Novelty and ADHD

How unexpected stimuli influence neural processing and behavioral performance in children and adolescents with and without attention deficit hyperactivity disorder

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von *Dipl.- Psych. Jana Tegelbeckers*
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Gutachter: PD Dr. Kerstin Krauel
Prof. Dr. Kerstin Konrad

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ABSTRACT

Increased distractibility is one of the main symptoms in attention deficit hyperactivity disorder (ADHD). However, the underlying causes of this aspect of dysfunctional attentional processing are so far only poorly understood. Research has concentrated on a potentially diminished top-down control of attention whereas bottom-up responses to unexpected stimuli received comparatively little interest. In this regard, novelty plays an important role as it reliably induces an orienting response and attracts attention. The present dissertation therefore aimed to systematically investigate the processing of novelty in children and adolescents with ADHD. First, it was examined whether ADHD patients differ from typically developing peers in their neural representation of novelty. A visual oddball study conducted during functional magnetic resonance imaging (fMRI) revealed an overlapping network for novelty processing in both groups. However, in the ADHD group, the same areas related to novelty were also activated for rare but familiar pictures. These results suggest that diminished regulation of the automatic orienting response might underlie the increased distractibility in the disorder.

Furthermore, increased distractibility in ADHD is supposed to lead to stronger impairments by irrelevant external stimuli on concurrent cognitive task performance. Instead, various studies found evidence for a potential benefit of novelty on attentional performance or motoric symptoms. The second step of this thesis therefore comprised the exploration of the influence of task-irrelevant novel sounds on behavioral performance in a flanker task as well as the investigation of the underlying neural modulation of these effects. First, a large behavioral study revealed beneficial effects of novel, task-irrelevant sounds particularly in ADHD patients in terms of improved error rates and decreased reaction time variability. An fMRI study using the same paradigm replicated these behavioral improvements and revealed consistent activation patterns when novel sounds preceded the task display in participants with and without ADHD. However, brain activity following a familiar sound was significantly enlarged in the ADHD group, indicating a greater benefit by a phasic alerting cue in the patients.

In summary, all studies showed normal neuronal activity patterns following novel stimuli but enlarged reactions for familiar/standard stimuli in children and adolescents with ADHD. These findings indicate intact functioning of the bottom-up orienting network while top-down regulation and the underlying alerting system are potentially impaired. However, the increased sensitivity for external cues improved the cognitive performance in patients with ADHD, an effect that might be usable to optimize learning and working conditions.

ZUSAMMENFASSUNG

Die Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung gehört weltweit zu den häufigsten psychischen Erkrankungen des Kindes- und Jugendalters und persistiert in ca. 60% der Fälle bis ins Erwachsenenalter. Die Bezeichnung des Störungsbildes folgt zwei Symptomkomplexen, die gemeinsam aber in unterschiedlich starker Ausprägung auftreten können. Das Aufmerksamkeitsdefizit zeigt sich bei Patienten in mangelnder Konzentrationsfähigkeit, Vergesslichkeit und erhöhter Ablenkbarkeit. Die Hyperaktivität bezieht sich auf motorische Unruhe, überschießende Bewegungen sowie eine Impulsivität, die häufig mit der Unfähigkeit zu warten und einem hohen Rededrang einhergeht. Die vorliegende Dissertation beschäftigt sich mit der erhöhten Ablenkbarkeit als einem der zentralen Symptome des Störungsbildes, welches insbesondere im Schul- und Arbeitskontext der Patienten zu Beeinträchtigungen führt. Prinzipiell stellt die Ablenkung der Aufmerksamkeit durch externe sensorische Reize einen wichtigen evolutionären Mechanismus dar, da das Auftreten eines plötzlichen, unerwarteten Stimulus eine mögliche Bedrohung anzeigen und eine Verhaltensanpassung erfordern kann (z.B. ein Feueralarm). Insofern lösen neue und unerwartete Reize eine automatische Orientierungsreaktion aus (bottom-up). Diese Orientierungsreaktion beeinträchtigt im experimentellen Kontext in der Regel die Leistung in einer zeitgleich durchgeführten Aufgabe in Form von längeren Reaktionszeiten und erhöhten Fehlerraten (Orientierungskosten). Tritt der neue Reiz wiederholt oder andauernd auf (z.B. bei einer Fehlfunktion des Feuermelders), habituiert das Aufmerksamkeitssystem und die ablenkende Orientierungsreaktion kann durch modulierende Systeme der Aufmerksamkeitskontrolle (top-down) unterdrückt werden.

Es besteht demnach die Möglichkeit, dass eine erhöhte Ablenkbarkeit im Zusammenhang mit ADHS aus verstärkten Orientierungsreaktionen auf externe Reize resultiert oder aber durch beeinträchtigte top-down Kontrolle verursacht wird. Bisherige Studien geben Hinweise auf eine verminderte ADHS-assoziierte Aufmerksamkeitskontrolle während der Aufgaben-bearbeitung, kommen allerdings zu uneinheitlichen Ergebnissen bezüglichen der Verarbeitung neuer Reize. Deshalb untersuchte die erste Studie der vorliegenden Dissertation zunächst die neuronale Repräsentation von Neuheit unter Beachtung der Einflüsse von Seltenheit und Aufgabenrelevanz. Jeweils 19 männliche Teilnehmer mit und ohne ADHS im Alter zwischen 11 und 16 Jahren bearbeiteten eine visuelle Oddball-Aufgabe, während mithilfe der funktionellen Magnetresonanztomografie (fMRT) ihre Gehirnaktivität

aufgezeichnet wurde. Die Aufgabe bestand für die Teilnehmer in der Detektion eines vorher zugewiesenen Zielbildes welches selten (12,5%) in einer Reihe aus häufig dargebotenen Standardbildern (62,5%) erschien. Zudem wurde aufgabenirrelevant ein seltenes Bild wiederholt (12,5%) und neue Bilder wurden einmalig präsentiert (12,5%). Es zeigte sich, dass die Verarbeitung neuer Reize in beiden Gruppen übereinstimmende bilaterale Aktivierungen in temporalen und okzipitalen Regionen sowie dem Gyrus parahippocampalis auslöste. Im Gruppenkontrast zeigte sich jedoch, dass die ADHS-Patienten im Gegensatz zu den gesunden Teilnehmern den Gyrus temporalis superior und Gyrus frontalis inferior und medius nicht deaktivierten. Diese Ergebnisse sprechen zunächst für eine altersgemäße Verarbeitung neuer Reize in Kindern und Jugendlichen mit ADHS, die jedoch mit einer verminderten Unterdrückung des Orientierungsnetzwerkes einhergehen. Weiterhin löste das selten, aber wiederholt dargebotene Bild bei den Patienten im Gegensatz zu den Teilnehmern der Kontrollgruppe signifikante Aktivierungen in neuheitsverarbeiten Arealen aus. Diese Beeinträchtigung in der Gewöhnung an seltene aber bekannte Reize könnte zu der erhöhten Ablenkbarkeit von ADHS-Patienten beitragen, da es impliziert, dass unbedeutende Reize eine Orientierungsreaktion auslösen.

Um die Auswirkungen solcher automatischen Orientierungsreaktionen auf das Verhalten zu untersuchen, wird häufig eine einfache visuelle Diskriminationsaufgabe mit aufgabenirrelevanten auditorischen Reizen gepaart. Ein solches Vorgehen bei Kindern mit ADHS führte bisher zu konfligierenden Ergebnissen: während einerseits die zu erwartende erhöhte Ablenkung durch neue Töne bei den Patienten gefunden wurde, berichtete eine ähnliche Studie davon, dass ADHS-Patienten durch aufgabenirrelevante neue Töne in ihrer Leistung profitierten. Um den Effekt neuer Töne auf die Aufmerksamkeitsleistung von Kindern und Jugendlichen weiterführend zu untersuchen, nutzten wir eine Flankeraufgabe, in welcher dem Zielreiz in 2/3 aller Durchgänge entweder ein wiederholt präsentierter Ton (Standard) oder ein einzigartiger, neuer Ton vorausging. 64 Kinder zwischen 8 und 14 Jahren (50% ADHS-Patienten) bearbeiteten diese Aufgabe in einer Verhaltensstudie am PC. Insbesondere die ADHS-Gruppe zeigte eine Verbesserung in ihren Fehlerraten und der Reaktionszeitvariabilität, wenn der neue Ton präsentiert wurde. Dieser Effekt basiert vermutlich darauf, dass neue Töne neben der Orientierungsreaktion einen Anstieg im allgemeinen Aktivierungsgrad (Alertness) bewirken. Wenn dieser Aktivierungsvorteil die Orientierungskosten übersteigt, kann es zu einer Verhaltenserleichterung kommen.

Die neuronalen Grundlagen dieser Effekte untersuchten wir in einer anschließenden fMRT-Studie. In einer älteren Stichprobe von Kindern und Jugendlichen mit und ohne ADHS zwischen 11 und 16 Jahren (N = 45, 22 mit ADHS) konnte der positive Verhaltenseffekt der Neuheit repliziert werden. Dieser ging in beiden Gruppen mit Aktivität im Orientierungsnetzwerk (Gyrus frontalis inferior und temporo-parietaler Übergang) einher. Allerdings verbesserten in dieser Studie auch die Standardtöne die Leistung der ADHS-Teilnehmer und zwar in wesentlich stärkerem Ausmaß als die Leistung der Kontrollgruppe. Zeitgleich zeigte sich für die ADHS-Gruppe ein stärkerer neuronaler Aktivitätszuwachs für Durchgänge mit dem Standardton im Vergleich zur Baseline ohne Ton in einem vorrangig linkshemisphärischen Netzwerk bestehend aus dem linken Gyrus frontalis inferior und medius, der Insula, dem Gyrus temporalis medius und dem bilateralen Gyrus temporalis superior. Dieses neuronale Aktivierungsmuster scheint dem Aktivierungsvorteil durch den warnenden Standardton zu entsprechen. Ein stärkerer Einfluss des Warntones in der Patientengruppe, unterstützt die Annahme, dass der ADHS-Symptomatik ein generelles Aktivierungsdefizit zugrunde liegt.

Insgesamt weisen die vorliegenden Studien darauf hin, dass Kinder und Jugendliche mit ADHS eine intakte Orientierungsreaktion nach neuen Reizen aufweisen. Diese kann sich positiv auf Verhaltensmaße wie die Genauigkeit oder Reaktionszeitvariabilität auswirken, wenn neue, irrelevante Töne in eine aufmerksamkeitsfordernde Aufgabe eingebettet werden. Patienten mit ADHS zeigen jedoch auch (neuronale) Orientierungsreaktionen bei wiederholt auftretenden bekannten Reizen, welche von der gesunden Kontrollgruppe unterdrückt werden. Die fehlende Anpassung der Aufmerksamkeitsorientierung spricht für Beeinträchtigungen der top-down Kontrolle als Grundlage der erhöhten Ablenkbarkeit bei ADHS-Patienten. Andererseits kann eine verstärkte Reaktion auf externe bekannte oder unbekannte Reize einen temporären Anstieg in der Wachheit (Alertness) bewirken und dadurch gegebenenfalls ein Defizit im generellen Aktivierungsniveau der ADHS-Patienten ausgleichen. In diesem Sinne werden zukünftige therapeutische Hilfestellungen denkbar, die die erhöhte Sensitivität von Kindern- und Jugendlichen mit ADHS gegenüber externen Reizen nutzen, um optimalere Lern- und Arbeitsbedingungen zu schaffen.

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LIST OF ABBREVIATIONS

ACC	- anterior cingulate cortex
ACh	- acetylcholine
ADHD	- attention deficit hyperactivity disorder
ANOVA	- analysis of variance
APA	- American Psychiatric Association
BOLD	- blood oxygenation level dependent
CBCL	- child behavior checklist
CBF	- cerebral blood flow
CD	- conduct disorder
CFT-R	- culture fair intelligence test - revised
CG	- comparison group
DA	- dopamine
DAN	- dorsal attention network
DDT	- dynamic developmental theory
DTD	- dopamine transfer deficit
DMN	- default mode network
DSM	- Diagnostic and Statistical Manual of Mental Disorders
EEG	- electroencephalogram
EF	- executive functions
EPI	- echo planar imaging
ERP	- event-related potential
fMRI	- functional magnetic resonance imaging
FOV	- field of view
FWHM	- full-width half-maximum
GLM	- general linear model
HFR	- hemodynamic response function
IFG	- inferior frontal gyrus
MNI	- Montreal Neurological Institute
MPRAGE	- magnetization prepared rapid gradient echo
NE	- norepinephrine
ODD	- oppositional defiant disorder
PFC	- prefrontal cortex
RFX	- random effects

RT - reaction time
RTV - reaction time variability
SD - standard deviation
SMA - supplementary motor area
SPM - statistical parametric mapping
STG - superior temporal gyrus
TE - echo time
TR - repetition time
TD - typically developing
TPJ - temporo-parietal junction
VAT - ventral attention network
VLMT - verbal learn and memory test
VTA - ventral tegmental area
YSR - youth self-report

1 General Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent childhood psychiatric disorders worldwide, known to cause significant impairments in social and academic functioning. Moreover, ADHD frequently persists into adulthood and is accompanied by an increased risk for traffic accidents, criminality, substance abuse and the development of other psychiatric disorders (Bush, 2010; Faraone et al., 2015). These manifestations on personal well-being and the social system elucidate the need to determine the underlying neurobiological substrate as well as to clarify specific ADHD symptomatology thoroughly. To understand the disorder is crucial to facilitate the diagnostic and furthermore to adapt the therapeutic processes. However, to date several aspects of ADHD neurobiology, pathophysiology and symptomatology still remain poorly understood or inconsistent. This thesis aims to contribute to a relevant topic within this research field, namely the investigation of novelty processing in children and adolescents with ADHD.

In doing so, I will first give an overview over the current state of knowledge about the disorder and introduce the main pathophysiological models and neuropsychological deficits of ADHD. After that, I will review what is known about the processing of novel stimuli in healthy humans and explain the rationale of my investigations in ADHD. As I used functional magnetic resonance imaging (fMRI) to examine the underlying neuronal activity, I will use the following second section to briefly introduce this method. Furthermore, I will go into detail about the diagnostic procedure during participant acquisition as an important aspect of clinical research, before the actual studies will be presented. The first experiment deals with differences and commonalities in salience processing in children with and without ADHD (already published in Human Brain Mapping, 2015:16(6)). The second study investigated the influence of novel sounds on performance during an attention demanding task. The results already appeared in Frontiers in Psychology (2016:6). Finally, the same experiment was conducted in an fMRI study of which the results will be presented in section 5. The thesis will be closed with a general discussion of all achieved results, a summary of limitations and an outlook of open questions and future investigations.

1.1 Attention Deficit Hyperactivity Disorder (ADHD)

The most recent definition of ADHD is provided within the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, 2013) published by the American Psychiatric Association (APA). This latest update adapted the diagnostic criteria for the disorder to account for current insights into the developmental course and persistence of ADHD into adulthood. However, the first notion of ADHD-like symptoms in children reaches back into the 18th century and the concept has changed constantly ever since: Sir Alexander Crichton (as cited in Lange, Reichl, Lange, Tucha, & Tucha, 2010) reported in 1798 about children suffering from “the incapacity of attending with a necessary degree of constancy”. About 50 years later, the physician Heinrich Hoffmann pictured in his children’s storybook “Struwwelpeter” the allegedly hyperactive “Fidgety Phil” who is not able to sit still at the dinner table and “Johnny Look-in-the-air” who is inattentive to his surroundings. Although these early mentions of ADHD symptoms are insufficiently detailed and leave room for alternative interpretations like constitutional disorders or naughtiness (Lange et al., 2010), they nevertheless give indication that the problems of some children today have already been noticed centuries before.

The starting point of a scientific investigation of ADHD lies in the 20th century when Frederic Still held a lecture series “On Some Abnormal Psychical Conditions in Children” (Still, 1902) and described, among the range of externalizing behaviors, children with a defect in moral control but normal intellectual abilities (Lange et al., 2010). This led to increased research on the causes of abnormal children’s behavior and shifted the focus of pediatricians on more detailed observations of children’s symptoms. Kramer and Pollnow (1932) then introduced the term “hyperkinetic disease of infancy” and described patients with increased motor activity that would fit today’s criteria for ADHD as well. By this time, it was assumed that behavior disorders in children result from head injuries, brain lesions, encephalitis or birth traumata, leading to the summarized diagnosis of “minimal brain damage” and later “minimal brain dysfunction” (Lange et al., 2010). This concept comprised a heterogeneous range of symptoms from hyperactivity to learning disabilities and persisted into the 1980s. It was abandoned due to a lack of specificity and missing evidence of brain damages in most affected children. Until then, the diagnosis ‘ADHD’ labels a disorder in childhood that is mainly characterized by inattention, hyperactivity and impulsivity. These deficits can differ in strength of their manifestation which led to the distinction of ADHD into subtypes in DSM IV (1994). With introduction of the fifth edition, the DSM’s diagnostic criteria of ADHD give further, more fine grained descriptions of the symptom manifestations in adolescents and adults.

1.1.1 Diagnostic criteria and primary symptoms

The diagnosis ADHD covers a persistent pattern of age-inappropriate degrees of inattention, hyperactivity and impulsivity that appears worldwide in 5% of children and 2.5% of adults (DSM V, 2013). The disorder can emerge in a predominantly inattentive, predominantly hyperactive/impulsive or combined subtype depending on the foremost impairments. Each of the subtypes is present when six or more (five or more from the age of 17 on) of the associated behavioral symptoms depicted in Figure 1 impair social, academic or occupational functioning permanently during a period of at least six month. The combined subtype requires six criteria of each domain to be met.

Inattention is characterized by failure to stay focused on a task, being easily distracted, accumulation of careless mistakes, not listening carefully and forgetfulness. Also, deficits in planning and organization belong in this domain. Hyperactive symptoms show in excessive motoric activity like fidgeting hands or feet, running/climbing or leaving seat when it is not appropriate, talking excessively and being unable to play quietly. In adults these symptoms can be reduced to a feeling of eagerness, tension or restlessness. Impulsivity is listed among hyperactivity and manifests in having difficulties to wait, blurting out of answers and interrupting others. Importantly, the listed problems have to appear before the age of 12 (DSM IV: before the age of 7) and have to affect the life of patients in different contexts such as school/work, family and social relationships. Furthermore, the current severity of the disorder can be rated as mild, moderate or severe depending on the strength and number of impairments (DSM V).

The severity can determine the developmental course of ADHD with approximately half of the cases persisting into adulthood (Faraone, Biederman, & Mick, 2006) but also comorbid disorders might have an influence (Castellanos, 1997). ADHD is commonly paired with oppositional defiant disorder (~35%) and conduct disorder (~25%; DSM V) but mood and anxiety disorders or substance abuse frequently co-occur as well (Barkley, 2003). Moreover, learning disabilities or tic disorders can accompany ADHD. Males are significantly more often affected than females. The gender difference ratios range from 4:1 (Cuffe, Moore, & McKeown, 2005) in the general population to 7:1 in clinical samples indicating that boys display the disorder not only more often but are also more impaired (Biederman, Faraone, & Monuteaux, 2002).

Despite extensive research, no clear biological marker of ADHD has been identified to date. Instead, evidence is growing that ADHD is a bio-psycho-social disorder (Tannock, 1998) depending on genetic, developmental and environmental factors that cause neurobiological abnormalities to appear at least in group comparisons although they are not sufficient for single-case decisions (DSM V).

Inattention

a) *often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities*
b) *often has trouble holding attention on tasks or play activities*
c) *often does not seem to listen when spoken to directly*
d) *often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (e.g., loses focus, side-tracked)*
e) *often has difficulty organizing tasks and activities*
f) *often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)*
g) *often loses things necessary for tasks or activities (e.g., toys, school materials, pencils, books, tools, wallets, keys, eyeglasses, mobile phones)*
h) *is often easily distracted by extraneous stimuli*
i) *is often forgetful in daily activities*

Hyperactivity/Impulsivity

a) *often fidgets with hands or feet or squirms in seat*
b) *often leaves seat in classroom or in other situations in which remaining seated is expected*
c) *often runs about or climbs excessively in situations in which it is inappropriate (adolescents or adults may be limited to subjective feelings of restlessness)*
d) *often unable to play or take part in leisure activities quietly*
e) *is often ‘on the go’ or often acts as if ‘driven by a motor’*
f) *often talks excessively*
g) *often blurts out answers before questions have been completed*
h) *often has difficulty awaiting turn*
i) *often interrupts or intrudes on others (e.g. butts into conversations or games)*

Fig. 1 Overview of ADHD diagnostic criteria according to DSM V (2013)

1.1.2 Etiology of ADHD

As the comprehensive symptom list shows, the diagnosis of ADHD frames a complex and heterogeneous clinical picture. Therefore, it is not surprising that the etiology remains poorly understood. Although it is an important research field, the etiology of ADHD is not the topic of this thesis and will therefore be reviewed only briefly. In a nutshell, it is by now assumed that different environmental risk factors interact with genetic predisposition to form multiple phenotypes of the disorder (for review, see Faraone et al., 2015).

Genetic. ADHD has been recognized to be highly heritable at a rate of 60-80% (Faraone et al., 2005). Monozygotic twins which share 100% of their genes showed concordance rates between 50-80% whereas dizygotic twins ranged between 30-40% (Thapar, Holmes, Poulton, & Harrington, 1999). Also, adoption studies suggested a three times heightened occurrence of the disorder in biological parents of patients compared to adoptive parents (Sprich, Biederman, Crawford, Mundy, & Faraone, 2000).

However, molecular genetic studies revealed only small associations of single candidate genes with ADHD and suggested a rather complex genetic architecture. The associations found so far implicate alterations in dopaminergic (dopamine D4 and D5 receptor as well as dopamine transporter genes) and serotonergic genes (serotonin transporter 5-HTT and HTR1B receptor genes) as well as SNAP-25, a synaptosome-associated protein (Faraone et al., 2005; Stergiakouli & Thapar, 2010). Genome-wide association studies furthermore pointed to the involvement of genes regulating basic processes like neuronal migration and plasticity, cell division, transcription, and regulation of extracellular matrices (for review see Franke, Neale, & Faraone, 2009).

Environment. Although the complex association of genetic variants and ADHD is not yet resolved, it is beyond controversy that a hereditary vulnerability exists which interacts with more or less beneficial environments. Several biological and environmental risk factors have been identified to play a role in the development of ADHD. Most of them take place in very early developmental phases such as fetal exposure to alcohol, nicotine or other drugs, maternal stress, preterm birth or low weight at birth (Banerjee, Middleton, & Faraone, 2007; Millichap, 2008). Furthermore, early childhood illnesses including head injuries especially involving the frontal lobes, meningitis, encephalitis, viral infections or epileptic seizures can cause ADHD symptoms (for review see Millichap, 2008). Later on, chaotic familial conditions, low social status, matrimonial conflicts, large family size, foster placement, parental criminality or mental disorders as well as maltreatment have been associated with the manifestation of ADHD symptoms (for review see Banerjee et al., 2007). However, these associations might as well be based on mutual underlying genetic factors in these families and rather contribute to the development of antisocial comorbidities than pure ADHD symptomatology (Shaw, Lacourse, & Nagin, 2005; Shaw, Owens, Giovannelli, & Winslow, 2001).

1.1.3 Pathophysiological Models

“Pathophysiology” paraphrases functional alterations that result from an injury or a disease (Medical Dictionary). Concerning ADHD, different theories exist about the nature of these functional alterations that underlie the behavioral symptoms. Hereafter, the currently most prominent models will be briefly described.

Monoamine Deficit Hypothesis. Alterations in the dopaminergic system belong to the most validated neurobiological deficits in ADHD and have been researched extensively. This interest was mainly driven by the powerful influence of stimulant drugs on the disorder. It was first described in 1937 that children with hyperactive symptoms improve in behavior but also school performance when they take stimulant medication (Bradley, 1937). Today, Methylphenidate, a psychostimulant of the phenethylamine group, is the most frequently prescribed substance used in drug therapy of ADHD (Faraone et al., 2015).

