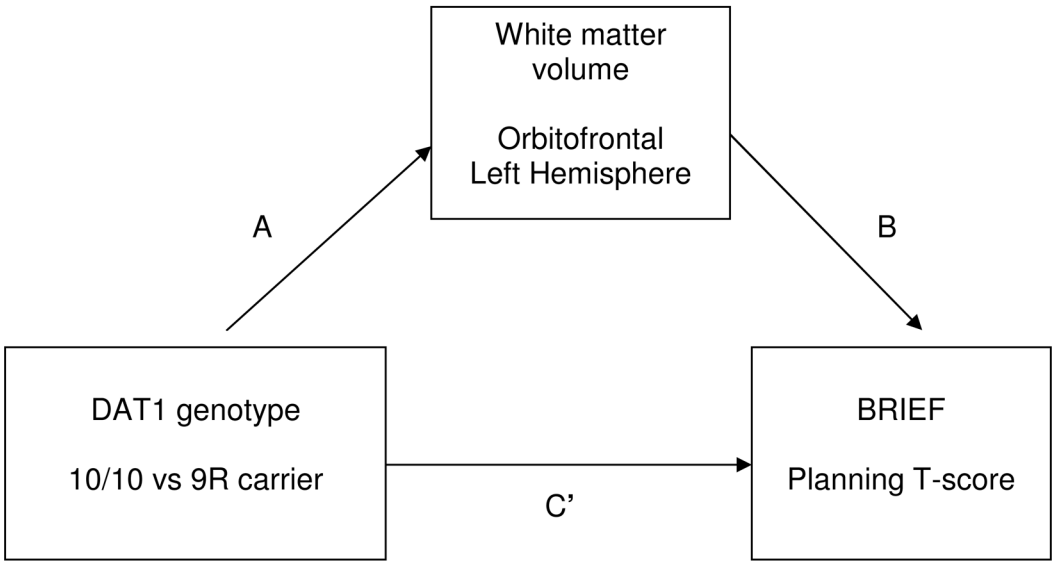

Figure 1.

Hypothesized mediation (indirect effects) model

Notes: n=38

10/10= DAT1 10R/10R homozygotes; 9R carrier= DAT1 10R/9R or 9R/9R

BRIEF= Behavior Rating Inventory of Executive Function-Self-Report Version

Table 1

Descriptive statistics for treatment and community subsamples

	TOTAL N=38		Treatment N=22		Community N=16	
Demographics	**n**	**%**	**n**	**%**	**n**	**%**
Female	16	42.1	9	40.9	7	43.8
Male	22	57.9	13	59.1	9	56.2
DAT1 genotype						
10/10	17	44.7	10	45.5	7	43.8
9 carrier	21	55.3	12	54.5	9	56.2
Baseline	Mean (SD)		Mean (SD)		Mean (SD)	
Age	16.6 (1.2)		16.8 (1.2)		16.3 (1.0)	
Socio-economic status (Hollingshead, 1975)	2.4 (1.0)		2.6 (1.1)		2.1 (0.8)	
WAIS Full Scale IQ	102.7 (13.5)		97.0 (12.3)		110.6 (11.2)**	
Planning T score	53.9 (13.1)		60.5 (11.3)		44.8 (9.4)**	
Barratt Impulsivity Scale score	69.2 (13.0)		76.0 (11.3)		59.9 (8.6)**	
Frequency of substance use (past 6-months)†						
Alcohol use	2.7 (2.0)		3.4 (1.9)		1.7 (1.8)**	
Marijuana use	3.5 (3.3)		5.5 (2.6)		0.7 (1.6)**	
Tobacco use	4.1 (3.6)		5.9 (3.1)		1.5 (2.6)**	
	n	%	n	%	n	%
Lifetime DSM-IV alcohol use disorder	15	39.5	14	63.6	1	6.2**
Alcohol Abuse	12	31.6	1	50.0	1	6.2
Alcohol Dependence	3	7.9	3	13.6	0	0.0
Lifetime DSM-IV cannabis use disorder	24	63.2	22	100.0	2	12.5**
Cannabis Abuse	18	47.4	16	72.7	2	12.5
Cannabis Dependence	6	15.8	6	27.3	0	0.0
Lifetime DSM-IV nicotine use disorder	7	18.4	0	0.0	7	31.8*
Lifetime DSM-IV psychopathology						
Conduct disorder	11	28.9	11	50.0	0	0.0**

	TOTAL N=38		Treatment N=22		Community N=16	
Demographics	**n**	**%**	**n**	**%**	**n**	**%**
Attention deficit hyperactivity disorder	10	26.3	9	40.9	1	6.3*
Major depression	9	23.7	8	36.4	1	6.3*
White matter volume	Mean (SD)		Mean (SD)		Mean (SD)	
Prefrontal volume	7.12 (0.44)		7.01 (0.43)		7.29 (0.41)*	
Prefrontal volume (excluding orbitofrontal)	5.72 (0.38)		5.62 (0.36)		5.87 (0.38)*	
Orbitofrontal volume	1.40 (0.10)		1.39 (0.10)		1.42 (0.10)	
Left hemisphere	0.68 (0.05)		0.68 (0.05)		0.69 (0.06)	
Right hemisphere	0.72 (0.05)		0.71 (0.06)		0.73 (0.05)	

Notes: Baseline N=38; SD= standard deviation.

