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Altered neural connectivity during response inhibition in adolescents with attention-deficit/hyperactivity disorder and their unaffected siblings

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ABSTRACT

Introduction: Response inhibition is one of the executive functions impaired in attention-deficit/hyperactivity disorder (ADHD). Increasing evidence indicates that altered functional and structural neural connectivity are part of the neurobiological basis of ADHD. Here, we investigated if adolescents with ADHD show altered functional connectivity during response inhibition compared to their unaffected siblings and healthy controls.
Methods: Response inhibition was assessed using the stop signal paradigm. Functional connectivity was assessed using psycho-physiological interaction analyses applied to BOLD time courses from seed regions within inferior- and superior frontal nodes of the response inhibition network. Resulting networks were compared between adolescents with ADHD ($N = 185$), their unaffected siblings ($N = 111$), and controls ($N = 125$).
Results: Control subjects showed stronger functional connectivity than the other two groups within the response inhibition network, while subjects with ADHD showed relatively stronger connectivity between default mode network (DMN) nodes. Stronger connectivity within the response inhibition network was correlated with lower ADHD severity, while stronger connectivity with the DMN was correlated with increased ADHD severity. Siblings showed connectivity patterns similar to controls during successful inhibition and to ADHD subjects during failed inhibition. Additionally, siblings showed decreased connectivity with the primary motor areas as compared to both participants with ADHD and controls.
Discussion: Subjects with ADHD fail to integrate activation within the response inhibition network and to inhibit connectivity with task-irrelevant regions. Unaffected siblings show similar alterations only during failed stop trials, as well as unique suppression of motor areas, suggesting compensatory strategies. These findings support the role of altered functional connectivity in understanding the neurobiology and familial transmission of ADHD.

1. Introduction

Response inhibition, the process of actively suppressing an ongoing or inappropriate response, is considered one of the main cognitive control deficits underlying ADHD (Alderson et al., 2007; Goos et al., 2009; Crosbie et al., 2008, 2013). However, a recent meta-analysis has shown only moderate effect sizes and large heterogeneity in response inhibition performance in patients with ADHD, with half of the subjects showing no performance deficits (Lipszyc and R. Schachar, 2010). Brain activation during response inhibition, as measured by functional magnetic resonance imaging (fMRI), appears to be a more sensitive measure, as indicated by research in children (e.g. 12–14), adolescents

Abbreviations: ADHD, attention deficit/hyperactivity disorder; CD, conduct disorder; DMN, default mode network; GEE, generalized estimating equations; ICV, intraindividual coefficient of variance; ODD, oppositional defiant disorder; RD, reading disorder; ROI, region of interest; SSRT, stop-signal reaction time; SST, Stop-signal task; SI, supplementary information; WM, white matter.

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(Katya Rubia et al., 2005), and adults with ADHD (Cubillo et al., 2011; Mulligan et al., 2011), including a study by our group (Van Rooij et al., 2014). These studies demonstrated that alterations within the neural networks responsible for cognitive control, inhibition, and attention can be found in the absence of behavioral response inhibition deficits. These alterations have been found even in unaffected siblings of subjects with ADHD (Van Rooij et al., 2014), adolescents with subthreshold ADHD (Whelan et al., 2012), and adults with ADHD (Cubillo et al., 2010).

Neuroimaging studies of response inhibition in healthy subjects have identified a highly interconnected neural network. This involves nodes from the frontal–striatal network such as the inferior frontal gyrus, pre-supplementary motor area, basal ganglia, and suprathalamic nucleus (A.R. Aron et al., 2007a,b; Zandbelt et al., 2013a,b; Hampshire et al., 2010; Majid et al., 2012; Sebastian et al., 2012; Swick et al., 2011; Verbruggen and G. Logan, 2008), as well as nodes from the frontal–parietal network including supramarginal and temporal/parietal areas (C. Fassbender et al., 2006; Chambers et al., 2009; Hugh Garavan et al., 2006; Simmonds et al., 2008). Functionally, the inferior frontal gyrus is involved in salience processing and initiation of the inhibition signal (A.R. Aron et al., 2007b; Cai et al., 2011; Chevrier et al., 2007; Hampshire et al., 2010; N. Swann et al., 2009a). This is thought to be the most likely site for integration of response inhibition and higher order cognitive control processes, executed from the superior frontal areas (A.R. Aron, 2011). The pre-supplementary motor area and subcortical regions on the other hand are thought to be involved in the execution of the stop processes (A.R. Aron et al., 2007a; Cai et al., 2012; Chao et al., 2009; de Wit et al., 2012; N.C. Swann et al., 2012; Tabu et al., 2011), whereas the parietal areas are thought to reflect attentional redirection and task-set maintenance during response inhibition (C. Fassbender et al., 2006; Chambers et al., 2009).