The efficacy of methylphenidate but also other amphetamines on ADHD symptoms is based on their ability to block the dopamine (DA) and norepinephrine (NE) transporter and thereby increase the availability of DA and NE in the synaptic cleft (Volkow, Wang, Fowler, & Ding, 2005). This, in addition to the genetic findings on dopaminergic gene variants in ADHD as well as findings of reduced dopamine receptor density in several regions (Cortese et al., 2012; Fusar-Poli, Rubia, Rossi, Sartori, & Balottin, 2012; Tripp & Wickens, 2009) led to the development of the monoamine deficit hypothesis that suggests a hypofunctional dopamine system as the chemical basis underlying ADHD pathology.

Different theories focused heavily on the proposed dopamine hypofunction: The dynamic developmental theory (DDT) of ADHD by Sagvolden, Johansen, Aase and Russell (2005) explains ADHD symptomatology via the three branches of the dopamine system (Fig. 2). Mesolimbic dopaminergic dysfunction is claimed to cause lower levels of tonic dopamine and thereby alter the processing of reinforcement. Mesocortical dysfunction is supposed to cause deficient attention and behavioral organization and a dysfunctional nigro-striatal branch accounts for impaired motor functioning.

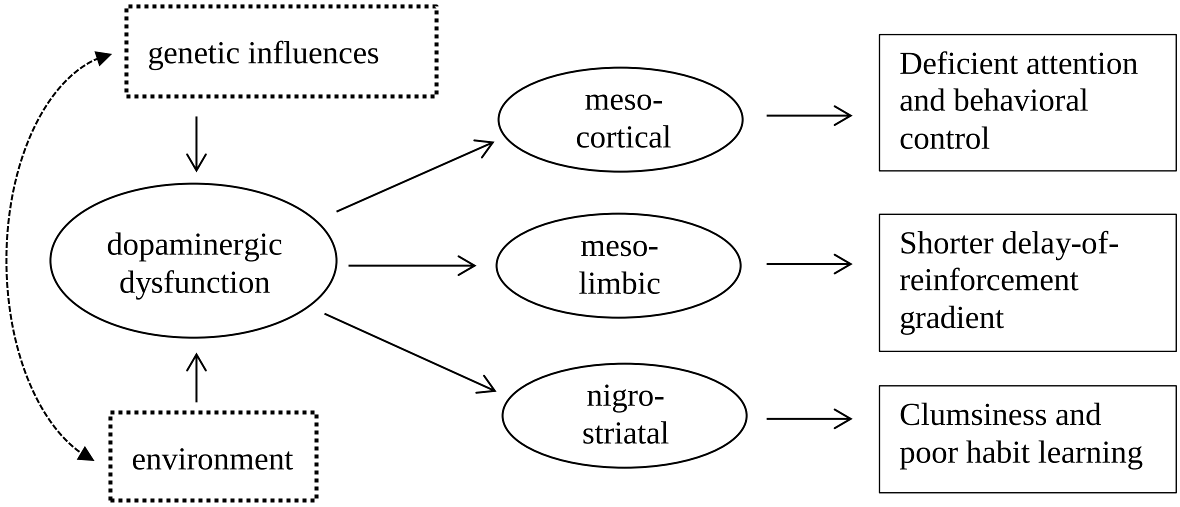


Fig. 2 Dysfunctional branches of the dopaminergic system and their potential consequences in ADHD (adapted from Sagvolden et al., 2005)

Compared with this, the dopamine transfer deficit theory (DTD) by Tripp and Wickens (2008) proposes that the failure in the dopaminergic system primarily manifests in altered phasic dopaminergic responses. Specifically, the transfer of the dopaminergic signal towards a reward announcing cue (anticipation) is supposed to be impaired. Thus, learning based on reward and accordingly improved behavioral control should be diminished in ADHD, but the actual response of dopaminergic cells should be unaffected. This theory has received support by Scheres, Milham, Knutson, and Castellanos (2007) who found reduced activation in the ventral striatum in children with ADHD compared to typically developing (TD) children during anticipation but not reception of reward, a finding that has been replicated also in adults with ADHD (Ströhle et al., 2008). Furthermore, in recent years, positron emission tomography (PET) enabled the investigation of dopamine release in humans. In doing so, Badgaiyan, Sinha, Sajjad, and Wack (2015) currently showed reduced tonic as well as increased phasic dopamine output in adults suffering from ADHD.

Energetic Models. Other theories attribute impairments in ADHD to a dysbalance in the energetic state. In 1983, Zentall and Zentall suggested that organisms endeavor a certain level of stimulation to function at optimum (Optimal Stimulation Theory). In their view, hyperactive behavior serves to compensate for low levels of arousal as a form of self-simulation. Accordingly ADHD patients are considered to suffer from under-arousal.
Similarly, the Cognitive-Energetic Model emphasizes the role of energetic state factors (effort, activation and arousal) on the inhibitory deficits in ADHD (Sergeant, 2000). Among these state factors the “necessary energy to meet the demands of a task” (Sergeant, 2000, p.8) is termed effort (motivation). Activation is defined as the tonic status of physiological activity (the readiness to respond) and arousal is considered to be the phasic increase in this activity due to stimulus processing. Children with ADHD are supposed to be particularly impaired in the energetic mechanisms underlying effort and activation (Sergeant, 2005).

Neuroanatomy. Furthermore, with proceeding advances in human imaging techniques, various structural and functional brain alterations have been associated with ADHD. First of all, patients show a volumetric reduction in whole-brain size ranging between three to five percent when compared to typically developing children (Castellanos et al., 2002; Valera, Faraone, Murray, & Seidman, 2007). Regionally, smaller volumes and reduced cortical thickness have been reported consistently for the prefrontal cortex, caudate nucleus, right globus pallidus and putamen as well as for cerebellar regions (meta-analyses by Ellison-Wright, Ellison-Wright, & Bullmore, 2008 or Valera et al., 2007). As caudate and putamen in particular possess a high density of dopaminergic neurons, a volumetric reduction in these areas also supports the concept of dopaminergic dysfunction.
During adolescence, regional thinning seems to normalize to some extent leading to the hypothesis of an delayed cortical maturation in ADHD (Castellanos et al., 2002). In line with that, the peak of cortical thickness as well as the final development of the brain’s surface area was reached on average three years later in patients than in typically developing children (Shaw et al., 2012). This delay of maturation was most prominent in the lateral prefrontal cortex (Shaw et al., 2007).

However, besides grey matter alterations, diffusion tensor imaging (DTI) revealed further changes at the neuronal network level in white matter integrity (van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). Particularly fronto-striatal, fronto-parietal, cingulate and cerebellar tracks seem to show reduced connectivity in ADHD (Ashtari et al., 2005; Davenport, Karatekin, White, & Lim, 2010; Konrad & Eickhoff, 2010).

Fronto-striatal alterations. One of the most influential theories in the pathophysiology of ADHD implicated dysregulation in fronto-striatal circuits (Castellanos & Tannock, 2002; Castellanos, 1997) including prefrontal cortical areas (dorsolateral prefrontal cortex, inferior frontal cortex), anterior cingulate cortex (ACC), caudate and supplementary motor area (SMA). The model gained prominence on the basis of lesion studies in animals (Levin, 1938; Richter & Hines, 1938) as well as patients with frontal lobe dysfunctions (Luria, Karpov, & Yarbuss, 1966) which exhibited ADHD-like symptoms. It was further supported by findings that prefrontal circuits are modulated by dopamine (Castellanos, 1997) and especially because of robust evidence for prefrontal hypofunction during tasks requiring response inhibition in ADHD (for review see Dickstein, Bannon, Castellanos, & Milham, 2006 or Rubia, 2011).

However, the results of several studies were not limited to frontal and striatal differences in activation but showed alterations in parietal, occipital or temporal regions as well (Castellanos & Proal, 2012). Therefore, as fMRI methods evolved and resting state analyses came into fashion, the research focus in ADHD imaging also shifted from regional areas of interest towards the functional connectivity between brain areas.

Brain Networks. Resting-state imaging is functional MRI without an explicit task. Large scale brain networks are detected by coherent pattern in spontaneous low-frequency fluctuations in blood oxygenation level dependent (BOLD) signals (<0.1Hz). It is assumed that these synchronous fluctuations reflect functional connectivity (van den Heuvel & Pol, 2010). Using this method has led to the discovery and repeated description of several functionally distinguishable networks: the default mode network (DMN), dorsal and ventral attention networks (DAN/VAN), the motor network, two visual networks and a fronto-parietal network. The last is also termed executive control circuit as it encompasses the frontal pole, prefrontal regions, the anterior insula, caudate and inferior parietal lobe, which are all regions involved in executive processing. This network is also closely related to the already mentioned fronto-striatal circuit so that alterations associated with ADHD were expectably found (reviewed by Castellanos & Proal, 2012). However, an involvement of the other networks, especially the DMN, is equally well documented. The DMN consists of bilateral medial frontal areas, precuneus, inferior parietal cortex and medial temporal lobe. Activity in this network is functionally anti-correlated to task-related network activity which means that the DMN is deactivated during externally oriented cognitive tasks and active at rest. Therefore, the network has been linked to introspection, mind wandering and the integration of emotional and cognitive processes (for review, see e.g. van den Heuvel & Pol, 2010). In ADHD, an impaired DMN suppression has been suggested so that ongoing cognition and behavior might be interrupted frequently (Sonuga-Barke & Castellanos, 2007). The attention networks as well as the visual and motor networks received lesser interest than the aforementioned in ADHD research but scattered studies suggest alterations in these circuits as well (Aboitiz, Ossandón, Zamorano, Palma, & Carrasco, 2014; Castellanos & Proal, 2012).

1.1.4 Neuropsychological Deficits

Cognitive differences between children with and without ADHD have been reported in a variety of neuropsychological tests and concepts. Although effect sizes fall in the medium range in meta-analyses and deficits do not seem to be specific or sufficient indicators for youth with ADHD, alterations in executive functioning and reinforcement mechanisms clearly play an important role in the disorder. Investigations of these domains explain ADHD symptomatology to a certain degree and give insight in everyday problems ADHD patients have to deal with. Therefore, the following section will aggregate study results concerning various neuropsychological deficits with regard to executive functions, attention processes and motivation. These are the most prominent domains in ADHD research. However, further deficits beyond the scope of this thesis have been proposed for memory processes and temporal processing (cf. Weyandt & Gudmundsdottir, 2014).

Executive functions (EF). Executive functioning refers to cognitive processes that are engaged in the top-down regulation of flexible and goal directed behavior, namely the maintenance and shifting of cognitive sets. This comprises planning, interference control, response inhibition and working memory (e.g. Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Of these, especially the ability to withhold a response is thought to be impaired in ADHD and it has even been stated that this inhibitory deficit may generate all further ADHD symptomatology (Barkley, 1997). To investigate response inhibition, stop-signal tasks and go-nogo tasks are most frequently used. The former require an interruption of an already initiated reaction and the latter involve the presentation of stimuli that demand no response among stimuli requiring a button press. In these tasks, ADHD patients usually display more commission errors to no-go stimuli and show greater stop signal reaction times compared to TD children (reviewed e.g. by Nigg, 2001 or Pennington & Ozonoff, 1996).

However, when additional behavioral measures are taken into account, ADHD is also often associated with higher mean reaction times and more reaction time variability. As these alterations might explain the longer stop signal RTs to the same extent as a singular deficit in motoric inhibition, the view of ADHD being a primarily inhibitory disorder has been challenged (Alderson, Rapport, Sarver, & Kofler, 2008; Killeen, Russell, & Sergeant, 2013). Furthermore, evidence for EF impairments beyond inhibition has been frequently found for other neuropsychological tasks involving planning, working memory and interference control (Fig. 3). The majority of studies assessing planning abilities in ADHD report impairments even though some found no difference between groups (for review see Weyandt & Gudmundsdottir, 2014; Willcutt et al., 2005). Furthermore, working memory capacity, that is the capacity to hold and manipulate information during ongoing mental operations, clearly distinguished between children with and without ADHD (Kasper, Alderson, & Hudec, 2012; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005). Moreover, interference control as typically investigated by variations of the Eriksen flanker task (Eriksen & Eriksen, 1974) or Stroop task (Stroop, 1935) seems to be impaired. The former requires participants to focus on a target stimulus while suppressing contradictory information of flanking stimuli. In the original Stroop task, the naming of the color of written words is complicated by the word being also a color (e.g. the content of the word red interferes with the green color it is written in). Different meta-analyses systematically reviewed the vast existing literature on variants of these paradigms and found reliable impairments in Stroop task reaction times in children with ADHD (Lansbergen, Kenemans, & van Engeland, 2007) as well as diminished efficiency concerning reaction times, error rates and the effect of distracting stimuli in flanker tasks (Mullane, Corkum, Klein, & McLaughlin, 2009).

Overall, deficits in executive functioning in ADHD can mostly be seen in comparison to typically developing groups while individual patients rarely score outside the normal range when traditional EF tests are applied (Willcutt, 2014). However, in everyday life patients with ADHD rate themselves as impaired and it is widely accepted that EF deficits play a role in general ADHD symptomatology.

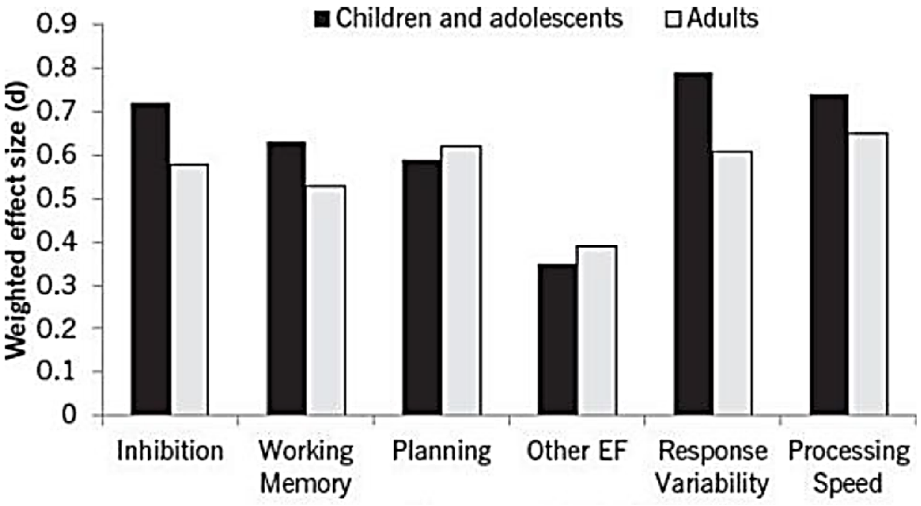


Fig. 3 Weighted mean effect sizes of group differences between children and adults with and without ADHD on measures of the neuropsychological domain (Willcutt, 2014 p.393)

Attention. Attentional dysfunction is already implemented in the naming of the disorder and reflects some of the core behavioral symptoms of the patients. However, behavioral inattentiveness might result from different cognitive or rather motivational dysfunctions. Therefore, it becomes necessary to investigate the underlying cognitive processes before speaking of an attentional deficit in cognitive terms in the disorder. The concept of attention can roughly be divided into sustained attention, the ability to maintain attention over time, and selective attention, the ability to attend to relevant aspects of a task preferentially. Selective attention is most frequently studied with visuo-spatial tasks that require the detection of a target under different perceptual load and/or cueing conditions. Overall, no consistent indication of deficient selective attention processes have been reported in ADHD (Huang-Pollock, Nigg, & Carr, 2005; Huang-Pollock & Nigg, 2003).

On the other hand, limitations of sustained attention become evident in a decline of performance over the course of an experimental session. If children with ADHD would suffer from impaired sustained attention, this decline should be worse than the one of TD children and this has been shown repeatedly: over time, increased reaction time variability (Epstein et al., 2003; Tamm et al., 2012) as well as increased performance differences between groups (Huang-Pollock, Karalunas, Tam, & Moore, 2012) have been reported. The former has recently been confirmed as one of the most robust correlates of ADHD with effect sizes in the range of those for response inhibition (Willcutt, 2014). It is assumed that the increased variability stems from sporadic extremely long reaction times (Hervey et al., 2006) due to attentional lapses.

Furthermore, the ability to sustain attention not only over time but also in the presence of distracting influences seems to be impaired in children suffering from ADHD. Some theories stated that increased distractibility in the disorder is caused by an inability to filter out irrelevant stimuli (Barkley, 1997) or by increased orienting reactions towards these stimuli (Gumenyuk et al., 2005). Indeed, increased distractibility could be shown under certain conditions (Gumenyuk et al., 2005; Radosh & Gittelman, 1981; Rosenthal & Allen, 1980) but other studies failed to find clear evidence (Mason, Humphreys, & Kent, 2003; Pelham et al., 2011) or even reported enhancing effects of allegedly distracting stimuli on performance (Abikoff, Courtney, Szeibel, & Koplewicz, 1996; van Mourik, Oosterlaan, Heslenfeld, Konig, & Sergeant, 2007). However, these inconsistent findings will be reviewed in greater detail in section 1.3.

Motivation. As an alternative to cognitive theories, other models have been developed that attribute the failure to perform persistently to a lack of effort in patients with ADHD. These theories argue that the underlying dysfunction is motivational and might be either based on general lower motivational resources or generated by impairments in the processing of reinforcement.

As a key factor of motivation, reinforcement plays an important role in the acquisition as well as maintenance of behavior and has been closely linked to dopamine (Schultz, 2000, 2002). Accordingly, based on the dopaminergic dysfunction in combination with prefrontal functional abnormalities, several alterations in reward processing have been proposed for children with ADHD: supposedly they are more sensitive to reward and suffer from increased frustration levels when reinforcement is only partially delivered or delayed (for review see Luman, Oosterlaan, & Sergeant, 2005). Furthermore, ADHD patients are more dependent on contingency of gratification than TD comparison groups; they are less able to delay reinforcement and respond more impulsively (cf. Tripp & Wickens, 2009). Most consistently, they prefer an immediate reward over a delayed one even if the latter is more attractive/valuable (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Luman, Tripp, & Scheres, 2010; Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008).

Although these alterations in reinforcement processing can partly be attributed to underlying factors like age, comorbidity of ODD/CD, an inherent tendency to develop addiction, the emotional or attentional state as well as general intelligence (Paloyelis, Asherson, & Kuntsi, 2009; Williams, 2010), most studies agree on an altered reward sensitivity in the disorder (Luman et al., 2010).

Most importantly, the increased reinforcement sensitivity in ADHD patients can be used to gain performance improvements and a positive effect on self-rated motivation when including incentives in tasks (Konrad, Gauggel, Manz, & Schöll, 2000; Luman et al., 2005; Slusarek, Velling, Bunk, & Eggers, 2001).

1.1.5 Summary

The previous chapter illustrated different pathophysiological models and related neuro-psychologic impairments. It has been emphasized that certain behavioral and cognitive deficits are more established than others to play a role in ADHD but that none of the findings is necessary or sufficient to diagnose the disorder in the single case. Moreover, none of the existing theories and models is to date able to fully explain ADHD symptomatology and, given the heterogeneity and complexity of the disorder in its current form, it is unclear whether this will ever be achieved. Comprehensive neurocognitive models will gain future interest and might integrate dysfunction in different domains by investigation of underlying distributed networks (Willcutt, 2014). Additive and interactive combinations of multiple deficits are probable and may lead to distinct subtypes in the ADHD population (Willcutt, 2014).

1.2 Novelty

From an evolutionary perspective, all species need to respond to unexpected and novel stimuli most rapidly because sudden changes in the environment may indicate danger and/or require behavioral adaptation. Above that, the urge to discover, explore and invent seems to be especially deeply connected to mankind. “Human nature is fond of novelty”, Roman philosopher Pliny, the elder, already stated 77 years AD. Today, this inner motivational drive has been implemented in recent personality constructs under the name of novelty seeking (Cloninger, Svrakic, & Przybeck, 1993) and the scientific investigation of the influence of novelty on perception, cognition and behavior gains increasing interest.

However, the term *novelty* is not uniformly used: in its pure form ‘novel’ implies something that has never been seen or experienced before. Therefore, stimulus novelty refers to input which cannot be categorized and recognized from memory (Courchesne, Hillyard, & Galambos, 1975). At the same time, novelty is often used to account for deviance from context that is when a stimulus stands out from other stimuli in a given environment. The contextual form also occurs, when stimuli in a given situation attract attention because they are not to be expected, for example the ringing of an alarm bell or one dog among others wearing a hat. For the purpose of this thesis, novelty will refer to contextual novelty because it has to be assumed that most presented stimuli are not unknown to the participants but new in the context of the conducted studies.

1.2.1 Neurobiology of Novelty Processing

The simple example of an alarm bell illustrates that unexpected changes in the environment require a rapid reaction of the executive control system to enable behavioral adaptation. Thus, novelty detection should take place early and efficiently during stimulus processing. To investigate the time-course of the brain’s reaction to novelty, several studies have used the scalp recorded electroencephalogram (EEG) particularly concentrating on event-related potentials (ERPs). ERPs are neuronal electrical potentials that are time-locked to specific events. Novelty is usually generated in form of contextually deviant, rare stimuli in a series of repeatedly presented standard stimuli and occasionally rare targets (oddball paradigm). Such studies showed a three-step cascade of explicit and indeed early novelty related ERP components independent of the investigated modularity: the N2, the P3a and the reorienting negativity (RON) (e.g. Daffner et al., 2000; Escera, Alho, Schröger, & Winkler, 2000; Schomaker, Roos, & Meeter, 2014). The former has been associated with a relative automatic detection of novelty after approximately 200ms (Chong et al., 2008; Tarbi, Sun, Holcomb, Daffner, & Avenue, 2011). The P3a or novelty P3, on the other hand, is believed to be the electrophysiological equivalent of an involuntary attentional orienting to deviant stimuli as proposed by Sokolov in 1963 (e.g. Escera et al., 2000; Escera, Alho, Winkler, & Näätänen, 1998; Escera, Yago, & Alho, 2001; Friedman, Cycowicz, & Gaeta, 2001). The P3a peaks at around 300ms after novel or unexpected stimuli in fronto-central electrodes and reflects an attention switch that, although involuntary, seems to be influenced by conscious evaluation of the unexpected stimulus as its magnitude is modulated according to the available attentional resources (Berti & Schröger, 2003; Chong et al., 2008). Furthermore, the P3 habituates with repetitive presentation of novel stimuli, indicating that the unexpectedness of occurrence plays a critical role in its generation (e.g. Cycowicz & Friedman, 1998; cf. Ranganath & Rainer, 2003). Finally, the RON is supposed to reflect the reorienting of attention back to the current primary task, if necessary (Schröger & Wolff, 1998).

However, scalp-recorded brain potentials insufficiently reveal information about the underlying cortical anatomy of novelty processing. Therefore, oddball paradigms have been transferred to functional magnetic resonance imaging (fMRI). Figure 4 summarizes the brain regions which have been associated with novelty processing as reviewed by Ranganath and Rainer (2003).

