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Stimulant treatment history predicts frontal-striatal structural connectivity in adolescents with attention-deficit/hyperactivity disorder

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Abstract
Diffusion tensor imaging (DTI) has revealed white matter abnormalities in individuals with attention-deficit/hyperactivity disorder (ADHD). Stimulant treatment may affect such abnormalities. The current study investigated associations between long-term stimulant treatment and white matter integrity within the frontal-striatal and mesolimbic pathways, in a large sample of children, adolescents and young adults with ADHD. Participants with ADHD ($N=172$; mean age 17, range 9–26) underwent diffusion-weighted MRI scanning, along with an age- and gender-matched group of 96 control participants. Five study-specific white matter tract masks (orbitofrontal-striatal, orbitofrontal-amygdalar, amygdalar-striatal, dorsolateral-prefrontal-striatal and medialprefrontal- striatal) were created. First we analyzed case-control differences in fractional anisotropy (FA) and mean diffusivity (MD) within each tract. Second, FA and MD in each tract was predicted from cumulative stimulant intake within the ADHD group. After correction for multiple testing, participants with ADHD showed reduced FA in the orbitofrontal-striatal pathway ($p=0.010$, effect size$=0.269$). Within the ADHD group, higher cumulative stimulant intake was associated with lower MD in the same pathway ($p=0.011$, effect size$=-0.164$), but not with FA. The association between stimulant treatment and orbitofrontal-striatal MD was of modest effect size. It fell short of significance after adding

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ADHD severity or ADHD type to the model ($p=0.036$ and $p=0.094$, respectively), while the effect size changed little. Our findings are compatible with stimulant treatment enhancing orbitofrontal-striatal white matter connectivity, and emphasize the importance of the orbitofrontal cortex and its connections in ADHD. Longitudinal studies including a drug-naïve baseline assessment are needed to distinguish between-subject variability in ADHD severity from treatment effects.

1. Introduction

Diffusion tensor imaging (DTI) has revealed abnormalities in white matter integrity, or structural connectivity, in individuals with attention-deficit/hyperactivity disorder (ADHD) (for extensive reviews, see Van Ewijk et al., 2012; Konrad and Eickhoff, 2010). Multiple parameters of white matter integrity can be derived from DTI, including fractional anisotropy (FA) and mean diffusivity (MD). FA measures directionality of water diffusion and is typically high in organized structures such as densely packed white matter bundles, as water is more likely to diffuse along the axons rather than perpendicular to the axons. MD measures the amount of water diffusion in any direction and is high in areas with few natural barriers to water diffusion, such as the ventricles. Less commonly reported are axial diffusivity (AD; measuring water diffusion along the main diffusion direction) and radial diffusivity (RD; measuring water diffusion perpendicular to the main diffusion direction). It is important to note that the interpretation of altered diffusion parameters is complex, especially in psychiatric disorders where changes are mostly subtle. Increased MD and decreased FA are often regarded as indications of impaired or decreased structural connectivity (Thomason and Thompson, 2011), but the neuropathological processes underlying such changes are largely unknown (Jones et al., 2013).

To date, findings on structural connectivity in individuals with ADHD compared to healthy controls have been mixed. Whereas some studies reported decreased FA and/or increased MD in individuals with ADHD compared to controls (Ashtari et al., 2005; Cao et al., 2010; Hamilton et al., 2008; Pavuluri et al., 2009), suggesting decreased structural connectivity in ADHD, others found increased FA and/or decreased MD (Li et al., 2010; Peterson et al., 2011; Silk et al., 2009b). Null findings of no changes in structural connectivity have also been reported (Silk et al., 2009a, 2009b). In recent work from our group, van Ewijk et al. found widespread FA reduction in both participants with ADHD and their unaffected siblings, compared to healthy control participants, suggesting that reduced FA may represent a genetic vulnerability to ADHD. In addition, higher FA and lower MD were observed in more severely affected compared to less severely affected individuals with ADHD, which may reflect a second, distinct, mechanism associated with ADHD symptom severity (Van Ewijk et al., 2014). Inconsistent findings in previous studies may partially be explained by these two seemingly opposing mechanisms being at play.

Inconsistent findings may also reflect differences between the ADHD samples with regard to stimulant treatment history. Individuals with ADHD often take stimulants for prolonged periods of time. Studies investigating long-term stimulant treatment effects on brain structure have almost exclusively focused on gray matter and/or subcortical structures. Several such studies (but not all) have suggested structural normalization with long-term stimulant treatment (Nakao et al., 2011; Shaw et al., 2009; Sobel et al., 2010), i.e. abnormalities typically associated with ADHD were smaller or absent in individuals with ADHD who had been treated with stimulants. Stimulant-induced changes in gray matter might be accompanied by changes in white matter.

Only few studies have explored long-term stimulant effects on white matter integrity quantified by DTI in individuals with ADHD. One study applied deterministic tractography to delineate the frontal-striatal tracts, and compared average FA within these tracts between children with a relatively short versus a relatively long history of stimulant treatment (De Zeeuw et al., 2012). No differences between the two groups were detected. Small sample size ($n=13$ per group) and using average FA across all frontal-striatal tracts as the primary outcome measure limits the interpretation of this negative finding. A second study used both tract-based spatial statistics (TBSS) and whole-brain deterministic tractography, to perform a hypothesis-free search for differences in FA or MD between young treatment-naïve children with ADHD, children with ADHD who had been treated with stimulants, and healthy control children ($n=16$, $n=24$, and $n=26$, respectively) (De Luis-García et al., 2015). Stimulant treatment was associated with decreased MD in several major white matter bundles, including the uncinate fasciculus connecting the medial temporal limbic structures to the orbitofrontal cortex. Importantly, differences in pre-treatment ADHD severity between children with and without stimulant treatment were not assessed, and may have confounded results. In a prior study of our own group on the association between structural connectivity and symptom severity, results did not change when history of stimulant treatment (treated/untreated) was taken into account (Van Ewijk et al., 2014).

In the current report, we investigated the association between stimulant treatment history and structural connectivity in a large sample of children, adolescents and young adults with ADHD. This investigation adds to the previous study from our group in two ways. First, in the current study we assessed stimulant treatment history to detail, and performed dimensional analyses of lifetime cumulative stimulant dose. Second, we applied a sensitive hypothesis-driven region-of-interest (ROI) approach based on the dopaminergic working mechanism of stimulants. Stimulants generate their clinical effects, at least partially,