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Double-dissociation between the mechanism leading to impulsivity and inattention in Attention Deficit Hyperactivity Disorder: A resting-state functional connectivity study

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ABSTRACT

Two core symptoms characterize Attention Deficit Hyperactivity Disorder (ADHD) subtypes: inattentiveness and hyperactivity–impulsivity. While previous brain imaging research investigated ADHD as if it was a homogenous condition, its two core symptoms may originate from different brain mechanisms. We, therefore, hypothesized that the functional connectivity of cortico-striatal and attentional networks would be different between ADHD subtypes. We studied 165 children (mean age 10.93 years; age range, 7–17 year old) diagnosed as having ADHD based on their revised Conner's rating scale score and 170 typical developing individuals (mean age 11.46 years; age range, 7–17 year old) using resting state functional fMRI. Groups were matched for age, IQ and head motion during the MRI acquisition. We fractionated the ADHD group into predominantly inattentive, hyperactive–impulsive and combined subtypes based on their revised Conner's rating scale score. We then analyzed differences in resting state functional connectivity of the cortico-striatal and attentional networks between these subtypes. We found a double dissociation of functional connectivity in the cortico-striatal and ventral

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attentional networks, reflecting the subtypes of the ADHD participants. Particularly, the hyperactive–impulsive subtype was associated with increased connectivity in cortico-striatal network, whereas the inattentive subtype was associated with increased connectivity in the right ventral attention network. Our study demonstrated for the first time a right lateralized, double dissociation between specific networks associated with hyperactivity–impulsivity and inattentiveness in ADHD children, providing a biological basis for exploring symptom dimensions and revealing potential targets for more personalized treatments.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neuro-developmental condition affecting approximately 8% of school-aged children (Bloom, Cohen, & Freeman, 2011) and 4% of adults (Kessler et al., 2006). Originally described in 1798 (Crichton, 1798; reprinted in Crichton, 2008) ADHD patients 'incessantly withdrawn from one impression to another' and 'excites such a degree of anger as borders on insanity' (for an historical review see Lange, Reichl, Lange, Tucha, & Tucha, 2010). These two core symptoms are interpreted as inattention and hyperactivity–impulsivity in the DSM5 (American Psychiatric Association, 2013) and can be of variable severity. Although these symptoms frequently come together, their expression can be unbalanced leading to the division of ADHD into three clinical subtypes: *predominantly inattentive*, *predominantly hyperactive–impulsive*, and *combined* (American Psychiatric Association, 1994). Whether the brain mechanism leading to these subtypes is different remains to be clarified in order to enhance personalised treatment.

The efficacy of current drug treatments is predominantly mediated by their effects on the dopaminergic, and/or noradrenergic systems. They are effective in many patients, but approximately 1/3 fail to respond – predominantly those with the 'inattentive' subtype (Hazell et al., 2011; Spencer et al., 1995; Weiss et al., 2005). This finding suggests that in addition to being clinically heterogeneous (Barkley, Fischer, Smallish, & Fletcher, 2002; Biederman et al., 2006); ADHD subtypes may be modulated by different brain systems with a variable response to pharmacological treatments.

There is increasing evidence that ADHD is associated with abnormalities in specific brain regions; and particularly dorsal anterior midcingulate cortex (daMCC), prefrontal cortex, parietal cortex, striatum, and cerebellum (see Bush, 2011; Cortese et al., 2012 for review). The significance of these areas is that they are involved with attention, executive function, motor control, response inhibition, and working memory. However, rather than a mosaic of functionally specialized areas, the human mind is believed to emerge from the coordinated activity of distant but anatomically interconnected regions. Advances in brain imaging have enabled us to study anatomical and functional connectivity within these networks *in vivo*.

One of the most consistent findings from studies of *anatomical* connectivity, in children and adolescents with ADHD, is reduced fractional anisotropy (Hamilton et al., 2008; Konrad et al., 2010; Luders et al., 2009; Makris et al., 2008) of fronto-striatal tracts (within the cortico-striatal network) and fronto-parietal tracts (within the ventral and dorsal attention network). These findings have been supported by some (Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Dickstein, Bannon, Castellanos, & Milham, 2006; Rubia, 2011) but not all studies of *functional* connectivity (Tian et al., 2006; Uddin et al., 2008).

Studies of *functional* connectivity have employed standard, task-activation, *f*MRI (task-*f*MRI), or resting-state *f*MRI (rs-*f*MRI). A key advantage of rs-*f*MRI is that participants are not required to focus on an explicit task. This is particularly beneficial in ADHD, where compliance and attention during scanning may be problematic, and confound interpretation of results. The underlying principle of rs-*f*MRI is that functional connectivity between brain regions can be successfully mapped by correlating spontaneous low-frequency (<.1 Hz) fluctuations in blood oxygenation level dependent (BOLD) signal at rest (Fox & Raichle, 2007). Previous rs-*f*MRI studies of ADHD have reported both hypo- and hyper-activation of fronto-striatal, fronto-parietal and other networks (see Konrad et al., 2010 for review). Also, whole brain voxel-based analyses revealed decreased entropy (Sokunbi et al., 2013) and decreased amplitude of low-frequency fluctuation (An, Cao, Sui, et al., 2013; Zang et al., 2007) in the frontal and the occipital lobes. These inconsistencies are likely to be due to a combination of methodological factors, including the method of analysis employed, micro-movements (Fair et al., 2012), variability in the subtype diagnosis and the age range of subjects. The small size of clinical samples has also been a significant limitation of the majority of imaging studies of ADHD to date. An important consequence of this has been the scarcity of studies with the statistical power to analyse ADHD as a heterogeneous condition. Therefore there has been a need for larger studies with sufficient power to fractionate ADHD into its clinical subtypes.

In the present study we accessed a recent, unrestricted public release, dataset of rs-*f*MRI images from 255 children and adolescents with ADHD (ages: 7–21 years old).[2] This has provided a valuable opportunity to analyse whether the

[2] ADHD-200 Sample; http://fcon_1000.projects.nitrc.org/indi/adhd200.