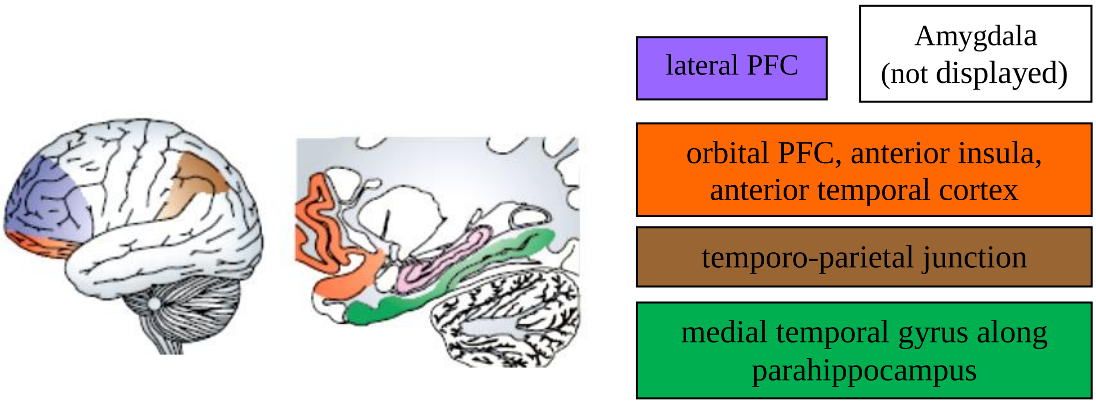


Fig. 4 Overview of brain areas related to novelty processing (adapted from Ranganath and Rainer, 2003). PFC - prefrontal cortex

In particular, the lateral inferior prefrontal cortices (PFC), lateral temporo-parietal cortex, cingulate gyrus, amygdala, hippocampus and parahippocampus are most commonly observed to respond to novelty (for review see Ranganath & Rainer, 2003). Also, if these areas are harmed by stroke, novelty processing has been shown to be impaired (e.g. Knight, 1984, 1996). Additionally, depending on the investigated modality, novelty related activation appeared in the respective association cortices, e.g. enhanced activity in the superior temporal cortex has been reported for auditory and in posterior occipital cortex for visual oddball stimuli (Kiehl, Laurens, Duty, Forster, & Liddle, 2001a; Stevens, Skudlarski, Gatenby, & Gore, 2000).

ERP source modelling provided further insight into the correlation between EEG and imaging data showing that particularly activity in the inferior frontal gyri takes part in generating the novelty P3 and reflects attentional orienting (Friedman et al., 2001; Opitz, Mecklinger, Friederici, & von Cramon, 1999; Strobel et al., 2008). The medial temporal brain response is on the other hand supposed to result from detection of a mismatch between incoming information and expectation (Lisman & Grace, 2005).

On the neuromodulatory level, the processing of novel stimuli has been associated with DA, acetylcholine (ACh), and NE (Rangel-Gomez & Meeter, 2015). Animal studies showed increased activity in the nucleus basalis (ACh) in primates (Wilson & Rolls, 1990) as well as in neurons of the locus coeruleus in rats (NE) following novel stimuli (Vankov, Herve-Minvielle, & Sara, 1995). Furthermore, the dopaminergic midbrain of monkeys (Schultz, 1998) reacted strongly when novel stimuli were presented. Investigations of these transmitter systems in humans are rare and revealed partially inconsistent results: no study examined the role of NE in novelty processing yet and only four addressed the influence of ACh (Rangel-Gomez & Meeter, 2015). Review of these studies showed that increased ACh transmission diminishes the neuronal activation differences between novel and familiar items in medial temporal lobes whereas frontal responses to novelty were enhanced.

However, the involvement of dopaminergic activity in novelty processing has recently received wider interest. Based on animal studies, Lisman and Grace (2005) proposed an influential model of a functional Hippocampal-VTA (ventral tegmental area) loop which associates the detection of novelty in hippocampal neurons with dopaminergic output in the midbrain to subsequently facilitate dopamine dependent learning in the hippocampus (Lisman & Grace, 2005). This model served as basis for the NOMAD framework which stands for “NOvelty-related motivation of anticipation and exploration by dopamine” (Düzel, Bunzeck, Guitart-Masip, & Düzel, 2010). The model closely links novelty processing via the dopaminergic system to motivated exploratory behavior. In line with these assumptions, the role of the human SN/VTA region in novelty processing has been shown (Bunzeck & Düzel, 2006).

However, other studies conducted so far point towards a positive correlation of dopamine availability and the detection of novel stimuli whereas evidence for the modulation of later processing remains inconsistent. In this regard, it has for instance been reported that Parkinson patients, which suffer from a dopaminergic deficit, show reduced P3 amplitudes in oddball paradigms (cf. Polich, 2007). In similar tasks, providing healthy subjects with Dextroamphetamine, and thus increasing the amount of available dopamine, also resulted in reduced novelty P3 amplitudes (Albrecht, Martin-Iverson, Price, Lee, & Iyyalol, 2011). These findings might be explained by an inverted U-shape course of the influence of dopamine on novelty processing so that both, a dopaminergic level above and below an optimum result in impairments. Furthermore, differences may exist between tonic and phasic modulation. However, further research is necessary to clarify the roles and interactions of the dopaminergic and other neurotransmitter systems in the processing of novel information in humans.

1.2.2 Behavioral effects of novelty

Although orienting to novel events is undoubtedly an evolutionary important mechanism, the automatic detection of novelty and its subsequent analysis come with behavioral costs, namely distraction from ongoing cognitive processes (Näätänen, 1992). A majority of studies incorporating unexpected or novel stimuli in a sequence of standard and target stimuli showed a momentary impairment of performance following the deviant. This impairment is usually evident by increased reaction times and attenuated accuracy in adults (e.g. Escera et al., 1998; Escera, Yago, Corral, Corbera, & Nuñez, 2003; Escera & Corral, 2007; Schröger & Wolff, 1998) as well as children and adolescents (e.g. Gumenyuk et al., 2001; Gumenyuk, Korzyukov, Alho, Escera, & Näätanen, 2004; Wetzel, Berti, Widmann, & Schröger, 2004; Wetzel, Widmann, & Schröger, 2009; Wetzel & Schröger, 2007).

On the other hand, a beneficial effect of novelty on performance has been reported: unexpected events are for example stored in memory very effectively (see Lisman & Grace, 2005). Moreover, when participants in a learning task were briefly exposed to a novel pre-learning context, they performed better during recognition and free recall than a comparison group who did not undergo the novel context manipulation (Fenker et al., 2008). These effects have been interpreted in terms of the aforementioned close functional loop between dopamine and memory. However, studies sometimes failed to find deteriorated performance by novel sounds in attentional tasks and reported a modulation of the amount of distraction depending on different task parameters (SanMiguel, Linden, & Escera, 2010a). Task difficulty and type seem to affect the magnitude of disturbance: Spinks, Zhang, Fox, Gao, and Hai Tan (2004) showed reduced behavioral distraction by pictures with increasing difficulty in an arithmetic task. Similarly, working memory load increment (Berti & Schröger, 2003; SanMiguel, Corral, & Escera, 2008) as well as a faster event-rate (SanMiguel et al., 2010a) decreased the distracting influence of novel auditory stimulation. Another line of research even reported facilitating effects of novelty. The most prominent examples included novel sounds which preceded a visual task display and thereby act as cue and result in decreased reaction times (Parmentier, Elsley, & Ljungberg, 2010; Ruhnau, Wetzel, Widman, & Schröger, 2010; SanMiguel, Morgan, Klein, Linden, & Escera, 2010b). This enhancing effect has been shown to be specific to novelty because standard sounds and rare but repeated deviants failed to result in facilitation (Wetzel, Widmann, & Schröger, 2012). In fact, the dissociation between rare deviant and novel stimuli is important. Although deviance from expectation can and has been interpreted as contextual novelty, it has been shown that a difference exists in the processing and behavioral modulation of the two with stronger effects of novel compared to repeatedly presented stimuli (Berti, 2013; Bunzeck & Düzel, 2006; Escera et al., 1998; Wetzel et al., 2012). The repetition of deviant stimuli leads to a suppression of the brain’s response to novelty despite the mismatch of expectation (Berti, 2013; Ranganath & Rainer, 2003; Yamaguchi, Hale, D’Esposito, & Knight, 2004). Therefore, the term “novel” in the following sections will always refer to unique, unrepeated stimuli.

However, the opposing effects of novel stimuli on performance led to more fine-grained theories about novelty related orienting. In 1992, Näätänen already suggested that the orienting response consists of two components: the attention switch and an increase of unspecific arousal (Näätänen, 1992). SanMiguel and colleagues (2010a) termed these effects as orienting costs and alerting benefits and stated that the influence of novel sounds on performance highly depends on the attentive state the participant is in. With other words, if alerting benefits exceed orienting costs, which is easily reached for instance in tiring tasks, facilitation will occur. If the task is demanding and the participant already highly attentive, orienting towards a deviant stimulus will result in distraction (SanMiguelet al., 2010a; Wetzel et al., 2012).

1.3 Novelty Processing and ADHD - Motivation of the current thesis

The human information processing system is of limited capacity and cannot handle all of the incoming information simultaneously. Goal-directed behavior therefore requires voluntary control of attention to channel and select which information is relevant for a given task and suppress irrelevant aspects (top-down). On the other hand, sudden unexpected changes in the environment need to break through the behavioral control of focused attention (bottom-up) as rapid adaption of behavior might become necessary. In this regard, novelty plays an important role as unexpected and therefore novel stimuli reliably evoke an attentional orienting response (Sokolov, 1963). Hence, a cognitive state is evolutionary most efficient when top-down control and bottom-up susceptibility are in balance. This balance seems to be disturbed in patients suffering from ADHD leading to the stereotype of an easily distracted child whose behavior is disrupted by insignificant stimuli occurring outside the focus of attention. This increased distractibility manifests in early childhood by frequent changes in activities and leads to extensive problems in academic surroundings (DSM V).

Several of the abovementioned models of ADHD pathophysiology explain the disorder-specific increased distractibility based on their theoretical assumptions about the causes of the disorder: theories focusing on fronto-striatal dysfunction highlight the diminished inhibitory abilities that lead to an enhanced breakthrough of irrelevant information in children and adolescents with ADHD (Barkley, 1997). Accordingly, task-irrelevant stimuli are supposed to cause stronger neural reactions and disturb performance to a greater extent in patients compared to TD children and adolescents. These effects have been shown for instance in continuous performance tasks: when task-irrelevant distracting stimuli were embedded in these paradigms, participants with ADHD were significantly more affected in their performance than TD children (Berger & Cassuto, 2014; Slobodin, Cassuto, & Berger, 2015). Furthermore, when novel sounds were presented before a simple visual decision task (animal vs. non-animal), children with ADHD showed enhanced omission error rates and increased P3a amplitudes compared to TD participants (Gumenyuk et al., 2005).

Energetic theories, on the other hand, expect ADHD patients to be easily distracted as well, but attribute this symptom to the underlying state of diminished alertness. The under-arousal allegedly not only leads to difficulties in sustained attention but also accounts for increased responses toward extraneous stimuli. These attentional switches might serve in form of a self-stimulation to regain an optimal level of functioning that has decreased over time (Sergeant, 2000). Thus, enhanced distractibility should especially occur in situations where ADHD patients are not particularly interested in the ongoing activity/task, but, on the other hand, a short distraction might as well have a beneficial effect on the attentional capacity by increasing the energetic state. In fact, ADHD patients showed reduced motoric activity in a waiting situation that contained novel stimuli compared to the same situation without (Antrop, Roeyers, Oost, & Buysse, 2000), a result that clearly fits the everyday observation of parents that ADHD children and adolescents can indeed focus on varied, interesting activities as for instance computer games. Furthermore and in contrast to the aforementioned study of Gumenyuk and colleagues (2005), the incorporation of novel sounds in a different simple visual decision task (runner looking left vs. right) led to an improvement in error rates for a group of ADHD patients (van Mourik et al., 2007).

Finally, the relationship between novelty processing and the dopaminergic system can lead to speculations about a special significance of novelty for patients with ADHD. Following the theoretical assumptions described above, children with ADHD suffer from a dopaminergic deficit and might thus either show increased responses to novel stimuli due to their decreased underlying tonic level of dopamine (DDT) or not differ from their typically developing peers as the phasic response is intact (DTD).

However, besides the already mentioned, surprisingly few studies directly investigated distractibility, even less the relationship between novelty and ADHD or the underlying neural substrate of possible alterations in novelty processing in ADHD. Most studies in this line of research focused on oddball tasks in which an infrequent target stimulus had to be detected amongst a series of frequent standard stimuli and occasionally appearing distracting novel stimuli. In these tasks, behavioral and neural differences between TD children and children with ADHD frequently appeared for the processing of target but rarely for novel stimuli (Jonkman et al., 2000; Kemner et al., 1996). In ERP studies, neural alterations involved the reduction of target related P3 components whereas the novelty P3 appeared intact (Barry, Johnstone, & Clarke, 2003). Stevens and colleagues (2007) have been the only ones so far incorporating unique novel sounds into an fMRI oddball study with ADHD patients. Surprisingly, they found diminished activation for novel and target sounds in the patients, a result that clearly needs further investigation and replication.

Taken together, the existing research on the processing of novelty in ADHD remains fragmentary and inconclusive but two main research directions emerged: on the one hand, it is unresolved whether children and adolescents with ADHD differ from typically developing peers in their processing of novelty per se. On the other hand, the influence of task-irrelevant novel stimuli on task performance requires further investigation as the current findings are highly contradictory.

However, as the identification of (dys-) advantageous task-stimulus constellations is of utter importance and high clinical relevance for children and adolescents with ADHD, the current thesis aimed to shed light on the relationship between novelty processing and ADHD. First, the neural basis of novelty processing was systematically examined in children and adolescents with and without ADHD. To do so, an established modified version of the oddball task (Bunzeck & Düzel, 2006) was used in fMRI to disentangle neural effects of novelty, rareness and target processing and compare the related activity between both experimental groups (Experiment 1). Furthermore, to clarify the effects of novel sounds on attentional performance and overcome the shortcomings of previous studies, a flanker task was paired with task-irrelevant sounds. This cued flanker task was first employed in a large behavioral study (Experiment 2) before being transferred into fMRI to reveal the underlying neural processes of novelty-related effects on task performance (Experiment 3).

2 General Methods

2.1 Functional magnetic resonance imaging (fMRI)

The idea to measure nuclear magnetic resonance (NMR) signals originated from the analysis of biological tissue samples and was at first used in studying cancer cells for tumor detection (for review of MRI history see e.g. Prasad, 2007). The later usage of these signals to depict the anatomy and physiological processes of the human body required an advanced understanding of the responding of different cell types to magnetic fields as well as the development of sophisticated technologies. Since then, MR techniques have revolutionized scientific research (Ashby, 2015), especially by functional imaging as it allows the non-invasive examination of human brain activity in (almost) real time. On the other hand, compared to EEG technologies, fMRI clearly lacks temporal precision but this comes with the advantage of an outstanding spatial resolution.

2.1.1 Basic principles of fMRI

Nuclear magnetic resonance (NMR) emerges when atomic nuclei which possess a magnetic momentum interact with an applied magnetic field. This momentum is referred to as ‘spin’ and it occurs in nuclei with an odd proportion of neutrons and protons resulting in rotation around the longitudinal axis. When these atoms are exposed to a magnetic field, they align accordingly, but still spin around their own axis (precession). This spinning takes place in a certain frequency depending on the strength of the applied magnetic field (Larmor frequency). If one applies an electromagnetic radio frequency (RF) pulse on the atoms spinning in alignment, this energy will be absorbed by the protons changing the orientation of the atoms. When the RF pulse is switched off, the absorbed energy is retransmitted, causing the NMR signal, and the atoms return to equilibrium (relaxation). Relaxation hereby addresses two processes: T1 relaxation describes the recovery rate of the system whereas T2 relaxation encompasses the dephasing of the atoms by differences in rotation speed as well as inhomogeneity in the magnetic field. These relaxation times are constant and specific for different tissues and can therefore be used to reconstruct a structural image. Here, it depends on the weighting of the relaxation components how tissues will appear in the image: liquor will for instance be black in T1 and white in T2 weighted images.

For receiving images with sufficient spatial resolution not only one magnetic field but additional gradients are applied to produce discriminable signals in certain slices. These gradients are controlled via a sequence of electromagnetic pulses depending on the aim of the measurement. For the investigation of functional brain activity, the most popular sequence is called echo-planar imaging (EPI). It is characterized by rapidly cycling gradients and allows measuring the whole brain within few seconds (indexed by repetition time TR and echo time TE).

The ability to image neural activity by NMR is based on two discoveries: first, hemoglobin molecules differ in their magnetic properties when they are still able to bind oxygen (deoxygenated) compared to when they are fully saturated (oxygenated state) (Pauling & Coryell, 1936) which basically allows to display cerebral blood flow (CBF). Secondly, the CBF has been shown to be closely coupled with the glucose metabolisms of active cells (Raichle, 1987). In other words, neuronal activity requires glucose which is delivered via blood vessels and accompanied by oxygenated hemoglobin. Thus, the idea was to use the change in the local hemoglobin status as an endogenous contrast agent to indicate neural activity. The associated fMRI signal has been termed blood oxygenation level-dependent (BOLD) response. Figure 5 illustrates the properties of the BOLD signal resulting from a brief period of neural activity. It follows a stable, specific course termed the hemodynamic response function (HRF).

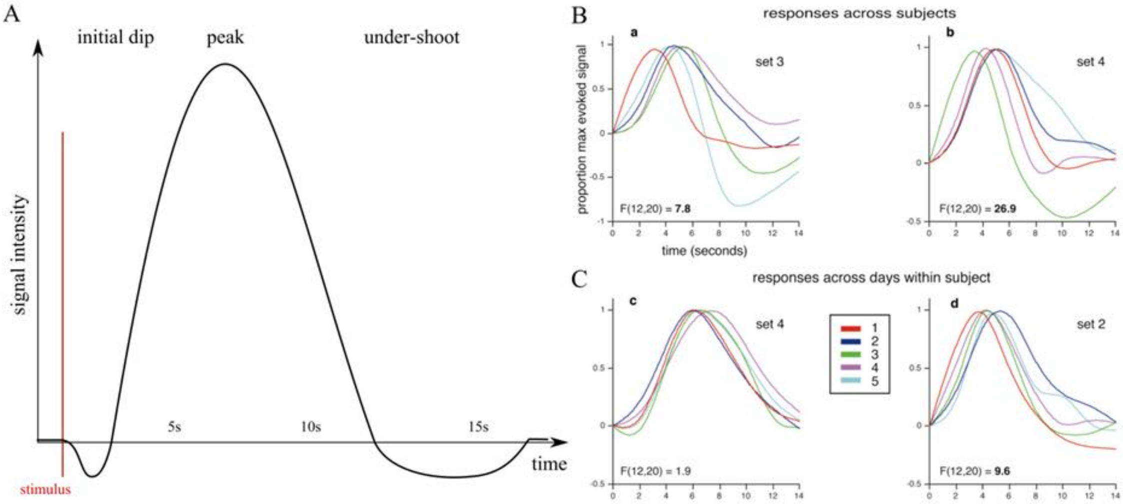


Fig. 5 Illustrations of the BOLD response: (A) schematic shape, (B) inter-individual variability (Aguirre, Zarahn, & D’Esposito, 1998) and (C) intra-individual courses over separate days (Aguirre et al., 1998)

The hemodynamic response following a certain stimulus typically begins with an initial dip followed by a rise and fall in signal intensity which reaches its maximum after approximately 6-8s. Then the signal decrease under baseline level (post-stimulus undershoot) before it reverts to the initial state. Thus, compared to the rapid temporal dynamics of neural activity, the BOLD signal is rather sluggish and limited in the potential temporal resolution it provides. However, it has been shown that it is not necessary to wait a complete BOLD response to disentangle neural activity following certain events. Instead sophisticated experimental designs presenting stimuli of different conditions block-wise or intermixed (event-related) can be used to detect neural activity associated with certain events with sufficient power (for review see Donaldson & Buckner, 2000). The studies presented here used rapid event-related designs which are characterized by randomly intermixed trials of all conditions of interest. The mutual signal of trials associated with each of these conditions is then deconvolved by time-locked averaging.

2.1.1 FMRI data processing

Contemporary fMRI analysis usually encompasses three major steps: preprocessing, first level analysis in form of model specification and model estimation for each participant and second level inference statistic over and between groups. Several software-packages exist for these steps (e.g. AFNI, BrainVoyager or SPM). As I used the statistical parametric mapping (SPM) toolbox running on MATLAB for analyzing the data of this thesis, this section will follow SPM rationale and procedure. For a more detailed description of the principles underlying SPM, compare Friston, Ashburner, Kiebel, Nichols and Penny (2007) or the SPM8 manual.

Preprocessing. Before the data sets of several participants can be analyzed statistically, a number of transformations have to be conducted to account for data displacements in time and space, which might have occurred during scanning, and to assure mutual alignment between subjects. The first step in the analysis, slice time correction, accounts for the slight timing differences that exist for different brain slices. During scanning, it demands a certain time to acquire one complete image of the brain (TR) and furthermore different orders of this acquisition procedure exist (ascending, descending or interleaved). Therefore, although the differences between the slices are small and this step is rather optional (Friston et al., 2007), most event-related studies still include it due to the rapid temporal series of experimental events.

Then, motion correction is accomplished via spatial realignment. This step is necessary as even the most motivated and co-operative participant shows small changes in position throughout a scanning session. Therefore, six motion parameters (displacement in x, y and z axis as well as roll, pitch and yaw) are estimated with reference to the first or an averaged scan. Then, these estimates are used to align all images. Later the motion parameters can furthermore be included as covariates into the statistical analysis to control for movement-related signal changes. Afterwards, the structural image can be coregistered to fit the functional images, if needed.

Now that the data sets are spatially adjusted on an individual level, images are spatially normalized. This step is most important for group analyses as well as to interpret and report results in a standardized way. Therefore, the individual anatomical image (if coregistered) or a realigned image (usually the mean) is computationally warped to match a reference brain template (e.g. conform to Montreal Neurological Institute (MNI) space or Talairach coordinates). These warping parameters are then applied to the functional images resulting in the transfer of all images into standard space. In the following studies, MNI coordinates will be used for spatial assignment.

Finally, a Gaussian smoothing kernel of several voxel width is applied to the images. This helps to overcome residual differences in anatomy between participants that might still exist and it furthermore reduces the problem of multiple comparisons during statistical analysis by introducing spatial correlation between neighboring voxel.

Finishing these steps, the preprocessed images can be used to set up a statistical model for each participant. The previous presentation encompasses the basic preprocessing procedure which can be expanded for instance by additional artifact correction, filtering or segmentation.

First level analysis. The aim of fMRI studies is usually to identify brain regions whose signal change correlates with the conditions of interest in the performed task. To achieve this, most common analyzing methods follow a general linear model (GLM) approach which proposes that a linear relationship between the conditions of the experiment (x) explains signal changes within any voxel (y).

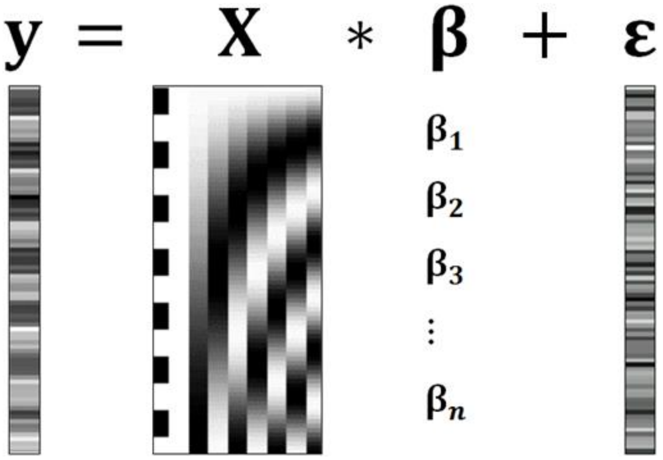


Fig. 6 Illustration of the matrix formulation of the GLM: the BOLD response in a single voxel (y) is described by a weighted (β) linear combination of all experimental conditions (X) plus an error term (ε)

Thus, a model is set up containing the onsets of all manipulations of interest during the experiment and the motion parameters from realignment as covariates of no interest. These covariates are then convolved with the assumed HRF and used as a linear combination to predict the signal change time series in every voxel (Fig. 6). This procedure results in beta values which indicate the association strength of each condition with the neural activity in each voxel. These beta weights can be used alone or in combination to produce statistical maps via t or F tests (contrast images).

