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Research report

The executive control network and symptomatic improvement in attention-deficit/hyperactivity disorder

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ABSTRACT

Background: One neurodevelopmental theory hypothesizes remission of attention-deficit/hyperactivity disorder (ADHD) to result from improved prefrontal top-down control, while ADHD, independent of the current diagnosis, is characterized by stable non-cortical deficits (Halperin & Schulz, 2006). We tested this theory using resting state functional MRI (fMRI) data in a large sample of adolescents with remitting ADHD, persistent ADHD, and healthy controls.

Methods: Participants in this follow-up study were 100 healthy controls and 129 adolescents with ADHD combined type at baseline (mean age at baseline 11.8 years; at follow-up 17.5 years). Diagnostic information was collected twice and augmented with magnetic resonance imaging (MRI) scanning at follow-up. We used resting state functional connectivity (RSFC) of the executive control network to investigate whether improved prefrontal top-down control was related to a developmental decrease in ADHD symptoms. In addition,

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Remission
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we tested whether non-cortical RSFC, i.e., cerebellar and striatal RSFC, was aberrant in persistent and/or remittent ADHD compared to controls.

Results: Higher connectivity within frontal regions (anterior cingulate cortex) of the executive control network was related to decreases in ADHD symptoms. This association was driven by change in hyperactive/impulsive symptoms and not by change in inattention. Participants with remitting ADHD showed stronger RSFC than controls within this network, while persistent ADHD cases exhibited RSFC strengths intermediate to remittent ADHD cases and controls. Cerebellar and subcortical RSFC did not differ between participants with ADHD and controls.

Conclusions: In line with the neurodevelopmental theory, symptom recovery in ADHD was related to stronger integration of prefrontal regions in the executive control network. The pattern of RSFC strength across remittent ADHD, persistent ADHD, and healthy controls potentially reflects the presence of compensatory neural mechanisms that aid symptomatic remission.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) has a variable clinical course. While 30–50% of children diagnosed with ADHD exhibit symptomatic improvement throughout development (Biederman, Mick, & Faraone, 2000), others show persistent ADHD behavior into adulthood (Faraone, Biederman, & Mick, 2006). Adult ADHD has a substantial impact on the public health system as it has been associated with impairments in multiple domains including family functioning, work, and leisure time (Biederman et al., 2006; Kessler et al., 2006). Few behavioral, environmental, and neurocognitive factors were found to predict clinical outcome (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011; Kessler et al., 2005; van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013). However, using brain measures we might be able to identify the mechanisms underlying remittent and persistent ADHD trajectories.

According to the neurodevelopmental theory formulated by Halperin and Schulz (2006) ADHD is characterized by relatively stable non-cortical dysfunctions. This theory is primarily based on evidence from cognitive investigations showing that ADHD is related to deficits in so-called lower cognitive mechanisms, as demonstrated by increased variability of reaction times in more automatic and less effortful tasks (Bedard, Trampush, Newcorn, & Halperin, 2010; Halperin, Trampush, Miller, Marks, & Newcorn, 2008). Recent magnetic resonance imaging (MRI) studies reporting on the cerebellum and subcortical structures including caudate, nucleus accumbens, and putamen, have provided additional neurobiological support for the hypothesized non-cortical dysfunctions in ADHD (Frodl & Skokauskas, 2012; Hart, Radua, Mataix-Cols, & Rubia, 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Stoodley, 2014; Valera, Faraone, Murray, & Seidman, 2007).

Importantly, stable non-cortical dysfunctions are not only hypothesized in persistent, but also in symptomatically improved (i.e., remittent) ADHD cases. Indeed, a recent functional MRI (fMRI) study in adults with childhood ADHD reported that reaction time task performance, which relies on non-cortical regions, was not related to symptom recovery (Clerkin et al., 2013). Furthermore, decreased activation in the thalamus was found independent of current diagnosis. Additional support was provided by structural MRI studies that reported non-progressive reductions in striatal surface area in ADHD (Shaw et al., 2014) and cerebellar volume reductions in remittent ADHD (Mackie et al., 2007), indicating persistent non-cortical deficits. However, also evidence has been reported that is in conflict with the developmental theory and points to absence of structural basal ganglia deficits in adults with ADHD (Frodl & Skokauskas, 2012; Nakao et al., 2011) and findings indicating volumetric normalization with aging (Castellanos et al., 2002).

Next to non-cortical dysfunctions, cortical dysfunctions have also been related to ADHD pathology. One of the most replicated findings is abnormal structure and functioning of the prefrontal cortex (PFC) (Cortese et al., 2012; Hart et al., 2012). Within the neurodevelopmental theory, the development of PFC has been hypothesized to parallel improvements in ADHD symptoms. Such PFC compensation would be reflected in improved performance on effortful executive functioning tasks that depend on PFC functioning. Indeed, better performance on working memory, inhibition, and, sustained attention tasks has been reported in remittent compared to persistent ADHD (Bedard et al., 2010; Fischer, Barkley, Smallish, & Fletcher, 2005; Halperin et al., 2008). However, other studies were unable to document improvements in performance of executive function tasks (Biederman et al., 2009; Mick et al., 2011; van Lieshout et al., 2013).

Measures of brain structure and function might augment our insight into the mechanisms underlying remission of ADHD by revealing normalization of brain function or by revealing compensatory changes (Fassbender & Schweitzer, 2006; Giedd & Rapoport, 2010; Rubia, 2002; Shaw, Gogtay, & Rapoport, 2010). Accordingly, previous studies have linked diagnostic outcome to the status of the PFC. ADHD outcome has been associated with the developmental trajectories of