While each of these nodes plays a distinct role in response inhibition, the overall inhibition efficiency may depend on the degree of integration between the different parts of the network. Diminished functional connectivity between the left and right inferior frontal gyrus, caudate/thalamus, cingulate gyrus, and temporal/parietal regions during a response inhibition task has previously been found in adults with ADHD as compared to healthy controls (Cubillo et al., 2010). Additionally, evidence from structural (De La Fuente et al., 2013; N.C. Swann et al., 2012) and resting-state network studies (D.A. Fair et al., 2010; Mennes et al., 2011; Tian et al., 2006) have supported the necessity of network integration during response inhibition and have confirmed altered patterns of connectivity in subjects with ADHD. It is, therefore, specifically interesting to investigate to what extent the functional connectivity is altered in subjects with neural hypoactivation within the response inhibition network.

In a previous paper we showed decreased neural activation during response inhibition in left inferior frontal, left superior frontal, and bilateral temporal/parietal areas in adolescents with ADHD and their unaffected siblings as compared to healthy controls (Van Rooij et al., 2014). The primary aim of the current study was to investigate whether subjects with ADHD would also show decreased functional connectivity between these nodes of the response inhibition network and whether the degree of hypo-connectivity would be linked to ADHD severity. Secondarily, we aimed to investigate the familial nature of functional connectivity by comparing subjects with ADHD not only with healthy controls, but also with their unaffected siblings. Since unaffected siblings of subjects with ADHD share on average half of the genetic risk factors with their affected siblings, we expected similar but less extensive decreases in functional connectivity in this group (Bidwell et al., 2007; Crosbie et al., 2008, 2013). This would support the familial nature of decreased functional connectivity during response inhibition and its possible use as an endophenotype in ADHD. Finally, we aimed to investigate neural connectivity related to compensatory strategies in both subjects with ADHD and unaffected siblings. Previous investigations had suggested that subjects with ADHD may be able to recruit alternative neural recourses to compensate for deficits in prefrontal functioning (Catherine Fassbender and Schweitzer, 2006), although we previously did not encounter such compensatory mechanisms in our study sample with regard to neural activation (Van Rooij et al., 2014). We expected that compensation for deficits in neural connectivity within the response inhibition network might occur by recruiting compensatory resources in other brain regions, leading to increased connectivity with these areas.

2. Methods and materials

2.1. Participants

All subjects participated in the NeuroIMAGE project, the Dutch follow-up of the International Multicenter ADHD Genetics (IMAGE) study. Details about ethics approval, recruitment, assessment, and the general testing procedures can be found in the general methods and design paper of the NeuroIMAGE project (Von Rhein et al., 2014).

In short, ADHD diagnosis was based on semi-structured interviews (the Schedule for Affective Disorders and Schizophrenia for School-Age Children [K-SADS] (C. Kaufman et al., 1997)) as well as the Conners ADHD questionnaires (Conners et al., 1998a,b). Probands with ADHD had to have six or more hyperactive/impulsive and/or inattentive symptoms according to DSM-IV criteria (American Psychiatric Association, 2000); unaffected siblings and unrelated controls had to have less than two symptoms overall, based on a structured psychiatric interview (K-SADS) and Conners questionnaires.

Inclusion criteria for MRI participation consisted of the absence of claustrophobia and any metal in the body. Informed consent was acquired from all participants, with parents supplying consent for participants less than 16 years old. Subsequently, 208 participants with ADHD, 116 unaffected siblings, and 129 healthy controls successfully performed the stop signal task within an MRI scanner. Of these, 21 participants only completed three out of four response inhibition runs (12 subjects with ADHD and six unaffected siblings). Six participants were excluded after reaching an accuracy of <70% on the go-trials, indicating inadequate performance on the task and leaving an insufficient number of trials to estimate inhibition measures (four subjects with ADHD, two healthy controls). Eleven participants were removed after excessive movement (>3 mm within a single run) in the scanner (nine subjects with ADHD, one healthy control). Sixteen participants were excluded due to incidental neuroradiological findings. This led to a final inclusion of 185 subjects with ADHD, 111 unaffected siblings, and 124 controls in our analyses (see Table 1).

2.2. Stop signal task

A visual version of the stop signal task (Logan et al., 1984) was used to measure response inhibition during fMRI acquisition. In this task, participants had to respond as quickly as possible to a go-stimulus by left or right button press, unless shortly after presentation it was followed by a stop signal, in which case they were to withhold their response (25% of trials). The task difficulty was adaptive, meaning delays between the go- and stop stimulus were adjusted by 50 ms after every failed or successful response, leading to an approximately 50% success rate on the stop-trials for all subjects (except for the aforementioned six removed from the data). The task consisted of two practice blocks and four test blocks, each consisting of 60 trials.

The Stop Signal Reaction Time (SSRT) was the main measure of response inhibition efficiency, calculated by subtracting the eventual delay between the go and stop signals. Secondary task outcome measures were the intraindividual coefficient of variation (ICV; derived by dividing the reaction time variance by the mean reaction time), and the total number of errors. We included both omission and commission errors on go-trials in the error scores, since insufficient numbers of either event occurred to model them separately. Both secondary