The problem in this procedure lies in the simultaneous, discrete analysis of a several thousands of voxel leading to a massive multiple comparison problem which is further complicated by the fact that neighboring voxel are not independent of each other in many cases. For instance, testing 10,000 voxels at a significance threshold of $p<0.05$ will on average lead to 500 falsly activated voxels by chance. To date, different solutions exist to deal with this problem when using this statistical approach, e.g. family-wise error correction, computation of false discovery rates or usage of predefined regions of interest. Moreover, other approaches have been developed that search for activation patterns in multiple voxel simultaneously (multivariate techniques, e.g. ICA or MVPA). However, when proceeding with the univariate approach, this analyzing step finishes with a specified individual statistical model of brain activity during the experiment and estimated contrast images of the conditions of interest.

Second level analysis. Finally, the individual images can be used to make inferences on group level. Here, two options exist: fixed-effects analyses allow inferences for the analyzed sample only whereas random effects (RFX) analyses produce results that are generalizable by including inter-individual variability. As most studies aim to give evidence about processes in the population rather than in a particular sample, contrast images of the first level analysis are usually taken into a second-level RFX analysis to test the null-hypothesis that no activation exists for the group. Several options of RFX analyses have been implemented in SPM of which one- or two-sample t-tests and analyses of variance (ANOVA) are the most frequently used. In addition, the inspection of beta values has been established as an useful tool to gain insight into the direction and strength of group differences or interaction effects. Furthermore, these beta weights can be correlated with performance measures to link neural activity directly to behavior. Several toolboxes have been developed to extract beta weights from the data (e.g. marsbar or rfxplot).

2.2 Diagnostic procedure

Clinical research in neuroscience usually aims to draw inferences about patients suffering from a disorder or disease compared to a healthy comparison group. Accordingly, the demands differ from other research fields insofar as it usually requires more participants and more information about them than is necessary in fundamental research. For one thing, the diagnosis of a potential patient has to be validated and the comparison group has to be disorder-free. Furthermore, it is important to match the groups on basic neurocognitive measures which have to be assessed. Finally, children and adolescents are particularly challenging as the parents need to approve and support their child’s participation.

During the past five years of this thesis, we recruited 252 families for the initial diagnostic assessment. Of these, 130 still remain in our database and frequently participate in different experiments. To do so, potential participants have to be in the age-range between 8 and 16 years for behavioral studies and at least 11years old for participating in fMRI experiments. To be included in the studies, it is crucial that participants can be unambiguously assigned to either the group of typically developing children without any further neurological disorder or fulfil the diagnostic criteria of ADHD according to DSM IV with or without comorbid ODD/CD. Furthermore, no evidence of substance abuse is allowed to be present and participants must have achieved an IQ over 80.

In accordance with the already mentioned gender difference, most of the potential participants in our data base are male. As we try to keep the gender ratio equal between the experimental groups and not so many girls with ADHD apply, we mainly look for boys when recruiting. This recruitment primarily takes place via advertisement in the local newspaper and by info-leaflets put on display at local pediatrics. Furthermore, ADHD patients are referred to us by the department of child and adolescent psychiatry when they match the above-mentioned criteria and are interested.

All children/adolescents and their parents receive comprehensive written information about the experimental procedure including a notion on voluntariness of their participation and the subsequent use of the experimental data for publication. All information is furthermore explained orally so that participants have the opportunity to ask questions. Afterwards, they attest their assent (child/adolescent) and respectively consent (parent) in written from. The participants are reimbursed for all appointments (diagnostic and experiment) with 5€ per hour in form of a voucher for a local shopping center. Parents can receive travel costs if accrued.

The diagnostic approach and all implemented studies reported here have been approved by the local ethics committee of the Faculty of Medicine (University of Magdeburg) and are in accordance with the ethical standards of the Declaration of Helsinki.

Diagnostic assessment. As mentioned above, it is important to validate the ADHD diagnosis in the sample but also to receive detailed information about symptom severity and individual manifestation of the disorder as well as exclusion of the existence of other disorders. Therefore, all participants older than 11 years and all parents are interrogated separately with a semi-structured clinical interview that assesses symptom-based whether child- and adolescent specific disorders previously or currently occur. We use the German translation of the Revised Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL; Delmo et al., 2000) which generates diagnoses by integrating children's and parents' reports (Kaufmann, Birmaher, Brent, Rao, & Ryan, 1996). The interview possesses a high inter-rater reliability as well as concurrent validity in accordance with rating scales, resulting in frequent use when children and adolescents are investigated (Kaufmann et al., 1996; Kim et al., 2004). Additionally, participants as well as parents fill out standardized questionnaires to further quantify the clinical impairments. Children and adolescents finish the Youth-Self-Report (YSR) while parents obtain the Child-Behavior-Checklist (CBCL) (Achenbach, 1991a, 1991b). These questionnaires are paralleled versions and both are characterized by sufficient reliability and validity with the CBCL being slightly better in assessing externalizing while the YSR is advantageous for screening internalizing problems (Leung et al., 2006).

Supplemental to these clinical measures, the diagnostic procedure encompasses several standardized cognitive tests. On the one hand, their results are used to form a more complex clinical picture and thus contribute to the diagnostic decision. On the other hand, standardized values of attentional and memory capacity or intelligence are used as exclusion criteria, indicate whether the experimental groups differ already in their baseline level and can furthermore be used to investigate whether performance differences in the experiments correlate with these differences if existent.

To assess intelligence, we use the Culture Fair Intelligence Test – Scale 20 (CFT-20-R; Weiss, 2008) which is a basic measurement of general cognitive abilities particularly of cognitive flexibility and problem solving. Its advantage lies in the short duration of approximately 30min and its non-verbal content (visual puzzles) enabling an optimal comparability of the results between children with and without ADHD. For children younger than 9 years, an age-appropriate version exists with the CFT-1 (Cattell, Weiß, & Osterland, 1995). Furthermore, we are interested in a basic assessment of the individual ability to concentrate. Therefore, we apply the d2 - Attention Endurance Test

(Brickenkamp, 2002) which measures selective and sustained attention via a visual scanning task. Participants have to cross out every “d” with two marks above or below it in a series of similar distractors (“d” with one/three marks and p-letters with marks). An analogous version exists for children younger than nine years (bp-test; Esser, Wyschkon, & Ballaschk, 2008). Finally, the neurocognitive tests are completed by the Verbal Learning and Memory Test (VLMT; Helmstädter, Lendt, & Lux, 2001) to identify differences between the groups in their general ability to encode and recall verbal information. This test provides us with insight into the individual memory capacity with regard to verbal encoding capability, immediate and delayed recall quality as well as recognition skills. Finally, handedness is evaluated by the Edinburgh Handedness Inventory (EHI; Oldfield, 1971).

Altogether, the complete diagnostic procedure requires at least 2h. Children first perform the tests and are subsequently interviewed with the K-SADS-PL. One or both parents are interrogated simultaneously, if possible. The questionnaires can be accomplished immediately or at home.

3 Experiment 1: Altered salience processing in attention deficit hyperactivity disorder

The following study was first published in:
Tegelbeckers, J., Bunzeck, N., Duzel, E., Bonath, B., Flechtner, H. H., & Krauel, K. (2015). Altered salience processing in attention deficit hyperactivity disorder. Human Brain Mapping, 36(6), 2049-2060.

3.1 Introduction

The maintenance and regulation of attention are a particular challenge for ADHD patients, as they are easily distracted by external stimuli and have severe difficulties to organize sensory and cognitive information according to their relevance (Satterfield, Schell, & Nicholas, 1994). To date, it is unclear whether these problems are solely associated with diminished cognitive control (top-down) or whether there is also an increased sensitivity to external sensory stimuli (bottom-up).

Deficits in cognitive control have been repeatedly demonstrated in tasks that require the detection of a target stimulus among a frequently presented standard stimulus (oddball paradigm). Event-related potential (ERP) studies revealed that the target-related P3b was reduced in children with ADHD relative to healthy comparison groups (Jonkman et al., 2000; Kemner et al., 1996). Additionally, recent fMRI studies reported reduced neural activity in patients with ADHD during target processing in a wide range of areas typically involved in cognitive control, including temporal, parietal and cingulate regions (Rubia, Smith, Brammer, & Taylor, 2007; Tamm, Menon, & Reiss, 2006).

However, beside intentional shifts of attention toward task-relevant stimuli, attention can also be involuntarily captured by salient stimuli for instance due to their novelty or unexpectedness. This mechanism is crucial for adaptive behavior because disruption of an ongoing task might be necessary when rare or particularly novel stimuli signal that something threatening or potentially rewarding is happening. However, enhanced bottom-up processing of external novel stimuli can also contribute to increased distractibility in terms of so-called “orienting costs” (SanMiguel et al., 2010a). So far, surprisingly few studies have addressed this issue in ADHD and have systematically investigated the neural correlates of novelty processing in this patient group. To our knowledge, only one study included novel stimuli in an auditory fMRI oddball task (Stevens, Pearlson, & Kiehl, 2007). Stevens and colleagues showed diminished activity in ADHD patients compared to a TD comparison group in response to novel tones in the left parietal lobule and the posterior part of the left superior temporal gyrus. Moreover, participants with ADHD showed no activation in half of the expected novelty related regions of interests (ROIs) indicating impaired processing of novel stimuli in these patients.

On the other hand, ERP studies have suggested normal orienting responses to novel stimuli in ADHD, since children with and without the disorder did not differ in parameters of novelty-associated ERP components (P3a) (Jonkman et al., 2000; Kemner et al., 1996). Some studies have even shown a particular significance or beneficial influence of novelty for ADHD patients, as, for example, the presentation of task-unrelated novel tones in comparison to standard tones improved their performance accuracy in a visual attention task (van Mourik et al., 2007). Furthermore, motor symptoms are reduced when children and adolescents with ADHD are exposed to a novel environment (Antrop et al., 2000).

Summarizing, even though novelty appears to be behaviorally important in ADHD, it is unresolved how novelty affects perceptual and attentional processes in this patient group. In the current fMRI-study, we therefore aimed to characterize the neural representation of novelty in children and adolescents with ADHD in more detail. We used a modified visual oddball paradigm (Bunzeck & Düzel, 2006) to isolate effects of novelty from effects of mere rareness and relevance in an event-related functional magnetic imaging (fMRI) study. Considering previous studies, we predicted that children and adolescents with ADHD would show activation differences during target processing but not during the processing of novel stimuli.

3.2 Methods

Participants. 38 boys between the age of 11 and 16 participated in this study. They underwent diagnostic procedure as described in section 2.2. 19 boys met the diagnostic criteria for ADHD according to the DSM-IV, 13 for the combined subtype and six for the primarily inattentive subtype. Two patients additionally fulfilled diagnostic criteria for oppositional defiant disorder (ODD). In the comparison group, no participant was diagnosed with a current or previous psychiatric disorder.

Table 1. Sample description and comparison of the ADHD and the typically developing group (TD) in the oddball task

	ADHD N=19	TD N=19	t
Age (years)	13.32	13.58	0.52
Diagnoses:			
ADHD – combined	13	-	
ADHD – inattentive	6	-	
Oppositional Defiant Disorder	2	-	
IQ (CFT)	104.89	108.63	0.96
Attentional Performance (d2; PR)*	55.23	77.79	2.5
Attentional Problems – self rating (YSR; T)**	60.50	53.48	-3.52
Attentional Problems – parental rating (CBCL; T)***	68.06	54.26	-9.28

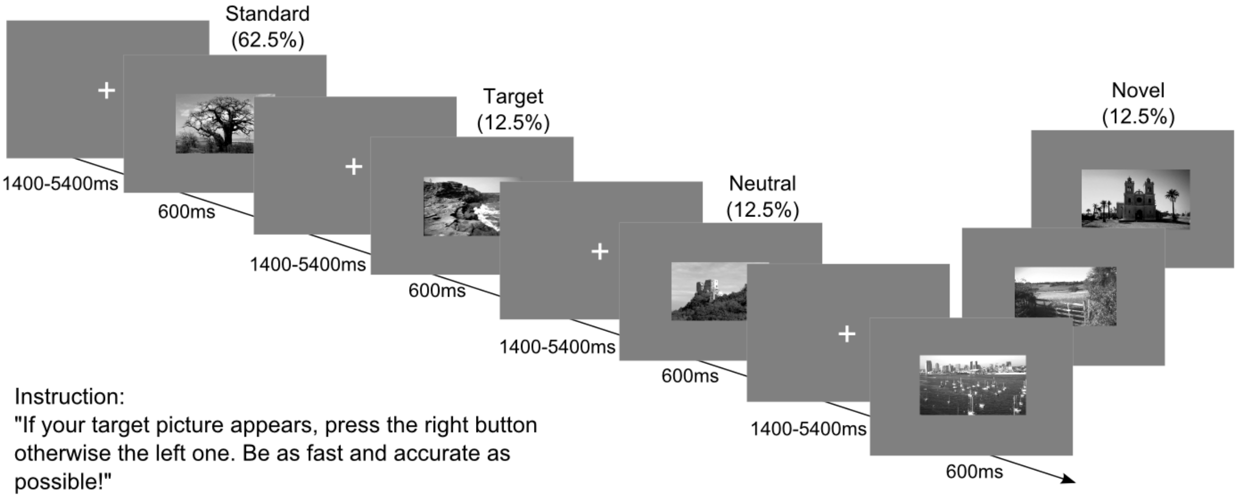
*p < .05, **p < .01, ***p < .001;   PR – percentile range

As Table 1 shows, the groups did not differ in age nor intelligence (CFT-R, Weiss, 2008), but the TD group scored significantly higher in a standardized measure of selective attention (d2, Brickenkamp, 2002). Furthermore the ADHD group as well as their parents reported significantly more attentional problems than the comparison group as assessed by the YSR (Achenbach, 1991a) and the CBCL (Achenbach, 1991b). Four patients and one participant of the comparison group were left handed – all others were right handed. ADHD patients who currently used stimulant medication (n=10) discontinued intake at least 48h before the experiment.

All participants and their parents gave written informed assent/consent. The study was approved by the local ethics committee and followed the ethical standards of the Helsinki declaration. As a reimbursement for their participation, children and adolescents received vouchers for a local shopping center (5€ per hour).

Experimental Design and Task. For the visual oddball task, black-and-white pictures of landscape scenes were used. For each participant, one picture was randomly selected as a frequently presented standard picture (62.5%), one as the task-relevant target and one as a task-irrelevant neutral oddball (12.5%). Furthermore, 50 novel pictures were interspersed (12.5%). In each run, the standard picture was presented 50 times intermixed with 10 target and 10 neutral oddballs as well as 10 novel pictures (total of 80 pictures per run). The experiment contained five runs with short intermediate breaks.

Participants were instructed to respond to every appearing picture as quickly and accurately as possible. A button press with the right index finger indicated target detection, whereas the left index finger button was associated with all non-targets. In contrast to previous studies, every stimulus required a button press to assure that participants attended to all items. To familiarize the participants with the task and their standard, target and neutral oddball picture, they performed a training block outside the MRI scanner. As Figure 7 illustrates, each picture was presented on a grey background for 600ms followed by a white fixation cross with a duration randomly sampled from an exponential distribution with a mean of 3s (range of 1.4–5.4s). The last button press within the inter-trial interval was counted as the final answer. Before each experimental run started, the target picture was presented again as a reminder for 5s.



Instruction:
"If your target picture appears, press the right button otherwise the left one. Be as fast and accurate as possible!"

Fig. 7 Schematic illustration of the modified visual oddball task

fMRI Methods - Image Acquisition and Processing. Imaging data were acquired on a 3T Siemens Magnetom Trio whole-body MRI scanner equipped with an eight-channel head coil. Structural images were collected by a T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence (192 sagittal slices, voxel size of 1x1x1 mm, field of view of 256 mm). Functional images were obtained in 32 slices by a whole-brain T2*-weighted echo planar imaging (EPI) sequence in interleaved order with a repetition time of 2 s (voxel size of 3.5x3.5x3.5 mm, field of view of 224 mm). The echo time was 30 ms and the flip angle 80°. The initial two images were not included in further processing.

In total, 725 EPI - images (145 per run) of each participant were analysed using statistical parametric mapping software (SPM8, Wellcome Trust Centre for NeuroImaging, London) running with MatlabR2009b (The MathWorks, Inc., Natick, Massachusetts, United States). During preprocessing, they were corrected for slice-time differences with regard to the first slice, realigned (reference = mean functional image) and spatially normalized to Montreal Neurological Institute (MNI) space. Furthermore a 6 mm Gaussian kernel was applied for spatial smoothing and a high-pass filter of 1/128 Hz for removal of low frequency confounds.

fMRI Statistics. For each subject, an event-related statistical model was computed by creating a ‘stick function’ for each event onset (duration = 0 s), which was convolved with the canonical hemodynamic response function (HRF). Modeled conditions included standard, neutral oddball, target and novel images as well as errors (incorrect, multiple and no responses). To capture residual movement-related artifacts, six covariates were included (the three rigid-body translation and three rotations resulting from realignment) as regressors of no interest. Regionally, specific condition effects were tested by employing linear contrasts for each subject and each condition (first-level analysis). The resulting contrast images were entered into a second-level random-effects analysis separately for each group with age as a covariate (one-sample t-test). Activations were thresholded at $p<0.05$ using cluster-wise false discovery rate (FDR). Differences between groups were analyzed by two-sample t-tests using a threshold of $p<0.001$ (uncorrected) for increased sensitivity and an extend range of $k=10$ voxel.

To investigate the nature of group differences, individual beta weights were extracted by rfxplot (Gläscher, 2009) from the maximum peak voxel of the cluster differentiating between children and adolescents with and without ADHD. These beta weights were also subsequently used to assess potential relationships between brain activity and behavioral measures/group characteristics. The influence of mean reaction time, reaction time variability to the standard, mean accuracy, performance in the d2 test, age and IQ on brain activation was assessed via Pearson’s product moment correlation and the effects of medication usage and subtype in ADHD were investigated by point-biserial correlations. Statistical significance was only assumed when Bonferroni corrected thresholds were exceeded.

We also explored whether age modulated activation during processing of novel and rare neutral stimuli. Activation differences between both groups were separately assessed in a young (11-13 years, N=11) and an old (14-16 years, N=8) ADHD and comparison group (young: N=10, old: N=9) by two-sample t-tests.

Moreover, we examined common activation patterns to novel (novel > standard) as well as rare familiar (neutral oddball > standard) stimuli in children and adolescents with and without ADHD by applying inclusive masking. Overlapping activation between rare familiar and novel pictures was also assessed by inclusive masking separately for each group. Based on the conjunction null hypothesis a threshold of $p<0.05$ FDR corrected and $k>10$ voxel was applied to all contrast images used (Nichols, Brett, Andersson, Wager, & Poline, 2005).

Behavioral Statistics. Error rates, reaction times and number of trials with multiple button presses (as indicator of impulsivity) were analyzed in R (version 2.14.1, 2011) by two-way repeated-measures ANOVAs with the factors stimulus category (standard vs. target vs. neutral oddball vs. novel) and group (ADHD vs. healthy comparison group). Trials with multiple button presses or with errors were not considered for reaction time analysis.

3.3 Results

Behavioral Data. The analysis of error rates revealed a very high accuracy in both groups. The average error rate was 0.88% over the whole experiment with a range between 0% and 4.5%. Stimulus category significantly affected the error rate ($F(3,108)=10.03$, $p<0.0001$), the number of trials with multiple button presses ($F(3,108)=65.4$, $p<0.0001$) and reaction times ($F(3,108)=72.97$, $p<0.0001$). No main effect of group or interaction of stimulus category and group were found (all $p>0.11$). Post hoc paired t-tests revealed that the responses to the target picture were associated with significantly higher error rates compared to all other stimulus categories (all $t(37)>3.1$, $p<0.0005$). Reaction times were fastest for the standard picture followed by the neutral oddball, the novel pictures and the target picture (all paired comparisons $p<0.001$).

fMRI - rare novel (novel > standard). Novel compared to standard images evoked activity in a bilateral network comprising the parahippocampal gyrus and fusiform gyrus extending to the hippocampus as well as middle temporal gyrus and reaching into the inferior and middle occipital gyrus in both groups (Fig. 8A, Table 2). The right thalamus was activated only in the comparison group of TD participants, but not in patients with ADHD. Inclusive masking revealed common activation in both groups in most of these areas (Table 2).

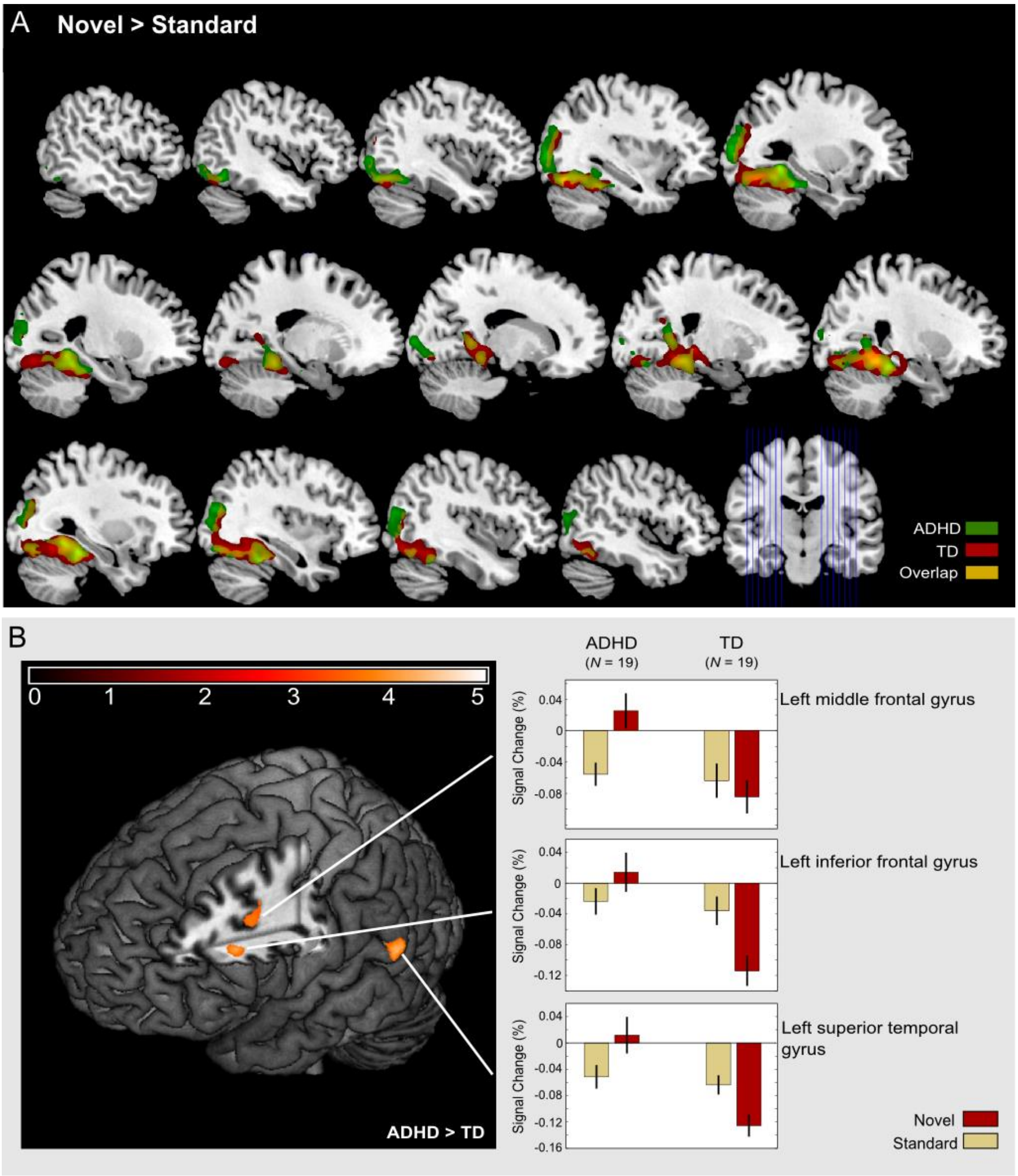


Fig. 8 Processing of novel visual stimuli. (A) Activation overlap between participants with attention deficit hyperactivity disorder (ADHD) and a typically developing comparison group (TD). (B) Areas showing stronger activation in ADHD patients than TD participants

The direct comparison of the groups (ADHD > TD) showed significant differences in the left superior temporal gyrus, the left middle and the inferior frontal gyrus (Table 3). The analysis of beta weights in these three regions revealed that activation differences were based on a deactivation following novel pictures in the comparison group but not in the patient group (Fig. 8B).

