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# Impairment of fronto-striatal and parietal cerebral networks correlates with attention deficit hyperactivity disorder (ADHD) psychopathology in adults — A functional magnetic resonance imaging (fMRI) study

Marc F. Schneider[a,*,1], Christoph M. Krick[b], Wolfgang Retz[a], Georges Hengesch[a], Petra Retz-Junginger[a], Wolfgang Reith[b], Michael Rösler[a]

[a]Neurocentre, Institute for Forensic Psychology and Psychiatry, Saarland University Hospital, Homburg, Germany
[b]Neurocentre, Department of Neuroradiology, Saarland University Hospital, Homburg, Germany

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a common, genetically transmitted common childhood-onset disorder with a high rate of persistence in adulthood. Although many studies have shown anatomical and functional abnormalities in children and adolescents, studies with adult patients are rare. Nineteen adults with ADHD (11 ADHD, combined type; 8 ADHD, partially remitted) and 17 controls were included in this functional magnetic resonance imaging (fMRI) study. Brain activation was investigated with a continuous performance test (CPT). Impaired activation of a fronto-striatal and a parietal attentional network was observed during the NoGo condition in ADHD subjects. Correlations of reduced activity of the caudate nuclei, the anterior cingulate cortex, and parietal cortical structures, as well as increased activity in the insular cortex, with inattention and impulsivity symptom scores were found. The activation patterns were similar to those known from children and adolescents with ADHD. In conclusion we found not only a widespread dysfunction of brain regions that are involved in cognitive processing in adults with ADHD compared with controls, but also correlations between symptom severity and dysfunction of neuronal systems across adult subjects with a history of ADHD in childhood but whose symptoms did (persistent ADHD) and did not (not persistent ADHD) qualify for a full diagnosis of ADHD in adulthood.
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## 1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common childhood-onset disorder characterized by inattention, hyperactivity and impulsivity (Wender, 1995). According to the dimensional character of ADHD psychopathology, this condition has been suggested to be the extreme variant of a psychopathological continuum rather than a distinct disorder. Follow-up studies show that up to 60% of patients suffering from this disorder still show some or all of the ADHD characteristics as adults (Barkley, 2002). A cross-national prevalence of 3.4% for adult ADHD has been reported (Fayyad et al., 2007). Regarding the negative impact of ADHD concerning functional impairment and social outcome, and the need for optimizing diagnosis and treatment in adulthood, there is high interest in understanding the pathophysiological mechanisms in ADHD across the lifespan.

Structural and functional imaging data are mainly based on studies with ADHD children (Sowell et al., 2003; Pliszka et al., 2006). Studies with functional neuroimaging techniques performed with ADHD children suggest dysfunction of the ventral and dorsolateral prefrontal cortex, the anterior cingulate, insula, amygdala, hippocampus, and ventral striatum (Ernst et al., 2002; Elliott et al., 1999, 2000; Rogers et al., 1999; Knutson et al., 2001; Bussey et al., 1997; Schultz, 1999). In addition, it has been reported that methylphenidate, which is highly effective in the treatment of ADHD and which exerts its effects via dopaminergic pathways, was able to normalize striatal circuitry function and could improve frontal activation in children and adolescents with ADHD (Vaidya et al., 1998; Shafritz et al., 2004).

In detail, imaging data seem to be somewhat divergent and suggest that many brain regions are involved in the pathophysiology of ADHD, which might be at least partially due to small samples investigated and different neuropsychological paradigms applied. However, there is converging evidence from these studies that behavioural and cognitive problems associated with ADHD are mainly associated with dysfunction of fronto-striatal regions or mainly in the forebrain located regions that influence inhibitory control mechanisms (Durston et al., 2002).

In adults with ADHD marked reduction of global metabolism in both hemispheres (Zametkin et al., 1990) and also diminished dopaminergic uptake in the left and medial prefrontal cortex have been reported (Ernst et al., 1998). Similar to findings in childhood ADHD, it has been shown that prefrontal cortex, anterior cingulate cortex and basal ganglia

* Corresponding author. Neurocentre – Saarland University Hospital, Building 90.3, 66421 Homburg/Saar, Germany. Tel.: +49 6841 1626350; fax: +49 6841 1626335.
*E-mail address:* MSchneider@GGZNML.NL (M.F. Schneider).
[1] Present address: Vincent van Gogh Institute for Psychiatry, Centre of Excellence for Neuropsychiatry; 5803 AC Venray, The Netherlands.

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are also involved in adult ADHD (Bush et al., 1999; Ernst et al., 2003; Zametkin et al., 1990). In a functional magnetic resonance imaging (fMRI) study, Bush et al. (1999) showed that specific regions of Anterior Cingulate Cortex (ACC), which have been shown to be involved in attention focusing and mediation of response selection were disturbed in patients with ADHD, but a frontostriatal-insular network was activated instead.

The literature provides evidence for a negative correlation of ventro-striatal activity with impulsivity and hyperactivity in adolescents and adults with ADHD (Scheres et al., 2007, Ströhle et al., 2008). ADHD patients can also overreact in defined cerebral regions in response to reward outcomes (Ströhle et al., 2008). Thus, recent imaging data underline the central role of fronto-striatal circuits in ADHD, including the orbitofrontal, mesial and lateral prefrontal brain regions (Ernst et al., 2003; Durston et al., 2003; Rubia et al., 1999). Bush et al. (2008) pointed out the importance of the dorsal anterior midcingulate cortex, which plays a key role in cognition, attention, target detection, motor control, error detection and feedback-based decision making; these investigators found using fMRI that methylphenidate administration in adults with ADHD was able to reverse hypofunction in this area.