†Frequency coded: 0=never used, 1=no use in the last 6-months, 2=used < once per month, 3= once per month, 4=2–3 times per month, 5=once per week, 6= 2–3 times per week, 7= 4–6 times per week, 8=daily;

*comparison of treatment vs community $p<0.05$;

**$p<0.01$

Table 2

Descriptive statistics for DAT1 10/10 homozygotes and 9R carriers

	10/10 n=17		9R carriers n=21	
Demographics	**n**	**%**	**n**	**%**
Female	8	47.1	8	38.1
Male	9	52.9	13	61.9
Substance use treatment	10	58.8	12	57.1
Community	7	41.2	9	42.9
Baseline	Mean (SD)		Mean (SD)	
Age	16.8 (1.2)		16.4 (1.2)	
Socio-economic status (Hollingshead, 1975)	2.6 (1.1)		2.2 (1.0)	
WAIS Full Scale IQ	105.4 (14.2)		100.6 (12.9)	
Planning T score	54.9 (12.6)		53.0 (13.6)	
Barratt Impulsivity Scale score	67.4 (13.4)		70.7 (12.8)	
Frequency of substance use (past 6-months)†				
Alcohol use	2.8 (2.3)		2.6 (1.9)	
Marijuana use	4.2 (3.5)		3.0 (3.1)	
Tobacco use	3.9 (3.4)		4.2 (3.9)	
	n	%	n	%
Lifetime DSM-IV alcohol use disorder	7	41.1	8	38.1
Alcohol Abuse	4	23.5	8	38.1
Alcohol Dependence	3	17.6	0	0.0
Lifetime DSM-IV cannabis use disorder	12	70.6	12	57.1
Cannabis Abuse	7	41.2	11	52.4
Cannabis Dependence	5	29.4	1	4.7
Lifetime DSM-IV nicotine use disorder	4	23.5	3	14.3
Lifetime DSM-IV psychopathology				
Conduct disorder	6	35.3	5	23.8
Attention deficit hyperactivity disorder	3	17.6	7	33.3
Major depression	5	29.4	4	19.0
White matter volume	Mean (SD)		Mean (SD)	
Prefrontal volume	6.94 (0.36)		7.27 (0.45)*	
Prefrontal volume (excluding orbitofrontal)	5.58 (0.31)		5.84 (0.40)*	
Orbitofrontal volume	1.37 (0.10)		1.43 (0.10)	
Left hemisphere	0.66 (0.05)		0.70 (0.05)**	
Right hemisphere	0.71 (0.05)		0.73 (0.06)	

Notes: Baseline N=38; SD= standard deviation.

†Frequency coded: 0=never used, 1=no use in the last 6-months, 2=used < once per month, 3=used once per month, 4=used 2–3 times per month, 5=used once per week, 6=used 2–3 times per week, 7=used 4–6 times per week, 8=daily

*comparison of 10/10 vs 9 carrier $p<0.05$;

** comparison of 10/10 vs 9 carrier p=0.01

Table 3

Partial correlations of DAT1 genotype, white matter volumes in regions of interest, and self-report measures

	DAT1 genotype	Prefrontal	Prefrontal (no orbitofrontal)	Orbitofrontal	Orbitofrontal Left Hemisphere	Orbitofrontal Right Hemisphere
DAT1 genotype		0.38*	0.35*	0.30	0.41*	0.15
Brief Planning T-score	−0.03	−0.08	−0.02	−0.26	−0.36*	−0.12
Barratt Impulsivity Scale score	0.23	0.03	0.06	−0.07	−0.07	−0.06

Notes: N=38,

* p<0.05

DAT1 genotype: 10/10 homozygote coded 0, 9R carrier coded 1

Partial correlations controlling for recruitment source (treatment vs community), sex, and age

Table 4

Parameter estimates for regression model testing indirect effects of regional white matter volume on the association between DAT1 genotype and BRIEF Planning T-score

		B	**SE**	**t**	**p**
A path	"mediator"=LH OF	0.05	0.02	2.81	0.01
B path		−76.01	33.46	−2.27	0.03
C path		−2.91	3.58	−0.81	0.42
C′ path		1.01	3.78	0.27	0.79
Controls	Recruitment source	8.91	8.08	1.10	0.28
	Sex	−4.98	3.26	−1.52	0.14
	Age	0.83	1.56	0.53	0.60
	IQ score	−0.29	0.14	−2.06	0.048
	Alcohol diagnosis	3.23	4.34	0.74	0.46
	Marijuana diagnosis	−0.30	8.39	−0.04	0.97

Model summary: R^2=0.59, $F(8, 29)$=5.13, p=0.0005

Notes: n=38

DAT1 genotype: 10R/10R coded 0, 9R carrier coded 1

B = unstandardized coefficient, SE=standard error. "Mediator"=intervening variable being tested.

LH OF=white matter volume in left hemisphere of orbitofrontal region of interest

Recruitment source: treatment coded 1, community coded 0

Sex: female coded 1, male coded 2

Alcohol diagnosis= lifetime DSM-IV alcohol use disorder, absent coded 0, present coded 1

Marijuana diagnosis=lifetime DSM-IV marijuana use disorder, absent coded 0, present coded 1

Replacing lifetime alcohol and marijuana diagnosis with frequency of alcohol and marijuana use in the past 6 months did not change the pattern of results; and alcohol and marijuana use frequency were not significant covariates.

A path (see Figure): independent variable (DAT1 genotype) to intervening variable (LH OF). B path: direct effect of intervening variable (LH OF) on dependent variable (Planning T-score). C path: Total effect of independent variable (DAT1 genotype) on dependent variable (Planning T-score). C′ path: Direct effect of independent variable (DAT1 genotype) on dependent variable (Planning T-score), after controlling for the intervening variable (LH OF). Controls: partial effect of control variables on dependent variable.