The beta weights were not modulated by medication usage, ADHD subtype, age or any of the behavioral measures (RT, accuracy, IQ, d2) except for reaction time variability. For the superior temporal and middle frontal gyri the product-moment correlations were r=0.39 (p<0.05) and r=0.4 (p<0.05). Activity in the inferior frontal gyrus correlated with reaction time variability at r=0.58 (p<0.01) (Fig. 9). Separate group comparisons in the younger and the older group did not yield different results.

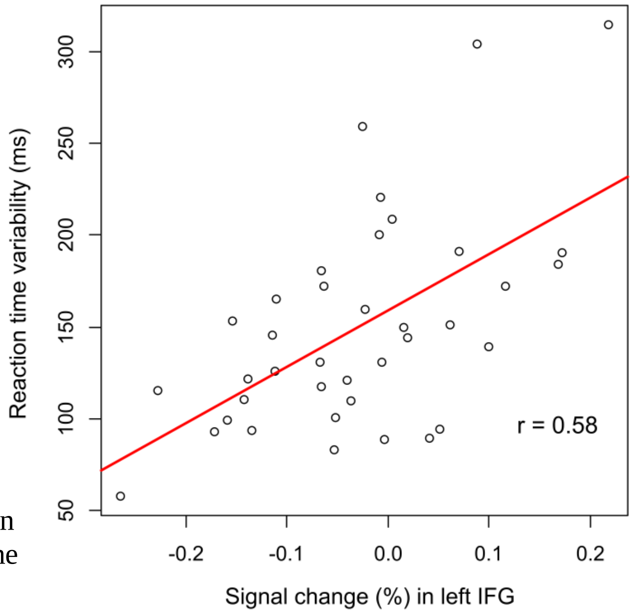


Fig. 9 Relationship between individual novelty-related activation and reaction time variability in standard trials in the left inferior frontal gyrus (IFG)

fMRI - rare familiar (neutral oddball > standard). For the TD group, there were no significant activation differences between the neutral oddball and the standard picture at the applied threshold. Children and adolescents with ADHD, however, showed activation bilaterally in the fusiform and parahippocampal gyrus, right cuneus, right precuneus, left posterior cingulate and left middle occipital gyrus (Table 2). Significant group differences (ADHD > TD) were found in the bilateral lingual and fusiform gyrus, the left parahippocampal and middle occipital gyrus as well as the right middle temporal gyrus, right cuneus and precuneus (Fig. 10A, Table 3). Conjunction analysis in the form of inclusive masking revealed no common activity in both groups at the chosen threshold for the contrast rare vs. standard, but it revealed an overlap between novelty and rareness related activity in children and adolescents with ADHD: Figure 10B shows the common activity within the bilateral fusiform and parahippocampal gyri and the left middle occipital gyrus.

Focusing on the areas differentiating between ADHD and control participants, we found no correlation between the beta weights in the areas differentially activated by the groups and any performance measure, ADHD subtype, medication use or age. Yet, when the groups were split halfway by age differences in the two sample t-tests between young children with and without ADHD clearly reached significance (p<0.001, uncorrected) in the bilateral fusiform gyri, the left middle occipital gyrus, the right precuneus and both lingual gyri, whereas the effect in the same areas was less pronounced in the older subsamples (p<0.01, uncorrected).

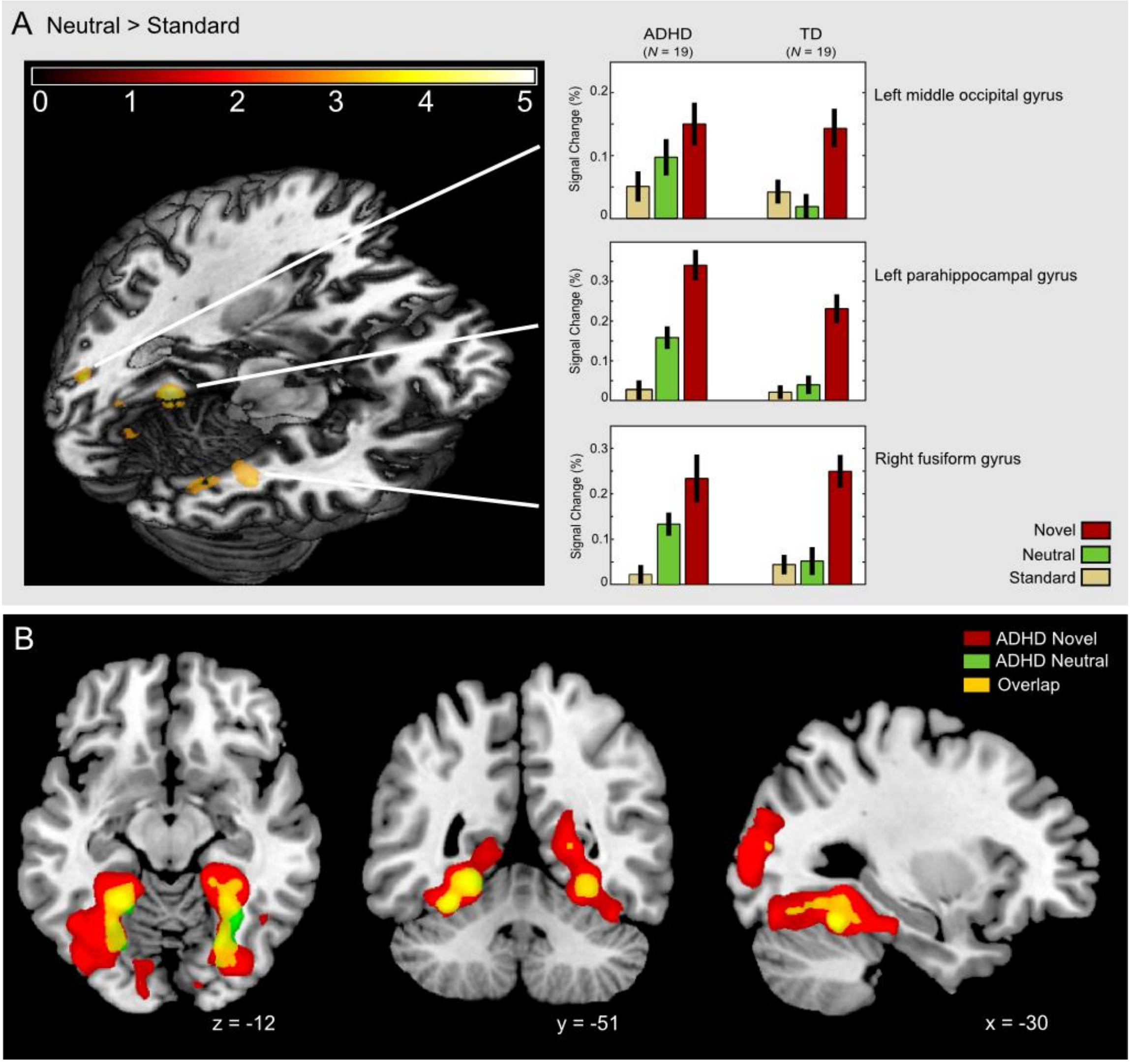


Fig. 10 Processing of the neutral visual oddball. (A) Activation differences between the attention deficit hyperactivity group (ADHD) and the typically developing group (TD). (B) Overlapping activation for novel pictures and the neutral oddball in ADHD

fMRI - rare target (target > standard). In both groups, the correct detection of the rare target stimulus was associated with activation in the left postcentral gyrus, bilateral medial frontal gyrus, cingulate gyrus and right precuneus. Furthermore, activation was found in the insula bilaterally, the left thalamus as well as the right anterior cerebellum and the right culmen (Table 2). The TD group also activated the left culmen and left middle occipital gyrus extending into the fusiform gyrus. ADHD patients showed activation in the right superior temporal gyrus reaching into the right inferior parietal lobule. However, the direct comparison did not reveal any statistically significant differences between the groups.

Table 2. Activated brain regions in children and adolescents with ADHD and a typically developing comparison group (TD) for three oddball categories against a standard picture

Activation Cluster	**ADHD Group (*N* = 19)**					**TD Group (*N* = 19)**				
	Local Maxima			Voxel per Cluster	t	Local Maxima			Voxel per Cluster	t
	x	y	z			x	y	z		
Novel > Standard										
R parahippocampal gyrus* (incl. hippocampus)	28	-36	-16	10694	13.30	24	-50	-8	10828	18.92
R fusiform gyrus*	36	-44	-22		10.87	34	-38	-24		10.95
R inferior temporal gyrus*	50	-56	-18		9.01					
R middle temporal gyrus*	36	-80	20		8.89					
L parahippocampal gyrus*	-28	-48	-6		12.50					
L fusiform gyrus*	-30	-36	-20		10.81	-30	-68	-14		12.62
L middle occipital gyrus*	-36	-72	-16		10.86	-34	-72	-16		12.20
R middle occipital gyrus*						38	-72	-12		10.03
L inferior occipital gyrus*	-44	-60	-14		9.19					
R inferior occipital gyrus*						44	-62	-16		9.59
R thalamus						20	-30	-2		10.90
L precuneus	-16	-74	50	233	5.33					
R superior parietal lobule	28	-68	46	125	5.06					

Neutral > Standard										
R fusiform gyrus/ parahippocampal gyrus**	30	-60	-10	777	6.47					
L fusiform gyrus/ parahippocampal gyrus**	-32	-52	-18	725	7.95					
R cuneus	18	-90	30	184	5.66					
R precuneus	1	-68	24	503	5.05					
L posterior cingulate	-8	-60	10	95	4.47					
L middle occipital gyrus**	-32	-80	14	237	5.66					
Target > Standard										
L postcentral gyrus*	-48	-28	56	995	11.45	-46	-24	56	2474	11.33
L medial frontal gyrus (reaching in anterior cingulate)						-2	-2	52	1007	7.66
R medial frontal gyrus	6	10	50	706	7.35					
R anterior cingulated (extending to posterior region)	6	-18	28	268	6.30					
R posterior cingulate						6	-32	24	510	7.72
R precuneus	4	-72	40	242	5.06	8	-72	40	454	7.21
L thalamus	-10	-18	8	127	6.80	-12	-24	8	555	7.05
L insula	-46	-4	4	472	6.60	-34	12	4	99	5.41
R insula						32	16	4	490	6.91
R superior temporal gyrus (incl. right insula)	46	12	4	268	6.50					
R inferior parietal lobule	48	-44	44	143	6.25					
L middle occipital gyrus/ fusiform gyrus						-36	-82	-16	299	6.15
R anterior cerebellum/	28	-46	-20	1047	11.15	18	-52	-28	1139	9.36
L culmen						-38	-52	-26	216	5.84

$p < 0.05$, cluster-wise FDR corrected; ADHD = attention deficit hyperactivity disorder; L = left; R = right

* areas that showed common activity in both groups (inclusive masking)

** areas that showed common activity for novel and neutral pictures in ADHD (inclusive masking)

Table 3. Activated brain regions for two-sample t-tests ADHD > TD

Brain Region	Local Maxima			Voxel per Cluster	t
Novel > Standard					
L superior temporal gyrus	-58	-50	10	68	4.44
L inferior frontal gyrus	-44	20	22	50	4.31
L middle frontal gyrus	-34	8	30	32	3.74
Neutral > Standard					
L parahippocampal gyrus	-24	-48	-10	114	5.10
L middle occipital gyrus	-32	-80	12	19	4.35
R fusiform gyrus	32	-58	-12	30	4.03
	22	-70	-12	15	3.84
L fusiform gyrus	-40	-54	-20	28	3.93
R precuneus	20	-72	28	29	3.91
R cuneus	8	-88	2	41	3.73
L lingual gyrus	-16	-72	-10	14	3.69
R middle temporal gyrus	36	-76	18	11	3.57

$p < 0.001$, uncorrected, $k > 10$; ADHD = attention deficit hyperactivity disorder;
L = left; R = right

3.4 Discussion

We investigated the neural representation of novelty in children and adolescents with and without ADHD during a modified visual oddball task. As a main finding, we could show consistent neural responses to target and novel items in both groups. However, compared to TD children and adolescents, participants with ADHD did not show neural deactivation in frontal and temporal areas in response to novel stimuli. Moreover, only the patient group significantly activated a network of brain regions in response to rare but familiar pictures that showed a great overlap with novelty-associated areas. These findings seem to be unrelated to medication usage and subtype of ADHD as exploratory analyses revealed.

Novelty. In this study, novel stimuli activated a comparable network of brain regions in children and adolescents with and without ADHD. This network included the bilateral parahippocampal and fusiform gyrus, the hippocampus, temporal as well as occipital gyri, which is consistent with findings of novelty processing areas in visual oddball tasks in healthy adults (Kiehl et al., 2001a). The medial temporal areas and especially the hippocampus are known to detect deviance from expectation and novelty by matching incoming information with memory content (Kumaran & Maguire, 2009; Menon, White, Eliez, Glover, & Reiss, 2000). Increased activation in visual association cortices such as the fusiform gyrus and occipital regions has been associated with attention shifts driven by novel stimuli (Downar, Crawley, Mikulis, & Davis, 2000). The involvement of the parahippocampal area has been previously reported in association with visual oddball tasks and could also be attributed to the landscape scenes used as stimulus material (Epstein, Harris, Stanley, & Kanwisher, 1999). Our results are also in line with ERP studies that did not show differences between ADHD patients and TD comparison groups in the amplitude of the novelty related P3a component (Jonkman et al., 2000; Kemner et al., 1996) indicating intact detection of novelty in ADHD patients.

However, we also observed alterations in novelty-related BOLD modulation between both groups. The TD comparison group showed stronger deactivation of the neural signal within the left middle and inferior frontal gyrus as well as in the left superior temporal gyrus in response to novel pictures in comparison to the ADHD group. The middle frontal gyrus as well as the superior temporal gyrus are usually also activated during target processing in oddball tasks (Linden et al., 1999; Stevens et al., 2000), whereas the left inferior frontal gyrus has previously been associated with extraction of meaning and semantic analysis (Bookheimer, 2002; Friedman, Goldman, Stern, & Brown, 2009). The bilateral superior temporal gyrus and the right inferior and medial frontal gyrus are also part of the ventral attention network which is involved in bottom-up attentional reorienting to salient and behaviorally relevant external stimuli (Corbetta & Shulman, 2002). Interestingly, a recent meta–analysis of functional MRI studies in ADHD (Cortese et al., 2012) has found evidence for both hypoactivation as well as hyperactivation in these areas. However, the hyperactivation we found in this study is based on missing deactivation in the ADHD patients and this deactivation has been discussed to be associated with preventing shifts to irrelevant stimuli (Corbetta, Patel, & Shulman, 2008).

In our experiment, the novel pictures were not of particular behavioral relevance, since they required the frequent response of the left button. Accordingly, an efficient use of neural capacities in the current task could have entailed the suppression of a further analysis of the novel picture. Children and adolescents with ADHD failed to do so and allocated significantly more neural resources than the comparison group. This interpretation is further supported by moderate positive correlations between brain activity in these regions and the individual reaction time variability in standard trials which can be seen as a proxy of vigilance during the task. Therefore, in our study a general higher alertness was associated with higher deactivation.

Corbetta et al. (2008) argue that the ventral attention network is influenced by sustained top-down signaling (possibly by the dorsal attention network) which enables the control of stimulus-driven orienting and reorienting. The findings of both hyper- and hypoactivation in the ventral network in ADHD (Cortese et al., 2012) suggest that difficulties may lie in the top-down modulation of this network rather than an impaired orienting response per se. It is conceivable that hypoactivation in ADHD occurs in tasks that require activation of the ventral network to plan and maintain appropriate behavior whereas suppression of the same network is needed to avoid distraction during other tasks. A deficit in adaptive regulation of bottom-up processing would explain both findings.

On the other hand, the lack of deactivation could involve a more elaborate processing of the novel pictures. Buckner, Wheeler, & Sheridan (2001) showed that enhanced left frontal activation along the inferior frontal gyrus was linked to successful incidental encoding of novel information in healthy adults. Thus, it would be interesting to assess in further studies whether children with ADHD show better subsequent recognition of unrepeated pictures than control children.

In contrast to our results, Stevens et al. found diminished activity for ADHD patients in the left parietal lobule and a posterior part of the left superior temporal gyrus in response to novel auditory stimuli (Stevens et al., 2007). Our findings might result from the different sensory modality we used, since novelty processing networks have been shown to differ for distinct stimulus modalities. While visual novels engage posterior brain regions more strongly, auditory novel oddballs elicit responses in the superior temporal plane (Halgren et al., 1995) and the inferior parietal lobule (Kiehl, Laurens, Duty, Forster, & Liddle, 2001b). Moreover, in the study of Stevens and colleagues (2007), novel oddball tones did not require a response as they did in our experiment. Responding to every stimulus probably assured similar levels of attendance for novel pictures and the target picture. Thus, the observed activity in our study might be more clearly associated with pure novelty detection and less modulated by greater inattention in the ADHD group.

Rareness. Contrasting the contextually rare neutral oddball and the standard picture did not yield significant activation differences in the healthy comparison group. If a stimulus is repeatedly presented without further behavioral significance, the initial automatic novelty response associated with its first appearance declines throughout further processing (Cycowicz & Friedman, 1998). This habituation reflects an efficient use of limited neural capacity and enables to focus on an ongoing task. We assume that the lack of activation differences between the standard picture and the neutral oddball in healthy children and adolescents could be due to the previously described process.

In contrast to the comparison group, ADHD patients activated the parahippocampal and fusiform gyrus, the cuneus, the precuneus and bilateral middle occipital gyrus in response to the familiar oddball. Inclusive masking revealed that this activity pattern widely overlapped with the formerly identified novelty network (Figure 4B) indicating that participants with ADHD did not differentiate between novel and familiar items to the same extent as the comparison group.

Although no correlation with age could be found, the difference between the groups seemed to be more pronounced in the younger group (11 to 13 years) when the age groups were analyzed separately in an exploratory analysis. Thus, the involvement of novelty related structures in the processing of a familiar picture might decrease with brain maturation which is decelerated in ADHD (Shaw et al., 2007).

However, effects similar to our results have been also reported in other domains. For instance, ADHD patients did not show differences between novel and familiar rare stimuli in theta activity (Fallahpour et al., 2010) or between familiar and unfamiliar (abstract) novel pictures in the P3a component (Marzinzik et al., 2012). Furthermore, Jansiewicz, Newschaffer, Denckla, and Mostofsky (2004) revealed that the habituation to visual stimuli in the peripheral hemifield was slowed for children and adolescents with ADHD. These results point to deficits in the processing of stimulus relevance in ADHD which might already involve early categorization and habituation processes. Our study complements these findings by showing for the first time that rare but familiar pictures activate the novelty network in children and adolescents with ADHD. We assume that the lack of differentiation between novel and familiar stimuli in ADHD could significantly contribute to their increased distractibility as the involuntary attention shift usually caused by novelty also appears after the rare but familiar stimulus.

Task relevance. Target stimuli in our study elicited activity in medial frontal areas, the thalamus, insula and precuneus as well as in occipital and temporal areas which is consistent with similar investigations of visual oddball tasks using fMRI (Ardekani et al., 2002; Clark, Fannon, Lai, Benson, & Bauer, 2000; Kiehl et al., 2001; Stevens et al., 2000). Additional neural activity within the left postcentral gyrus and right anterior cerebellum might be associated with the required motor response using the right index finger.

Surprisingly, we did not find any differences in neural activation in the group contrast. This contradicts other reports showing diminished activity for ADHD patients compared to a healthy comparison group in parietal association cortices, right precuneus and thalamus (Tamm et al., 2006), as well as within the left middle frontal and the right superior temporal gyrus (Stevens et al., 2007) or basal ganglia, left and right superior temporal lobes and posterior cingulated (Rubia et al., 2007). However, these differences might be accounted for by differences in the experimental set-up. Our analysis included only trials with correct responses and without multiple button presses. Thus, only neural activity associated with correct task performance was extracted which might be similar in children and adolescents with and without ADHD. Alternatively, the more appealing stimulus material of landscape scenes compared to letters (Tamm et al., 2006), arrows (Rubia et al., 2007) or sine tones (Stevens et al., 2007) as well as the required button press for every picture could have improved the performance of participants with ADHD. It has been shown, that ADHD patients are able to show unimpaired performance when a task is more intriguing or when the frequency of target stimuli is high (Corkum & Siegel, 1993; Friedman-Hill, 2010).

3.5 Summary

To summarize, children and adolescents with ADHD and a TD comparison group showed similar activation patterns in response to novel scene images, indicating intact novelty processing in ADHD. However, compared to the healthy comparison group, ADHD patients additionally engaged frontal and temporal areas associated with further processing when task-irrelevant novel pictures were presented and activated the novelty network also in response to rare but familiar pictures.

In terms of a network approach as a framework to understand ADHD pathology, this study contributes to the existing literature by showing that missing deactivation in the ventral attention network can be linked to ADHD. The lack of deactiviation is probably related to a deficient top-down dorsal network modulation but further studies have to investigate this relationship more closely. Furthermore, the reported novelty processing network overlaps widely with the orienting network proposed as one of three relevant attention networks by Posner and Petersen (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005) which shows once more that novelty is a highly salient feature that attracts attention and induces an orienting response. Hyperactivation of this network in ADHD during reorientation in a flanker task has been shown before (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006) but not during the processing of familiar rare stimuli. Again, we argue that this altered bottom-up processing of familiar stimuli might be modulated by dysfunctional top-down processes because the contribution of the orienting network only appeared in children with ADHD but not in a healthy comparison group.

In conclusion, our findings on the processing of novel but also rare familiar stimuli suggest an inefficient use of neuronal resources in children with ADHD that might be closely linked to their increased distractibility.

4 Experiment 2: Task-irrelevant novel sounds improve attentional performance in children with and without ADHD

The following study was first published in:
Tegelbeckers, J., Schares, L., Lederer, A., Bonath, B., Flechtner, H. H., & Krauel, K. (2016). Task-irrelevant novel sounds improve attentional performance in children with and without ADHD. Frontiers in Psychology, 6.

4.1 Introduction

After showing altered salience processing following novel and rare visual stimuli in a group of ADHD children and adolescents, the second experiment aimed to investigate the effects of novelty on attentional performance. According to the diagnostic criteria of the DSM IV, ADHD is associated with severe attentional impairments that become evident in lapses of attention, carelessness in cognitive tasks, forgetfulness or increased distractibility. However, when investigated systematically, ADHD patients do not consistently show the expected attentional deficits (Huang-Pollock & Nigg, 2003). Various studies have even identified specific task conditions or stimulus features that normalize attentional functioning in ADHD patients, for instance, reinforcement enhanced response inhibition (Konrad et al., 2000; Slusarek et al., 2001) and higher task difficulty (Friedman-Hill, 2010) or increasing event rates (Sergeant, 2000) improved task execution in children with ADHD. Furthermore, ongoing background stimulation has been shown to have a beneficial influence on ADHD patients: arithmetic task performance benefitted from background-music (Abikoff et al., 1996) and white noise improved free recall performance (Söderlund, Marklund, & Lacerda, 2009). In addition to such concurrent auditory stimulation the influence of interspersed and novel sounds has recently received interest. Van Mourik and colleagues (2007) found first evidence that task-unrelated environmental novel sounds improve accuracy in a visual two-choice reaction time task in comparison to a standard tone (600 Hz), particularly in children with ADHD. This finding, which indicates a beneficial effect of novelty on attention, however, contradicts not only the ADHD-specific behavioral symptom of increased distractibility, it is also incompatible with earlier work showing increased error rates and altered P3a components following novel sounds in ADHD patients in a similar task (Gumenyuk et al., 2005).