Due to the still limited number of studies with adults with ADHD and the lack of follow-up investigations of ADHD children, it remains unclear whether disturbed network activation differs between ADHD children and adults and whether clinical remission of ADHD psychopathology runs parallel to normalization of brain function. It should be considered that adults with ADHD might be able to invoke compensatory mechanisms that are not yet present in ADHD children.

In this study we aimed to investigate activation patterns of attentional networks in adults with ADHD. Due to the dimensional character of the disorder and the decline of symptoms in a considerable proportion of patients with age, we hypothesized that compared to controls there might be not only different activation patterns in ventro-striatal and parietal cortex, but also correlations between symptom severity and brain dysfunction across adult subjects who met criteria for childhood ADHD, and whose symptoms did (persistent ADHD) and did not (not persistent ADHD) qualify for a full diagnosis of ADHD in adulthood.

## 2. Methods

### 2.1. Subjects

Adult patients were recruited from a specialized ADHD outpatient unit of the Neurocenter located at the Saarland University Hospital. ADHD was diagnosed according to DSM-IV criteria after careful clinical investigation. None of the participants of the study had previously received any kind of stimulant medication. They were diagnosed for the first time with ADHD. All participants of the study were right handed and without any medication. Subjects had no other psychiatric axis I disorder beside ADHD and no history of any CNS disorder in the 6 months before entering the study. SKID I interviews (Wittchen et al., 1997) were used to exclude relevant psychiatric and neurological disorders. IQ was assessed by use of the multiple-choice vocabulary test (MWT-B), which is a verbal test with German norms (Lehrl, 1995).

Only ADHD patients with a total score of 30 or more on the German-validated form of the Wender Utah Rating Scale (WURS-k; Retz-Junginger et al., 2003) participated in this study, in order to ensure for childhood onset of ADHD symptoms. According to former validation studies, scores above this cut-off are highly indicative for childhood ADHD. Quantification of current ADHD symptoms according to DSM-IV was performed using a standardized and validated self-rating scale for adults (ADHD-SR; Rösler et al., 2004, 2008). The ADHD-SR consists of 18 items according to DSM-IV ADHD symptoms, which are rated on a 0–3 Likert scale. The maximum total score is 54 points, those of the inattention subscale 27 (9 items), of the impulsivity subscale 12 (4 items), and of the hyperactivity subscale 15 (5 items), respectively. ADHD-SR total and subscores were used for further correlation analyses of brain activations in the fMRI procedures.

The term “not persistent ADHD” was used for patients with childhood ADHD who were partially remitted on the syndromatical level as discussed by Biederman et al. (2000). These patients no longer satisfied full diagnostic criteria according to DSM-IV but still showed symptoms of ADHD and functional impairment.

### 2.2. Continuous performance test (CPT)

According to Barkley (1997), the fundamental deficit in individuals with ADHD is one of self-regulation and the control over behavioral inhibition. It has been argued that this results primarily from frontal lobe dysfunction and not because of adverse environmental conditions. According to this concept, forms of executive dysfunction, including working memory, internalization of speech, sense of time, and goal-directed behavior, are secondary psychological and functional problems of impulse control deficit and frontal brain plays a crucial role in its regulation. Therefore, the CPT NoGo condition was chosen as the primary target stimulus in statistical analyses.

The continuous performance test (CPT) is conceptualized as investigating sustained attention, vigilance and inhibitory control (Rosvold et al., 1956; Fallgatter et al., 1997). Briefly, a pseudorandom sequence of letters was presented 420 ms each. Subjects were instructed to push a button of a MRI compatible optical fiber pad, if the letter ‘O’ (predatory condition) was immediately followed by the letter ‘X’ (Go condition), but not when another letter than ‘X’ followed the ‘O’ (NoGo condition). In neurophysiological studies a robust physiological frontalization of the brain electrical field during the NoGo condition and reduced frontal brain activity in ADHD children and adults has been shown (Fallgatter et al., 1997, 2004, 2005). CPTs with low rates of signal probability would likely demonstrate different relationships with ADHD symptoms and symptom domains (Conners, 1994). But there is a controversial discussion over which CPT gives the best correlates with the ADHD symptoms (Corkum and Siegel, 1993, 1995; Koelega, 1995). In a study examining performance on measures over time, increased mean hit reaction time and standard errors over time were highly associated with most ADHD symptoms (Epstein et al., 2003). In summary there is no “gold standard” version of the CPT that best fits with ADHD symptoms or subtypes.

The projection of the letters was performed by a computer-guided beamer on a screen while participants watched the screen through a mirror on the head coil positioned above their eyes. The speed of presentation for each letter in the CPT was set near the limit of overall cognitive attention and reaction time capacity. Thus, drifting away of the attention from the task presentation was minimized.

Given the fact that eye fields were limited through a mirror system and the narrowed projection into a relatively dark environment, there were few possibilities to lose the optical focus. An automatic eye tracking system was not used.

During fMRI recordings, 30 Go events and 30 NoGo events were presented in a pseudorandomized manner. A total of 285 sequences were recorded.

### 2.3. Magnetic resonance imaging

#### 2.3.1. Anatomical sequences

Imaging was performed with a 1.5 T Siemens Magnetom Vision whole body scanner system. A standard head coil was used. Head position was stabilized with vacuum cushion and fixed with adhesion bands to minimize head movements.

For each subject T2-weighted anatomic sequences (data matrix $256 \times 256$ voxel, $0.9375^2$ mm$^2$ pixel size, 5 mm slice thickness, TR 4.6 s, TE 99 ms) in plane with the echo planar images were performed. Thus, functional images could be aligned with the three-dimensional images. Anatomical abnormalities or symptomatic causes for attention deficit

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