In summary, the findings of impaired attentional functioning in ADHD are contradictory and diverse. In this regard, it is important to consider that the term *attention* is not uniformly used and covers a range of cognitive processes. According to the attention network theory, three functional components of attention can be separated based on distinguishable neural networks (Petersen & Posner, 2012; Posner & Petersen, 1990): First, alerting refers to the ability to maintain an alert state for a certain period of time (tonic) but also to make use of external cues increasing the readiness to respond (phasic). Second, the executive control network is crucial to resolve response conflicts. Finally, two orienting networks are involved in the voluntary guidance of attention towards a specific task (top-down) but also responsible for involuntary attention switches to salient sensory stimuli that appear outside the current attentional focus (bottom-up) (Corbetta & Shulman, 2002).

The influence of an irrelevant auditory stimulus on task performance is according to the attention network theory related to both, the alerting as well as the orienting component (SanMiguel et al., 2010a): behavioral facilitation is supposed to result in set-ups in which a sound induces an alerting effect, possibly by announcing a target (cf. Parmentier et al., 2010). Behavioral distraction, on the other hand, results from an orienting response that directs attention away from the task. A beneficial effect of novelty might thus be caused when the beneficial alerting effect exceeds the distracting orienting response (SanMiguel et al., 2010a; Wetzel et al., 2012). In the former experiment, focusing on the neural representation of novelty in ADHD, we found that task-irrelevant novel pictures increased activity in areas related to attentional orienting in ADHD patients compared to typically developing children and adolescents (Tegelbeckers et al., 2015). This finding suggests that behaviorally irrelevant novel stimuli are more likely to influence the patients than a TD comparison group. Whether this higher sensitivity leads to increased distraction or facilitation remains however ambiguous (Gumenyuk et al., 2005; van Mourik et al., 2007).

To shed light on this clinically relevant question, we decided to investigate the influence of novel sounds on a flanker paradigm because this task leads to sufficiently high error rates in children with and without ADHD (Mullane et al., 2009). Thereby, we hoped to overcome potential ceiling effects, particularly in the comparison group that previously might have prevented modulations of novel sounds to appear (Gumenyuk et al., 2005; van Mourik et al., 2007). Moreover, the flanker task enables the investigation of sound effects not only on sustained attention, as in simple visual decision tasks, but also on interference control evident in the degree of performance deterioration due to the incongruent flanking stimuli. Furthermore, we introduced a no-sound condition in addition to a repeatedly presented standard sound and the unique novel sounds to assess facilitating and distracting effects of both sounds against a baseline. To moreover separate effects of novelty from rarity, we presented novel sounds with the same probability as the standard sound and the no-sound condition. Finally, we wanted to overcome the differences in stimulus salience between novel and standard tones in previous studies (Gumenyuk et al., 2005; van Mourik et al., 2007). Therefore, both categories were chosen from a pool of meaningful environmental sounds in this experiment.

As both sounds conditions contained temporal information about the upcoming task display, we expected that all participants would show lower error rates and faster reaction times in the sound conditions compared to the no-sound baseline (Parmentier et al., 2010). In line with van Mourik et al. (2007), we furthermore expected to find an improvement in error rates for novel compared to standard sounds and more pronounced in children with ADHD than in the healthy comparison group.

4.2 Methods

Participants. Overall, 72 children aged between 8 and 13 years participated in this study. They were mainly recruited through advertisements in the local newspaper or referred to us by the Department of Child and Adolescent Psychiatry and Psychotherapy and underwent the diagnostic procedure as presented in section 2.2. The diagnostic criteria for ADHD according to DSM IV were met by 31 boys and five girls (mean age: 10.61±1.61). Among them, 29 participants were diagnosed with the combined subtype of ADHD, six with the primarily inattentive and one with the hyperactive/impulsive subtype. Participants with stimulant medication (N=18) discontinued the intake at least 24h before and on the day of the experiment. The comparison group consisted of 31 boys and five girls (mean age: 10.58±1.71) considered typically developing based on the diagnostic interview, questionnaire results, and test performance. ADHD patients who met present or lifetime criteria for any psychiatric disorder other than oppositional defiant disorder (ODD, n = 12) or conduct disorder (CD, n=1) were excluded from the sample. Control participants were excluded if there was evidence of any previous or current psychiatric disorder. Furthermore, exclusion criteria for all subjects included the existence of hearing impairments, an IQ below 80, or evidence for substance abuse. All participants had normal or corrected-to-normal vision.

As shown in Table 4, patients and typically developing participants showed no significant differences in age, but differed significantly when tested for their IQ. However, as groups were not randomly assigned, such differences were to be expected as ADHD is often associated with lower IQ values (Kuntsi et al., 2004). Furthermore, groups differed significantly in their attentional performance (d2) and self-and-proxy assessment of attention related problems (YSR, CBCL). Memory measures of the VLMT showed as well a significant difference between groups with regards to learning, delayed recall, and recognition.

All participants and their parents received detailed information about the study and gave written assent/consent. Children and adolescents received 5€ per hour in the form of gift vouchers. The study was approved by the local ethics committee of the University of Magdeburg, Faculty of Medicine, and followed the ethical standards of the Declaration of Helsinki.

Table 4. Sample description and comparison of the ADHD and the typically developing group (TD) in the behavioral flanker task

	ADHD Mean (SD)	TD Mean (SD)	t
Gender	31 male, 5 female	31 male, 5 female	
Age	10.61 (1.61)	10.58 (1.71)	-0.71
IQ (CFT-20-R/CFT-1)	101.92 (13.76)	110.08 (11.97)	2.69**
Attentional Performance (d2/bp-test)	54.36 (30.46)	74.56 (24.42)	3.10**
Verbal Learning and Memory Test			
- Learning	48.89 (10.44)	54.2 (8.93)	2.3*
- Delayed recall	50.38 (8.87)	55.13 (8.32)	2.33*
- Recognition	48.74 (10.2)	55.71 (10.82)	2.77**
Attentional Problems (self-rating, YSR)	60.42 (8.44)	53.00 (5.11)	-7.62***
Attentional Problems (parental rating, CBCL)	67.71 (7.06)	55.10 (5.34)	-3.23**
Diagnoses			
ADHD – combined	29		
ADHD – inattentive	6		
ADHD – hyperactive/impulsive	1		
Oppositional defiant disorder	12		
Conduct disorder	1		

Task and Procedure. To assess attentional performance in this study, we chose an adaptation of the Eriksen flanker task (Eriksen & Eriksen, 1974) that consisted of white arrows masked by a light-grey rhombus on grey background (Fig. 11). Participants had to indicate the direction of the target arrow in the center of the screen via button press. In line with previous studies, this target arrow appeared either alone (neutral flanker condition) or flanked by two simultaneously presented arrows on each side. These flanking arrows pointed into either the same direction as the target arrow (congruent flanker condition) or the opposite direction (incongruent flanker condition). Each condition (neutral, congruent, incongruent) was presented with equal frequency of 48 times.

Randomly intermixed with a baseline without sound stimulation, two-thirds of all trials per condition were preceded by a sound. In half of these trials (N=48) the sound was a repeatedly presented sound serving as standard. In the other half, novel nonrecurring sounds were presented. A pool of 140 auditory stimuli of environmental content (e.g. dog bark, doorbell) was selected for this study from a German commercial CD ("1.111 Geräusche", Döbeler Cooperations, Hamburg, Germany). All sounds were edited with the software audacity (www.audacity.sourceforge.net) to be of equal volume (60dB) and duration (500ms). Then, 49 sounds were randomly assigned to every participant: one to serve as the standard and 48 novels. All sounds were presented over headphones.

During task instruction, participants were informed that sounds would be presented throughout the experiment, but that they were unrelated to the task and could be ignored. The experiment started with a training run of 12 trials in order to familiarize the participants with the task and the standard sound. Subsequently, two experimental runs of the flanker task were carried out with a short break halfway through. Overall, the experiment lasted approximately 15 minutes and was carried out on a laptop with a 17.3 inch screen and Presentation software (Version 16.0, www.neurobs.com).

As Figure 11 shows, every trial started with the simultaneous presentation of a black fixation cross and the auditory stimulus for 500ms, followed by a blank screen for 100ms. Right after the display of the arrows (60ms), a blank screen was shown again for 500ms followed by the presentation of another fixation cross for 1500ms. Participants were instructed to be as fast and accurate as possible.

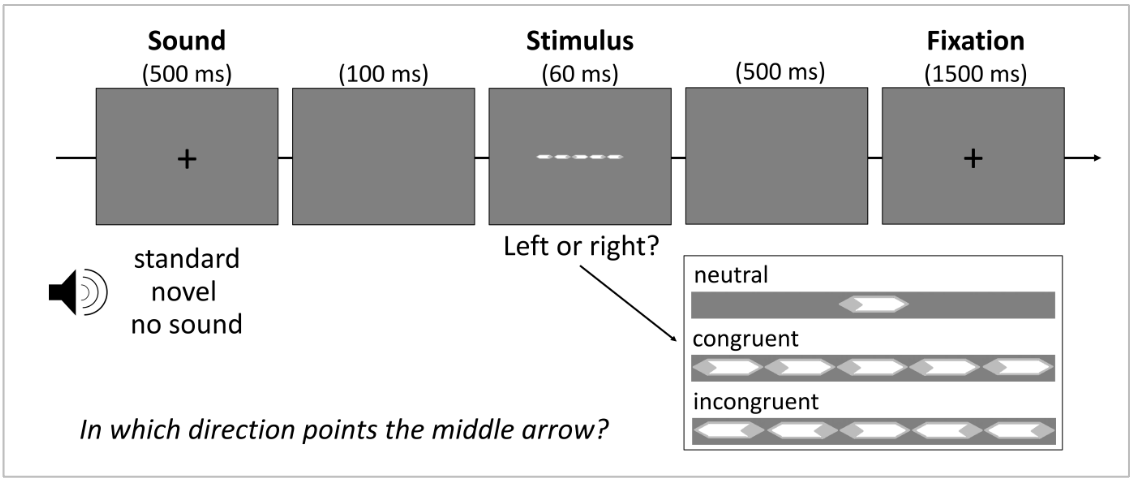


Fig. 11 Schematic illustration of the modified flanker task

Data analysis. Attentional performance was assessed via percentage of errors (commission and omission) as well as mean reaction time (mRT) and reaction time variability (RTV) for correct trials. The latter was computed by individually normalizing the standard deviation with the mean reaction time (SD/mRT). Furthermore, the flanker effect as a measure of interference control was computed by subtracting performance in congruent trials from incongruent trials for mean reaction times, RTV, and error rates respectively. Participants whose performance in overall error rate or mean RT differed for more than two standard deviations from their respective group mean were excluded from further analysis. This led to a final sample size of N= 64 (five girls per group). However, sample characteristics did not differ from the ones previously reported.

In the statistical analyses, we carried out 2x3 repeated-measures analyses of variance (ANOVA) on error rates, mean reaction times, and reaction time variability, including the factors group (ADHD vs. TD) and sound (standard vs. novel vs. no sound). To account for violations of sphericity, the Greenhouse-Geisser correction was applied if necessary. The results from the ANOVAs were further investigated by post-hoc t-tests, if applicable. Finally, we correlated all performance measures with IQ separately for each group.

4.3 Results

Accuracy in the flanker task is described by the percentage of commission errors (false responses) and omission errors (misses). Figure 12 shows the influence of the sound conditions on both error rates per group. The 2x3 ANOVAs revealed main effects of group and sound: Children with ADHD performed less accurately than the comparison group regarding the commission error rate ($Fgroup_{(1,62)} = 12.83$, $p = 0.001$) as well as omission error rate ($Fgroup_{(1,62)} = 14.47$, $p<0.001$). However, the modulatory influence of sound differed between the types of errors. Concerning commission errors, the main effect of sound ($F_{(1.8,124)} = 8.45$, $p = 0.001$) resulted from a significant decrease in performance following the standard sound compared to novel sounds ($t_{(63)}=3.25$, $p = 0.002$) or trials with no sound stimulation ($t(63) = -2.63$, $p = 0.011$) in both groups. For omissions, both sound conditions led to a significant improvement compared to trials without a sound ($Fsound_{(1.36,124)} = 11.99$, $p<0.001$; standard: $t_{(63)} = -3.29$, $p = 0.002$; novel: $t_{(63)} = -3.16$, $p = 0.002$).

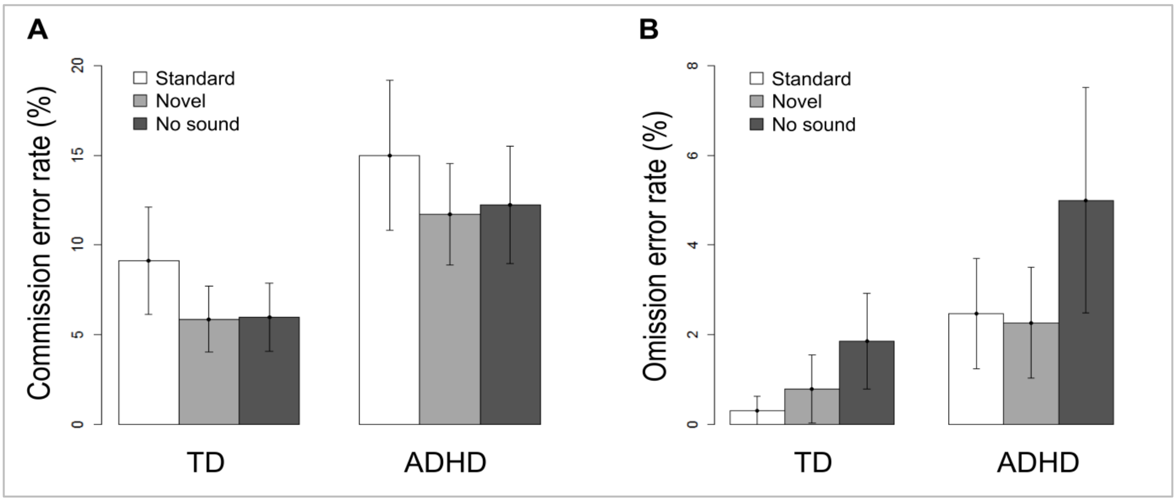


Fig. 12 Task performance separated into (A) commission errors and (B) omission errors per sound condition and group. Error bars denote confidence intervals of 95%

Similarly, the means and variabilities of reaction time were modulated by sound (mRT: $F_{(1.71,124)}= 51.65$, $p<0.001$; RTV: $F_{(2,124)} = 3.53$, $p<0.05$) (Fig. 13). Mean RT decreased in trials with a sound compared to the no-sound baseline (standard: $t_{(63)} = -6.9$, $p<0.001$; novel: $t_{(63)} = -4.92$, $p<0.001$) and was shorter when the standard sound was presented compared to novel sounds ($t_{(63)} =-2.38$, $p = 0.02$). Furthermore, novel sounds ($t_{(63)} = -2.85$, $p<0.01$) but not standard sounds ($t_{(63)} = -1.81$, $p = 0.08$) reduced RTV compared to trials without preceding sound. Group differences were only observed for RTV indicating that ADHD patients were significantly more variable in their reaction times than typically developing children ($F\mathit{group}_{(1,62)} = 13.21$, $p<0.01$).

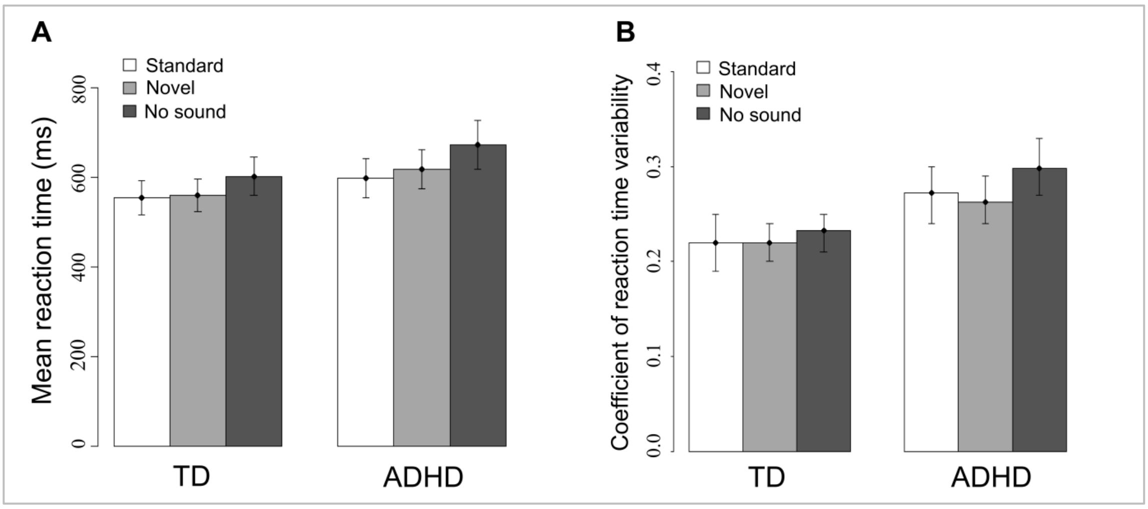


Fig. 13 Mean reaction times (A) and reaction time variability as coefficient of standard deviation/mean (B) for both experimental groups for all sound conditions. Error bars denote confidence intervals of 95%

None of the presented results changed when children with inattentivee subtype or comorbid dissocial disorders were excluded from the analysis. The analyses of the flanker effect (difference value: incongruent - congruent) for mean RT, RTV and error rates revealed no influence of sound nor group on interference control. Finally, none of the performance measures correlated significantly with IQ (all $r < 0.4$).

4.4 Discussion

The current study aimed to investigate the influence of task-irrelevant sounds on attentional performance of children and adolescents with and without ADHD during a flanker task. In particular, we were interested in the performance modulation by unique novel sounds compared to a repeatedly presented standard sound and a baseline without sound presentation. We found that both sounds improved reaction times and omission error rate compared to no sound but only novels also reduced reaction time variability. Moreover, standard but not novel sounds increased the commission error rate.

As expected from previous research on the flanker task (Mullane et al., 2009), children with ADHD performed worse than the comparison group regarding accuracy measures and reaction times. This could be associated with difficulties in interference control (Mullane et al., 2009), sustained attention (Huang-Pollock et al., 2012), or behavioral control (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). However, although they performed better than the ADHD patients in this study, the group of typically developing children produced error rates ranged between six and ten percent, indicating that the task was difficult enough to reveal sound modulations also in the comparison group. This resolved a potential limitation of previous studies, because beneficial effects of sounds on task performance can only unfold when performance is not at ceiling (Alderson et al., 2008; van Mourik et al., 2007). Indeed, we found performance modulations by sounds not only on reaction times and reaction time variability but also on error rates in healthy children as well as in children with ADHD. No interaction effects could be detected, indicating more similar processing in both groups than expected before (Gumenyuk et al., 2005; van Mourik et al., 2007).

Insufficient task performance in the flanker task is composed of two different types of errors that are based on different processes: missed responses follow lapses of attention and false reactions occur due to failure in behavioral control: namely, in interference control, the suppression of task-irrelevant competing stimuli, and in response inhibition, the suppression of a pre-potent response. Considering omission errors, we observed a beneficial effect of both sound conditions compared to the no-sound condition, indicating that they both served as alerting signals. The sounds announced the task display, functioning as cues, and enabled response preparation likewise in children with and without ADHD. Previous research has already shown that the impact of a task irrelevant sound depends more largely on the informational value it transmits than on the content (Parmentier et al., 2010) and that children with ADHD can benefit from meaningful sounds in the same way as typically developing children (Alderson et al., 2008; Mullane, Corkum, Klein, McLaughlin, & Lawrence, 2011).

However, although both sound conditions in our experiment were of identical informational value regarding the onset of the target display, we observed differential effects on commission errors, reaction times, and reaction time variability. Standard compared to novel sounds increased the commission error rate in both groups and decreased reaction times. These results suggest a speed accuracy trade-off similar to the findings by van Mourik et al. (2007): the repeated presentation of the standard sound might have favored the initiation of pre-potent responses thereby increasing the probability of mistakes. Novel sounds, on the other hand, also accelerated responses compared to the no-sound condition but apparently led to more thorough processing of task relevant stimuli than the standard sound. Similar effects of prolonged reaction times by novel sounds have been shown before (Wetzel et al., 2012) and can be attributed to attentional orienting towards incoming unexpected information. The necessity to reorient attention could lead to slower processing of the task display (orienting costs) but also cause an increased alertness (alerting benefits; San Miguel, Linden et al. 2010). This is supported by electrophysiological findings from comparable paradigms where children and adults showed larger P3a amplitudes towards novel task-irrelevant stimuli without behavioral costs (Ruhnau et al., 2010; van Mourik et al., 2007; Wetzel, Schröger, & Widmann, 2013).

Moreover, intra-individual variability of reaction times to the task relevant stimulus was only successfully reduced by preceding novel sounds. This is particularly relevant, because elevated RTV in cognitive tasks is one of the most stable characteristics in ADHD (Leth-Steensen, King Elbaz, & Douglas, 2000; Tamm et al., 2012; Vaurio, Simmonds, & Mostofsky, 2009). In previous studies, beneficial effects on RTV in ADHD have been reported for reward, increased event rate, and stimulant medication (for review see Tamm et al., 2012). In our setup, novel sounds seemed to improve behavioral monitoring compared to the no-sound condition, actually suggesting a potential facilitating role of novel sounds in cognitive tasks. However, in contrast to studies employing reward, the novel sounds did not normalize RTV in the patient group to the level of typically developing children.

Furthermore, it is worth noting that novel sounds did not decrease the commission error rate compared to the no-sound trials, indicating that when trials were successfully attended, performance of the task was equally accurate in trials with no and novel sounds. However, the latter accelerated the response compared to the no-sound baseline suggesting more efficient processing of the target stimulus and/or more efficient response selection.

The flanker effect, which can be seen in deterioration of accuracy and reaction times in the incongruent compared to congruent condition, was not modulated by the sounds. Thus, there was no specific beneficial effect on interference control which is in line with previous studies showing that the influence of novel sounds is independent of the task’s cognitive demands (Parmentier, 2014). We therefore think that the sounds did not influence cognitive execution of the task per se but rather improved the amount of attentional resources allocated to the task relevant stimulus.

Overall, task accuracy as a combination of sustained attention and correct execution benefitted from the presentation of novel compared to standard and no sounds in both groups. These findings contribute to the ongoing debate about novelty being a salient feature that induces unspecific activation and attracts attention leading to behavioral facilitation (SanMiguel et al., 2010a; Wetzel et al., 2012). With regard to ADHD, past studies already showed that orienting reactions following novel stimuli do not differ between patients and comparison groups (Jonkman et al., 2000; Kemner et al., 1996; Mullane et al., 2011). However, due to potential deficits in the alerting and executive attention networks (Konrad et al., 2006; Mullane et al., 2011) the influence of novel sounds might be particularly relevant for individuals with ADHD and different explanations for the impact of novel sounds are possible.

Firstly, various models of ADHD pathogenesis have been proposing that distractibility as well as hyperactive behavior could serve to compensate for cortical hypoarousal (e.g. optimal stimulation theory, Sergeant 2005; Zentall & Zentall, 1983). The cognitive-energetic model (CEM) (Sergeant, 2005) sees dysregulation of effort (motivation), arousal, and activation as key factors in ADHD interacting with attentional and executive problems. For example, arousal is supposedly evident in phasic responses during stimulus processing and can be increased by signal intensity or novelty whereas activation is associated with tonic physiologic readiness signifying alertness. The CEM predicts that the level of arousal/activation that is needed to achieve optimal performance is higher in individuals with ADHD than in healthy controls. This fits our results in the way that novelty could have induced phasic arousal and thereby provided patients with a temporarily optimized activation level at which better cognitive functioning, reflected in improved overall performance, was possible. However, in contrast to investigations using concurrent background stimulation during task execution (Abikoff et al., 1996; Söderlund et al., 2007), our setup might not increase activation permanently but specifically for trials in which novel sounds appeared. Furthermore, the beneficial effect of meaningless noise might rather be based on auditory masking and operate over screening out distracting influences.

On the other hand, task related beneficial effects of novelty may also stem from the disruption of the ongoing activity initiated by the orienting network that enhanced executive control (Fan et al., 2005) or by activation of the anterior cingular cortex and insula. The latter structures are not only involved in novelty processing but are also responsible for switching from default mode activation to task positive networks (Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008; Sripada, Kessler, & Angstadt, 2014). As children with ADHD are expected to suffer from poor regulation of the default mode network (Fassbender et al., 2009; Sonuga-Barke & Castellanos, 2007), increased involvement of these structures might also explain the behavioral benefit, especially the decreased reaction time variability. Future electrophysiological and/or imaging studies will have to clarify whether beneficial effects of task-irrelevant novelty are based on increased unspecific alerting, activation of the orienting network, or default mode network suppression.

However, our results of improved performance by task preceding novelty in children with and without ADHD contradict previous studies. In ADHD, distraction has been shown by the inclusion of neutral sounds or visual stimuli (Berger & Cassuto, 2014; Gumenyuk et al., 2005). Also in attentive children, distraction in terms of reaction time prolongation by novel sounds could have been expected (Wetzel & Schröger, 2014). However, former studies differ from ours in some aspects. First, we did not use a simple decision task but received moderate error rates in both groups. This might be important because the optimal stimulation level for an ongoing task might follow an inverted U-shape. When typically developing children perform at their optimum, additional stimulation might have a detrimental effect on specific cognitive functions (Helps, Bamford, Sonuga-Barke, & Söderlund, 2014). Moreover, the effect of novel sounds might differ inter-individually from beneficial to distracting. Secondly, novel sounds in our experiment occurred with the same probability as the standard sound, making their appearance much more predictable than in the usual oddball scenario (80% standard, 20% novel). Wetzel and colleagues (2007) already showed that the distraction by deviant sounds is reduced with the predictability of their occurrence. Therefore, previous findings might be biased by interacting effects of novelty and rarity. Furthermore, deceleration following the novel sound compared to the standard sound is frequently understood as evidence of distraction. In children with ADHD, however, slowing down could actually improve adaptive action selection, because these patients usually suffer from impulsive, variable reactions. However, without thorough understanding of the underlying neural mechanisms of the effect of particularly novel sounds on task performance the inconsistent findings are hard to resolve. Further research using imaging techniques and including children with varying degrees of attentional abilities is needed to better understand the bidirectional role of novelty in attention control.

Summarizing, our study shows that task-irrelevant novel sounds can facilitate attentional performance in children with and without ADHD indicated by reduced omission error rates, reaction times, and reaction time variability without compromising performance accuracy. These findings encourage exploring practical applications of task irrelevant novel stimulation in homework or classroom settings to improve attentional performance in ADHD.

5 Experiment 3: The neural basis of irrelevant sound effects on task performance in children with and without ADHD: alerting, orienting, and executive control

5.1 Introduction

Since experiment 2 provided evidence for novelty related beneficial effects on performance in children with and without ADHD, the underlying neural substrates of these modulations were of further interest. We hypothesized that the observed beneficial effect could be based on either a phasic increase in alertness, involvement of the orienting network or improved DMN deactivation. With regard to these considerations, I will shortly present the distributed neural equivalents of the already introduced three attention networks (Petersen & Posner, 2012). First, alerting is closely related to fronto-parietal noradrenergic brain circuits whereby the effect of warning signals has been associated more strongly with the left than the right hemisphere (Fan et al., 2005; Petersen & Posner, 2012). Second, the two orienting networks are not only functionally distinguishable but are also sub-served by different brain networks (Corbetta & Shulman, 2002): bottom-up processing and automatic allocation of attention to sensory stimuli involves the ventral attention network (VAN) consisting of the temporo-parietal junction (TPJ) and ventral frontal cortex. Top-down control of attention requires a dorsally located network consisting of the intraparietal sulcus (IPS) and frontal eye field (FEF) (dorsal attention network, DAN). Third, the executive control network consists of the dorsal anterior cingulate (ACC) and dorsolateral prefrontal cortex (dlPFC) (Fan et al., 2005; Raz & Buhle, 2006; Ullsperger, Danielmeier, & Jocham, 2014).

To measure all three networks efficiently in one experiment, the attention network task (ANT) was developed (Fan et al., 2002) as a combination of cued detection (Posner, 1980) and flanker task (Eriksen & Eriksen, 1974). The ANT is similar to our auditory cued flanker task (Tegelbeckers et al., 2016) except for its pure visual content. In the ANT, alerting as well as spatial orienting effects are induced by arrow stimuli. Behavioral studies using this test in children and adults suffering from ADHD revealed inconsistent results: some studies found no behavioral difference in any of the networks scores between ADHD patients and TD comparison groups (Adólfsdóttir, Sørensen, & Lundervold, 2008; Kooistra, Crawford, Gibbard, Kaplan, & Fan, 2011; Kratz et al., 2011; Oberlin, Alford, & Marrocco, 2005) while others reported stronger beneficial effects of alerting cues (Booth, Carlson, & Tucker, 2007; Casagrande et al., 2012; Johnson et al., 2008; Mullane et al., 2011) or spatial orienting cues in ADHD compared to TD participants (Mogg et al., 2015). Most studies agreed on impairments in executive functioning for ADHD patients (Gupta & Kar, 2009; Johnson et al., 2008; Konrad et al., 2006; Mullane et al., 2011). Furthermore, one study so far employed the classic ANT in an fMRI study with children suffering from ADHD. Konrad and colleagues (2006) revealed altered neural activity in all three attentional networks in the disorder but failed to find differences in behavioral performance.

We aimed to gain further insight into the attentional networks while investigating the influence of preceding sounds on task performance. The utilization of sounds to induce alerting and orienting effects has thereby certain advantages over the original ANT version when one is interested in ADHD related attentional functioning. Most importantly, the limitation to visuo-spatial attentional processes in the ANT might hinder the investigation of ADHD related impairments because when examined individually these processes seem to be intact in the disorder (Huang-Pollock & Nigg, 2003). Instead, attentional impairments in ADHD might show in more ecologically valid, multimodal designs. In line with this assumption, alerting effects are expressed more prominently in ADHD when induced by an auditory instead of a visual cue (Casagrande et al., 2012; Mullane et al., 2011) and also orienting response differences between TD and ADHD children have been most robustly found following auditory not visual stimuli (for reviews see Barry et al., 2003 or Kemner et al., 1996). These differences in modality cannot simply be explained by modality-specific underlying networks as the orienting network is supposed to cover responses for unexpected visual, tactile and auditory stimuli alike (Downar et al., 2000; Downar, Crawley, Mikulis, & Davis, 2002). The responsiveness of this network might however vary for different modalities. Insofar, the influence of novel sounds, which induce an orienting response, is of particular interest in ADHD (as outlined in 1.3) and has in the current form not been investigated in children and adolescents with ADHD nor typical development. To date, oddball studies revealed diminished (Stevens et al., 2007) or enhanced (Tegelbeckers et al., 2015) novelty related brain activation in ADHD but the neural modulation of task-related activity by novel stimuli has not yet been examined.

In doing so, we expected to find performance differences between the groups in form of impaired accuracy, reaction times and interference control (distraction by incongruent flanking stimuli) in the patients. At the same time we expected both sound conditions to improve performance, particularly in participants with ADHD compared to TD children and adolescents (in line with Tegelbeckers et al., 2016). Furthermore, with regard to brain activation pattern, we hypothesized that participants with ADHD would display enhanced activity in the fronto-parietal alerting network following the standard sound due to their underlying alerting deficit (Sergeant, 2005) as well as an increased reaction in the ventral attention network following novel sounds (Tegelbeckers et al., 2015). The neuronal executive control network was on the contrary expected to show decreased functioning in ADHD compared to TD children and adolescents (Vaidya et al., 2005).

Furthermore, we introduced one scanning run of experimental set-up without task execution to evaluate the neural influence of the sounds outside the context of an actual task. In doing so, we are able to investigate whether general auditory processing during passive listening differs for the groups. Furthermore, in the light of possible interactions between the attentional networks (Callejas, Lupiànez, Funes, & Tudela, 2005; Spagna, Mackie, & Fan, 2015; Xuan et al., 2016), it is interesting to gain insight into task-unrelated neural effects of familiar and novel sounds: during the first run, the standard sound should not yet have an alerting function and the orienting response following novelty would be unaffected by task demands.

5.2 Methods

The current study was approved by the local ethics committee of the University of Magdeburg, Faculty of Medicine, and followed the ethical standards of the Declaration of Helsinki. All families gave written assent/consent und the children and adolescents were reimbursed with 5€ - gift vouchers per hour for their participation.

Participants. 55 boys aged between 11 and 16 years participated in the study. Ten had to be excluded because of excessive motion (6, see below), incidental findings of brain abnormalities (2) or performance at chance level (2) which indicates misunderstanding of the task or lack of motivation. Thus, the final sample as described in Table 5 consisted of 22 ADHD patients and 23 typically developing children. All participants, either referred to us by the Clinic of Child and Adolescent Psychiatry or recruited via advertisement in the local newspaper, underwent the same diagnostic procedure as described in section 2.2.

Table 5. Sample description and comparison of the ADHD and the typically developing group (TD) in the fMRI flanker task

	ADHD	TD	t (p)
Number	22 male	23 male	
Age (years)	13.27	13.57	0.61 (.55)
IQ (CFT 20R)	97.24	105.3	2.62 (.012)
Attentional performance (d2; PR)	54.95	76.30	2.72 (.009)
ADHD symptoms – self rating (YSR, T)	58.85	53.43	3.56 (.001)
ADHD symptoms – parental rating (CBCL, T)	66.8	53.3	6.56 (<.001)
Diagnoses: ADHD *combined*	17		
inattentive	2		
hyperactive	3		
Oppositional defiant disorder	4		
Medication: current (lifetime)	11 (14)		

In the ADHD group 17 participants were diagnosed with the combined subtype of ADHD, two with the hyperactive form and three were primarily inattentive (DSM IV criteria). Furthermore, four participants in this group met diagnostic criteria for a co-morbid oppositional defiant disorder (ODD). 11 patients currently taking stimulants discontinued medication at least 24h before and during the experiment. The comparison group of TD children matched the patient group in terms of age but scored significantly higher in the IQ and attentional performance assessment. Furthermore, they had no indication of any previous or current disorder and scored accordingly lower in the rating scales of ADHD symptomatology (Table 5).

Task and procedure. Participants performed the already described modified version of the cued flanker task (section 4.2) implemented via Presentation software (www.neurobs.com). Minor changes in the task encompassed the abandonment of the neutral condition; congruent and incongruent trials appeared with equal frequency throughout each block. Furthermore, in no-sound trials, the fixation cross vanished for 500ms in the respective time slot of sounds to give a visual indication of the upcoming task.

All of the auditory stimuli were environmental sounds selected from the same German commercial CD as previously used (“1.111 Geräusche”, Döbeler Cooperations, Hamburg, Germany). For this study, we assessed measures of spectral content (spectral central of gravity and pitch), spectral structure (harmonics-to-noise ratio) and temporal variability (standard deviation of frequency and amplitude) of each sound using Praat software (www.praat.org) (cf. Leaver & Rauschecker, 2010). Based on these parameters, sounds were identified that achieved values within the second and third quartile of the respective distribution. The resulting selection of six sounds represented stimuli of medium salience compared to all other sounds. For each participant, one of them was randomly selected to serve as repeatedly presented standard sound. The remaining 140 sounds served as uniquely presented novels.

All sounds were presented for 500ms, followed by a 100ms delay and the task display shown for 60ms. Subsequently, a blank screen appeared for 500ms before a fixation cross that indicated the inter trial interval. The duration of this interval was jittered between two and four seconds (Fig. 14). Participants were allowed to respond to the target for up to a maximum of 2s.

Each session started outside the scanner with a training block of the task consisting of 24 trials. During training, no novel sounds appeared, but half of the trials were preceded by the individual standard. All participants had the opportunity to repeat the training block, if necessary and to clarify any questions before entering the scanner. In the scanner, a comfortable volume level was adjusted individually for each participant and they were presented with one run of a passive version of the task which was composed of 20 trials per cue condition (a total of 60). In this run, the original stimulus sequence was used with modified (filled) bidirectional arrows to allow us to compare the groups with regard to sound-related activity without the actual task demands (Fig. 14). Afterwards, participants performed three experimental blocks with 120 trials each (40 trials per sound condition) interspersed with short breaks.

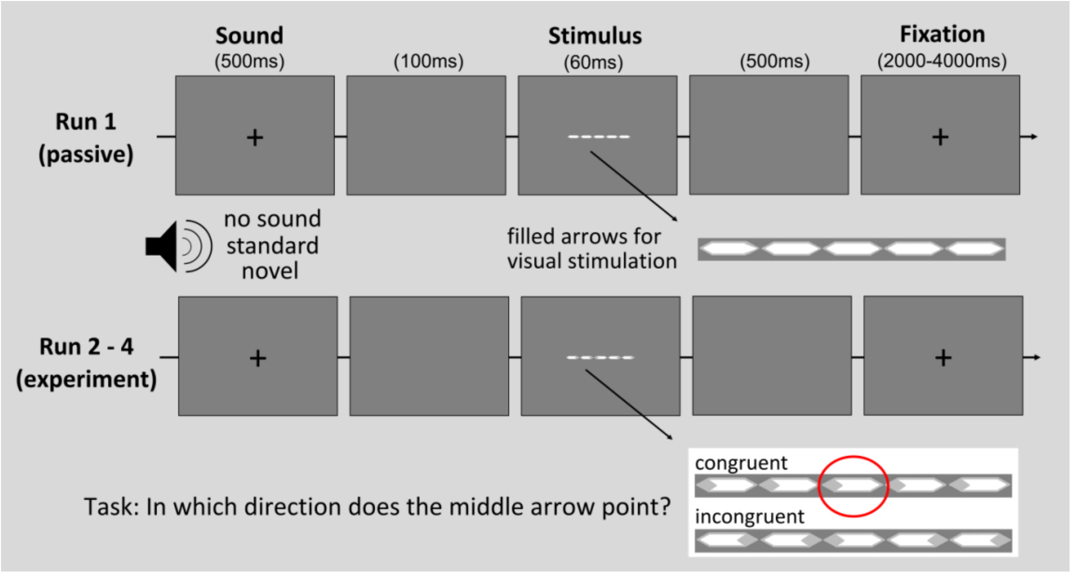


Fig. 14 Illustration of the cued flanker task in the experimental procedure of the fMRI study

fMRI image acquisition and processing. Image acquisition took place on a 3T Philips Achieva using a 32-channel head coil. First, a high resolution T1-weighted structural image was collected in 192 sagittal slices with a voxel size of $1mm^3$. Then, whole-brain functional images (run 1 = 141, run 2-4 = 290 each) were acquired via an echo planar imaging (EPI) sequence parallel to the anterior-posterior commissure in axial planes. The sequence was measured in 35 slices in ascending order with a spatial resolution of 3mm3 (FOV=240x240, flip angle=90, TR=2s, TE=30ms).

Functional images were preprocessed and analyzed using Statistical Parametric Mapping software (SPM8, Wellcome Trust Center for Neuroimaging, London) running on Matlab Version 2012b (the Mathworks Inc, MA). Preprocessing procedure started with correction for slice acquisition timing, followed by realignment to the first image in the respective run to account for head movement and co-registration of all images to the mean. Realignment produced six head motion parameters which were then used for an additional motion correction step via ArtRepair toolbox (Stanford Psychiatric Neuroimaging Laboratory) to account for increased movement in our young and partly clinically impaired sample. ArtRepair detects volumes with rapid scan-to-scan movements greater than 0.5mm/TR and substitutes them by interpolating the two nearest scans (Mazaika, Glover & Reiss, 2011). This procedure revealed six very noisy data sets in which more than 30% of all volumes would have had to be repaired. Thus, these participants had to be excluded from further analysis (Mazaika et al., 2011) and are not part of the reported sample. The repaired functional imagines were spatially normalized to the anatomical T1 template provided by SPM and smoothed with a 6mm FWHM istotropic Gaussian kernel. To remove low-frequency drifts, highpass filtering was applied at a cutoff of 1/128Hz.

Behavioral statistics. The behavioral influence of preceding sounds on task performance was investigated via accuracy (percentage of correct trials), reaction time and reaction time variability (standard deviation divided by mean reaction time) in correct trials. These measures were analyzed separately using a repeated measures analysis of variance (ANOVA) including the factors sound (no sound vs. standard vs. novel) and group (ADHD vs. TD). Furthermore, differences between incongruent and congruent trials (flanker effect) with regard to accuracy, reaction time (RT) and reaction time variability (RTV) were computed to serve as measures of interference control and analyzed via a sound x group ANOVA. Finally, all dependent variables were correlated with age and IQ to identify systematic associations with behavioral measures.

fMRI statistics. Statistical analysis with SPM followed the general linear model (GLM) approach. For each participant a stick function was defined at first level including the six effects of interest (three sound conditions with two levels of congruency each (congruent vs. incongruent), one effect of no interest (errors) and the six head movement parameters from preprocessing as confounds. These regressors were then used to convolve a canonical hemodynamic response function time-locked to the onsets of the flanker display. Finally, individual contrast images of interest were generated.

Second level statistical analysis of the fMRI data followed the rational of the behavioral analysis. First, to determine effects of alerting and orienting, we aimed to investigate the influence of both sound types compared to no sound in relation to group affiliation on brain activation before (run 1) and during task performance (runs 2-4). Therefore, first level individual contrast images of standard and novel sounds against no sound baseline respectively were entered into a whole brain full-factorial ANOVA with the factors Group (ADHD vs.TD) and Sound (Standard > No vs. Novel > No). Following this analysis, t-tests within and between the groups were conducted if appropriate. Furthermore, percentages of signal change in form of beta values were extracted in the peak voxel of areas of interest using rfxplot (Gläscher, 2009).

To investigate the influence of sounds on interference control, flanker effect contrast images (incongruent > congruent) for every sound condition were produced and entered into an additional full-factorial ANOVA with subsequent t-tests and extraction of betas. All contrasts were thresholded at $p>0.001$ (uncorrected) and an extend range of $k=10$ voxel.

5.3 Results

Behavior. The 3x2 repeated measures ANOVA revealed significant main effects of both factors sound ($F_{(2,86)} = 9.78$, $p<0.001$) and group ($F_{(1,43)} = 5.47$, $p = 0.024$) on accuracy in the flanker task. Children with ADHD performed worse (on average 91% correct) than their typically developing peers (on average 95% correct) but both groups benefitted when standard sounds ($t_{(44)} = 2.5$, $p = 0.016$) or novel sounds ($t_{(44)} = 4.82$, $p<0.001$) preceded the task display compared to the no sound baseline. However, in group-wise t-tests only the influence of novel sounds remained statistically significant (Fig. 15(A1)).

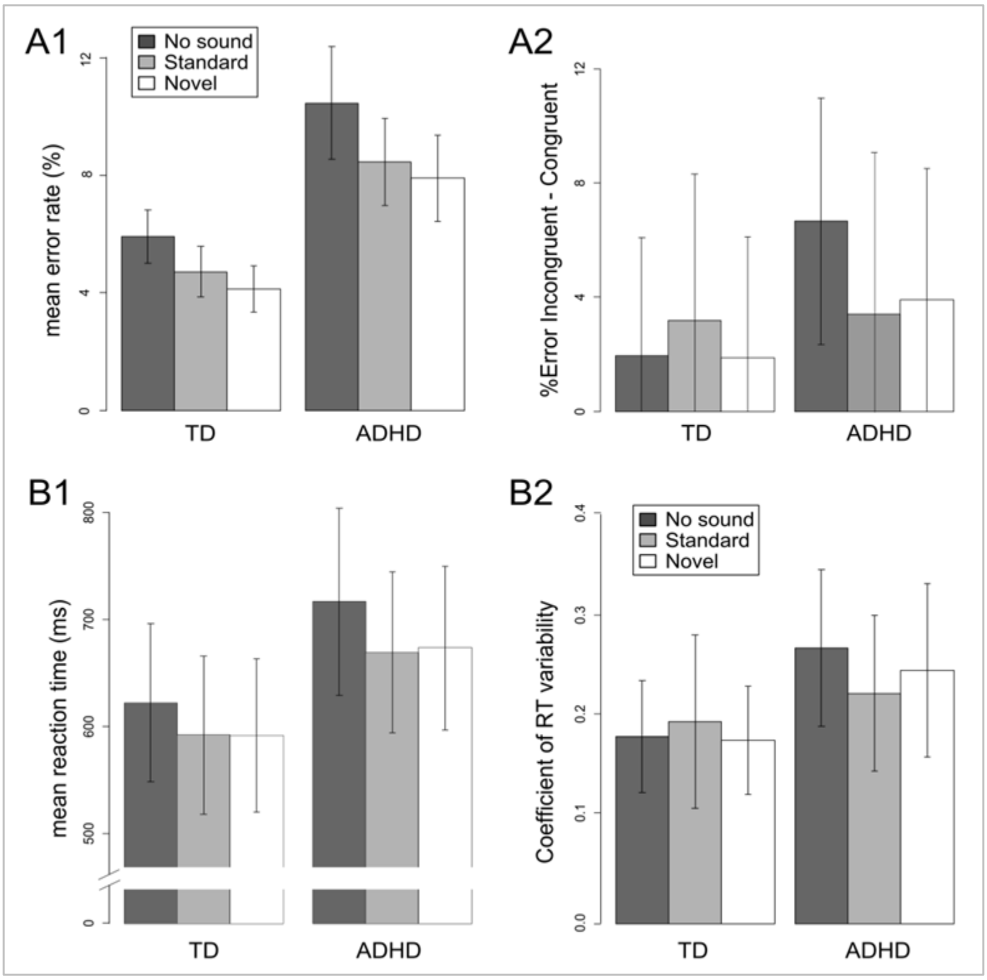


Fig. 15 Overview of behavioral modulations by sound condition per group:
(A1) Overall accuracy. (A2) Increase in errors by incongruent flanker stimuli.
(B1) Mean reaction times. (B2) Coefficient of reaction time variability (SD/Mean)

The results regarding reaction times are depicted in Figure 15(B). Children with ADHD showed slower (group: $F_{(2,43)} = 14.15$, $p = 0.001$) as well as more variable (group: $F_{(2,43)} = 10.33$, $p = 0.002$) responses than TD children. Furthermore, mean reaction times were influenced by sound ($F_{(2,86)} = 81.13$, $p<0.001$) interacting with group ($F_{(2,86)} = 3.41$, $p = 0.038$). Separate paired t-tests per group revealed a significant decrease in reaction times for both sounds compared to no sound for children with (standard: $t_{(21)}=7.34$, $p<0.001$; novel: $t_{(21)}=6.18$, $p<0.001$) and without ADHD (standard: $t_{(22)} = 7.08$, $p<0.001$; novel: $t_{(22)} = 8.65$, $p<0.001$). Both groups differed in reaction times in all sound conditions (all $p<0.01$) but the difference between standard sounds and no sound was significantly larger in ADHD children (-47,33ms) compared to the TD group (-29,98ms) ($t_{(43)} = 2.27$, $p<0.05$).

Moreover, sounds differentially influenced reaction time variability (group x sound: $F_{(2,86)} = 5.42$, $p = 0.006$): whereas response time variability was not modulated by sound in TD children (all $p>.23$), paired t-tests in children with ADHD revealed a decrease in reaction time variability in standard sound trials compared to the no sound baseline ($t_{(21)} = 4.03$, $p = 0.001$). Figure 15(B2) illustrates that the groups only differed in reaction time variability in trials without preceding sound ($t_{(43)} = 4.36$, $p<0.001$) and when a novel sound was presented ($t_{(43)} = 3.27$, $p = 0.002$).

Analyses on difference values between incongruent and congruent trials for mean reaction time and reaction time variability revealed no significant effect of sound or group. For accuracy, however, patients were more impaired by the flanking arrows than the comparison group ($F_{(2,43)} = 8.03$, $p = 0.007$). In addition, the interaction between sound and group reached marginal statistical significance ($F_{(2,86)} = 2.59$, $p=0.08$) leading us to explore the underlying data more thoroughly. Between-group comparisons showed that the groups differed in the flanker effect on accuracy only when no sound occurred ($t_{(43)} = 4.71$, $p=0.001$) but not during standard and novel sounds trials (both $p>0.13$). Furthermore, when analyzed separately, no influence of sound condition on the difference values could be found in TD children (all $p>.31$) whereas children with ADHD benefitted from standard ($t_{(21)} = 2.26$, $p = 0.035$) as well as novel sounds ($t_{(21)}=2.47$, $p = 0.022$) (Fig.15(A2)).

Neither age nor IQ significantly correlated with any of the performance measures. Furthermore, none of the behavioral results changed significantly when only ADHD participants with the combined subtype were considered.

fMRI – run 1. Results of the sound x group ANOVA on hemodynamic responses during the first run of passive listening are listed in Table 6. Analysis revealed a main activation difference for sounds in the bilateral superior temporal gyrus (STG), which was based on stronger activity following novel than standard sounds in both groups. Furthermore, the groups differed irrespective of sounds in the left middle temporal gyrus, right lingual gyrus, left medial frontal, precentral and inferior frontal gyrus. From these differential activations, the left middle temporal gyrus and uncus, left inferior frontal gyrus as well as right posterior lingual gyrus were generally more involved in ADHD whereas TD children showed stronger activations in the anterior part of the right lingual gyrus, left medial frontal and precentral regions, bilateral cingulate gyrus and left inferior parietal lobule. However, we also found interaction effects between sound and group in several areas, namely the bilateral medial frontal gyri, the right parahippocampal gyrus and precuneus reaching into mid-cingulum as well as left angular gyrus (Fig. 16). Post-hoc one sample t-tests for further exploration of the sound modulations per group (cf. Table S1 in supplement) exposed a more widespread network of novelty related activity in ADHD compared to TD participants. The former showed more bilateral activity following novel stimuli in the STG, posterior lingual gyri and inferior frontal gyri (IFG). For standard sounds on the other hand, the comparison group showed stronger activity than the patients particularly in the bilateral posterior cingulate, right parahippocampal gyrus and left medial frontal gyrus.

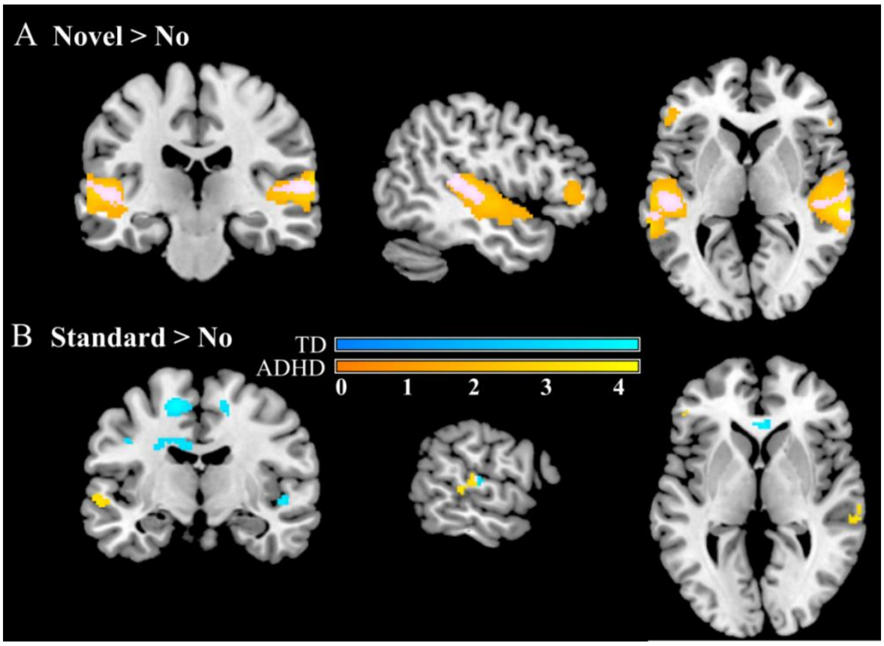


Fig. 16 Activation pattern elicited by novel and standard sounds for both groups during passive listening (run 1)

Table 6. ANOVA activation peaks and subsequent t-comparisons for the influence of novel and standard sounds in children with and without ADHD during passive listening

	k	MNI	Z
Main effect Sound			
R superior temporal gyrus	271	64 -32 6	5.15
L superior temporal Gyrus	265	-66 -38 8	4.18
Novel > Standard			
R superior temporal gyrus	370	64 -32 6	5.28
L superior temporal Gyrus	399	-66 -38 8	4.33
Main effect Group			
L middle temporal gyrus	69	-62 -16 -6	4.07
R anterior lingual gyrus	33	30 -48 -2	4.99
L medial frontal gyrus	27	-14 -8 58	3.87
R posterior lingual gyrus	13	24 -92 -10	3.60
L precentral gyrus	25	-44 -10 24	3.53
L inferior frontal gyrus	14	-52 36 0	3.36

ADHD > TD			
L middle temporal gyrus	100	-62 -16 -6	4.22
R posterior lingual gyrus	25	24 -92 -10	3.77
L uncus	13	-30 2 -26	3.73
L inferior frontal gyrus	31	-52 36 0	3.55
TD > ADHD			
R lingual gyrus	58	30 -48 -2	4.16
L medial frontal gyrus	53	-14 -8 58	4.03
L precentral gyrus	61	-44 -10 24	3.71
L inferior parietal lobule	11	-44 -26 28	3.62
L cingulate gyrus	12	-16 -18 32	3.31
R cingulate gyrus	15	18 -18 30	3.21
Interaction Sound x Group			
L medial frontal gyrus	95	-12 56 -2	4.24
R medial frontal gyrus	51	8 50 -8	3.82
R parahippocampal gyrus	38	20 -20 -24	3.55
R Precuneus	10	22 -58 46	3.30
R middle cingulum / precuneus	16	6 -50 36	3.27
L angular gyrus	24	-34 -62 34	3.25

fMRI - Main task. Concerning neural activity during task execution, the main ANOVA revealed a difference in neural activity for standard and novel sounds in a widespread area surrounding the superior temporal gyrus bilaterally (extending from TPJ to middle temporal gyri) as well as both inferior frontal gyri in children with and without ADHD. Except for one cluster in the middle frontal gyrus which was found to be more active for standard than novel sounds in subsequent t-tests, the aforementioned activations were predominantly based on stronger neural involvement following novel compared to standard sounds in both groups (Table 7). No main effect of group could be detected but the influence of sounds on brain activity interacted with group affiliation in the right pre-/postcentral gyrus, the medial frontal area, the superior frontal gyrus including the supplementary motor area bilaterally as well as the left inferior and right middle to superior temporal gyrus. Subsequent investigations of the beta values in these regions showed that true interactions occurred for the superior frontal cluster (activated by standard in ADHD and by novel in TD) and SMAs (no deactivation in ADHD) whereas the temporal areas differed between the groups for either standard (inferior and middle temporal) or novel sounds (superior temporal) (Fig. 17C).

Table 7. ANOVA activation peaks for the influence of novel and standard sounds in children with and without ADHD during task performance

	k	MNI	Z
Main effect Sound			
R superior temporal gyrus	4648	66 -26 8	>8
- middle temporal gyrus		62 -34 4	
- transverse remporal gyrus		48 -26 12	
- superior temporal pole		52 8 -10	
L superior temporal Gyrus	4436	-52 -34 8	6.94
- middle temporal gyrus		-60 -38 10	
R inferior frontal Gyrus	422	54 32 4	5.26
L inferior frontal Gyrus	123	-20 10 -20	4.25
	18	-56 20 20	3.49
Novel > Standard			
R superior temporal gyrus	4940	66 -26 8	>8
L superior temporal gyrus	5012	-52 -34 8	7.04
R inferior frontal gyrus	540	54 32 4	5.39
L inferior frontal gyrus	32	-56 20 20	3.67
L Amygdala	21	-16 -4 -18	3.64
Standard > Novel			
R middle frontal gyrus	22	34 22 48	3.41
Interaction Sound x Group			
R precentral/postcentral gyrus	51	16 -34 70	4.24
L inferior temporal gyrus	21	-48 -22 -18	4.04
R middle temporal gyrus	37	58 -40 -10	3.88
L supplemental motor area/ superior frontal gyrus	68	-14 -30 52	3.67
R superior temporal gyrus	23	60 -48 8	3.66
R supplemental motor area/ superior frontal gyrus	25	12 -28 54	3.55
R medial frontal area	12	8 -18 70	3.48

To further explore these interactions, one-sample t-tests per group and two-sample group comparisons were computed separately for novel and standard sounds (Fig. 17A & B). No difference between the groups in the processing of novel sounds could be found. Novel sounds induced activity in the bilateral STG and left IFG in both groups. Standard sounds, on the other hand, induced activation in comparatively small clusters in both STG in the TD group whereas additional involvement of the left hemispheric IFG, insular gyrus and bilateral middle temporal gyri was detected in children with ADHD. Direct group comparison yielded stronger activity for the patients compared to TD children and adolescents in the left insula extending to claustrum, left middle frontal gyrus, right paracentral lobule (SMA), left middle occipital gyrus, left superior temporal and right middle temporal gyrus for standard sounds.

Consequently, when the sound conditions were compared against each other in TD children, the differences between novel and standard were significantly stronger compared to the same contrast in the patient group. All peak activations of the group comparisons are presented in the supplementary Tables S2 and S3.

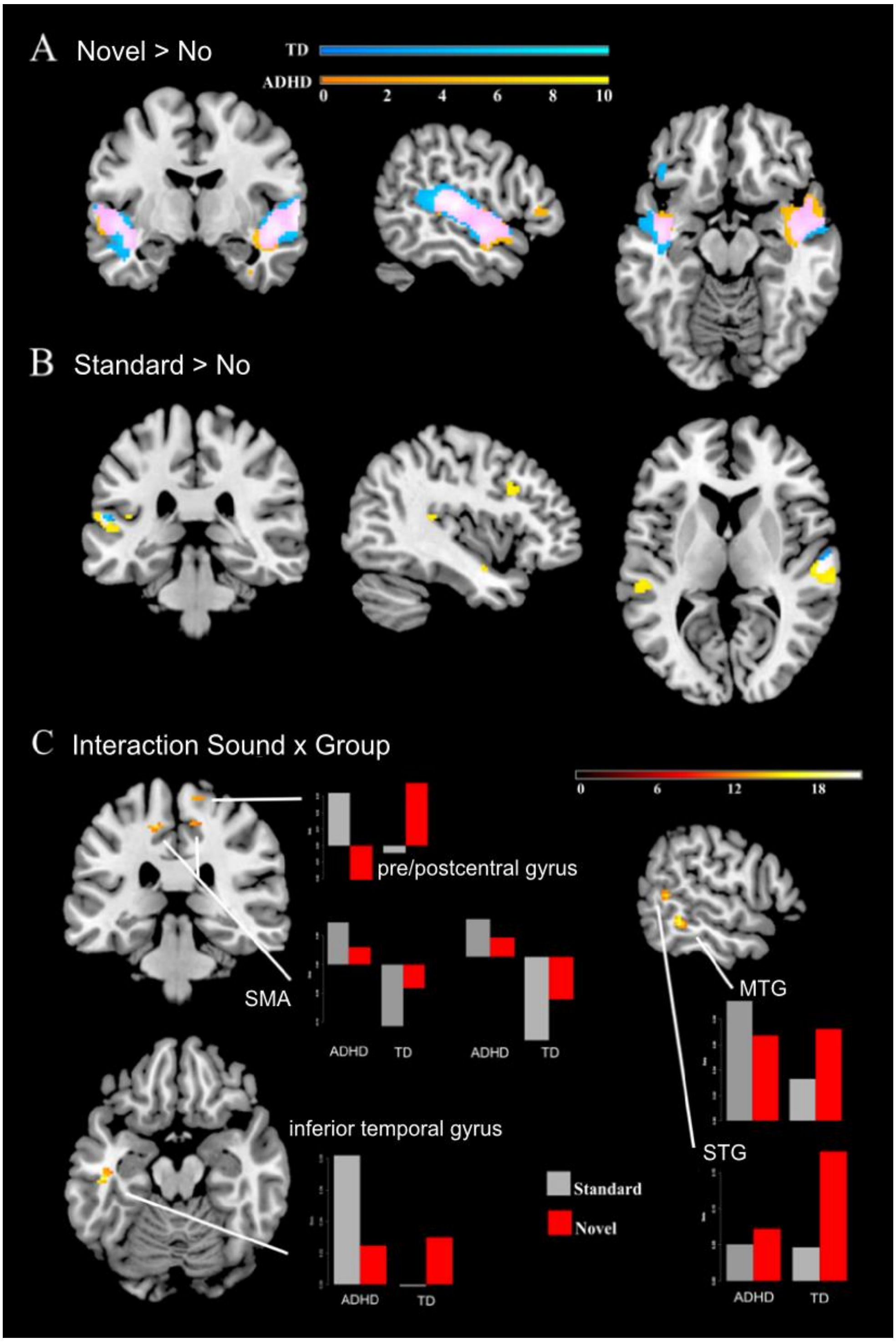


Fig. 17 Neural activation patterns during the experiment separately for both groups when novel (A) or standard (B) sounds preceded the task display. (C) Neural interaction between sound and group with corresponding signal changes (%) *SMA – supplementary motor area; STG – superior temporal gyrus*; *MTG – middle temporal gyrus*

fMRI - Interference control. The 2x3 ANOVA with contrast images of incongruent > congruent trials showed no main effect of group but differences in activation by sound for the right superior and left middle frontal gyrus (Table 8). Subsequent t-contrasts revealed that no region showed activity related to interference control when sounds preceded the task display compared to no sound. Instead, the above mentioned regions as well as the right putamen, caudate and inferior temporal gyrus were more strongly involved in incongruent than congruent trials without sounds compared to trials with novel sounds in both groups. Furthermore, the thalamus was more active in trials without a sound than standard sound trials. Standard sounds in turn were associated with more activity than novels for incongruent trials in the left middle frontal gyrus, right insula and left precuneus. Inspection of the respective beta-weights showed however that these differences were based on inverted activation patterns and not stronger activity in trials without sound stimulation per se (Fig. 18). Furthermore, the left superior frontal gyrus contrasted between group and sound conditions: while it was more active in incongruent trials preceded by standard or no sound in ADHD, for TD children, this pattern appeared only in trials with novel sounds.

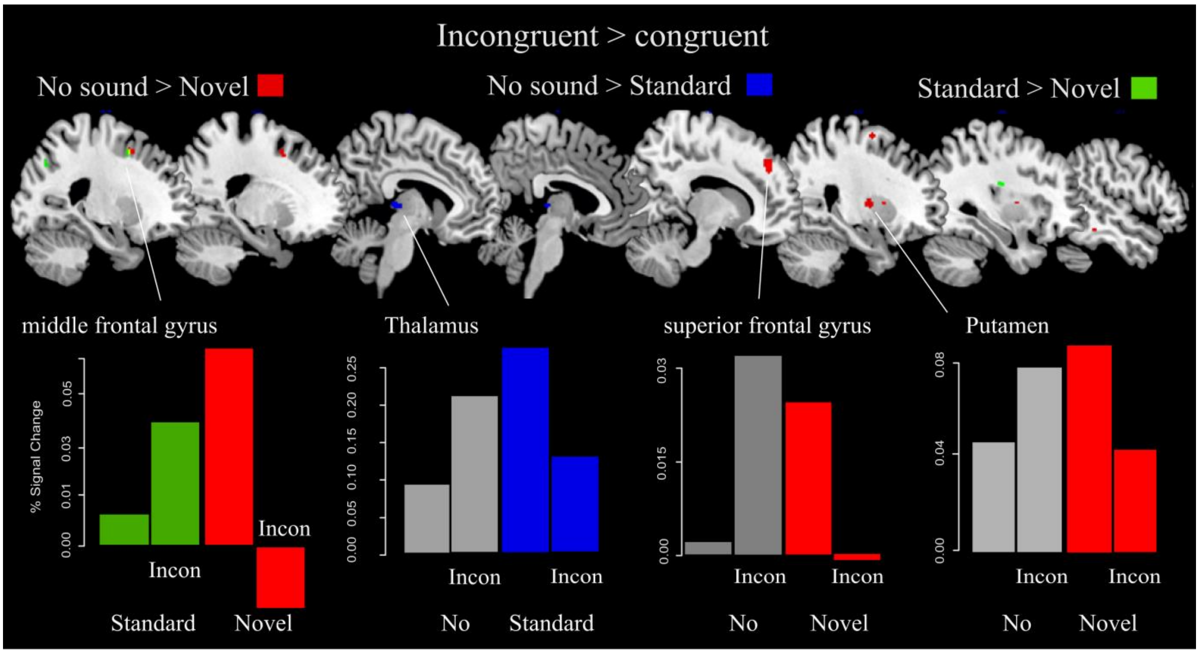


Fig. 18 Sound modulation of neural activity associated with interference control and selected examples of activity peak beta weights per condition averaged over both groups

Table 8. ANOVA activation peaks for interference control (incongruent > congruent) in the three sound conditions in children with and without ADHD

	k	MNI (mm)			Z
Main effect Sound					
R superior frontal gyrus	17	12	42	36	3.68
L middle frontal gyrus	12	-24	8	48	3.56
No > Novel					
R superior frontal gyrus	61	12	42	36	4.16
R superior frontal gyrus	45	24	0	62	3.91
L middle frontal gyrus	53	-24	10	48	3.73
R Putamen/ Lentiform Ncl	91	26	-6	6	3.63
R inferior temporal gyrus	21	46	-44	-12	3.50
R putamen	17	28	10	8	3.40
R caudate	13	20	-4	20	3.28
No > Standard					
Bilateral Thalamus	102	-2	-26	6	3.68
Standard > Novel					
L middle frontal gyrus	26	-24	8	48	3.71
R Insula	13	30	-14	22	3.57
L Precuneus	29	-24	-70	40	3.45
Interaction Sound x Group					
L superior frontal gyrus	11	-18	60	24	3.82

Group-wise contrasts showed that differential brain activity pattern for congruent and incongruent trials occurred only without an auditory cue (Table 9). In this condition, the left anterior cingulate and right inferior frontal gyrus were involved in the TD group. ADHD patients however, activated the left medial frontal gyrus and posterior cingulate as well as right middle frontal gyrus and bilateral precuneus (Fig. 19).

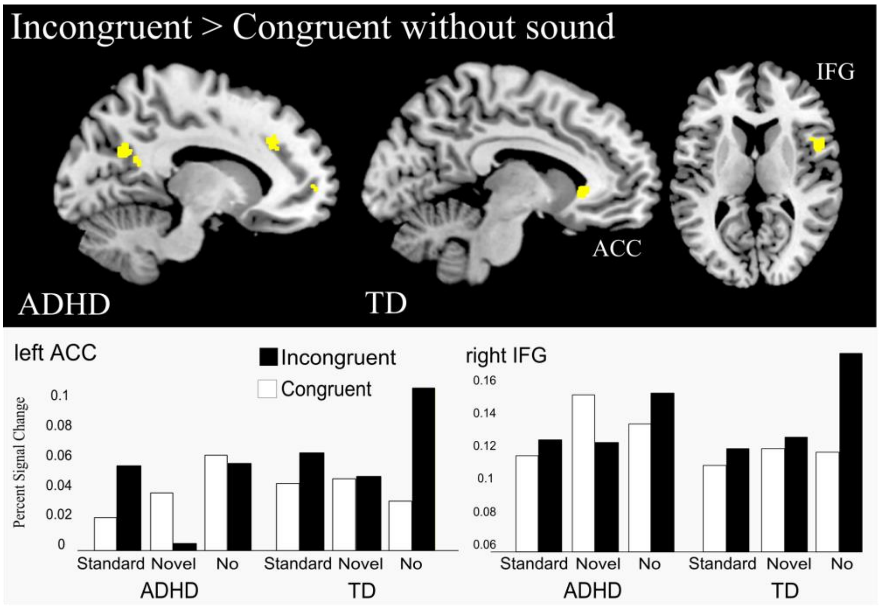


Fig. 19 Activity related to inter-ference control in trials without a sound for participants with and without ADHD. Below: influence of sounds on beta values in anterior cingulate cortex (ACC) and inferior frontal gyrus (IFG)

Table 9. Differences in brain activity related to interference control (incongruent > congruent) in children and adolescents with ADHD and a typically developing comparison group (TD)

	ADHD					**TD**				
	k	MNI (mm)			Z	k	MNI (mm)			Z
No Sound										
L anterior cingulate						25	-10	26	0	4.19
R inferior frontal gyrus						37	50	8	10	3.78
L medial frontal gyrus	33	-16	30	30	3.96					
R middle frontal gyrus	18	28	36	0	3.84					
L precuneus	47	-14	-62	26	3.43					
R precuneus	13	14	-62	24	3.42					
L posterior cingulate	12	-14	-52	20	3.29					
	ADHD > TD					**TD > ADHD**				
Novel Sound										
R middle frontal gyrus						19	24	-4	50	3.48
No Sound										
R middle frontal gyrus	13	28	36	0	3.86					
L medial frontal gyrus	15	-16	58	0	3.84					
L precuneus	24	-8	-64	22	3.34					
R Precuneus	13	4	-66	24	3.33					

5.4 Discussion

The current study aimed to investigate the influence of repeatedly presented standard and unique novel sounds on the performance and neural processing during a flanker task in children and adolescents with and without ADHD. In doing so, both types of sounds could be compared to a baseline without auditory stimulation and hence be investigated in terms of their function as alerting cues. Furthermore, the influence of novel sounds was of interest as it extends the alerting effect by eliciting an orienting response. The neural processing of these effects could be investigated outside (run 1) and within (run 2-4) the context of an actual task. Finally, executive control could be examined by contrasting trials in which flanking stimuli had to be suppressed to successfully perform the task against trials with congruent distractor arrangement.

Passive listening. During the first run, the timing and audio-visual stimulation were identical to the following experiment except for the visual array containing no task-relevant information and requiring no action. In this situation of passive listening, participants with and without ADHD expressed opposing patterns in their brain activations: while TD children displayed stronger neuronal reactions during the processing of the familiar standard sound, children with ADHD showed more brain activation after presentation of unique novel tones. These novelty related activations expectably involved the bottom up orienting network of attention consisting of TPJ and IFG (Corbetta & Shulman, 2002) mostly in the patient group whereas the comparison group exclusively showed activation in bilateral temporal regions. The reaction of typically developing children further contributes to past findings which showed that the VAN is not involved in orienting towards salient stimuli per se but rather reacts to potential (behavioral) relevance and thus interrupts ongoing processes only if necessary (for review see Corbetta & Shulman, 2008; Downar et al., 2002). Novel sounds were of no further importance in this setup and no attentional switch was required which might explain the lack of activation in TD children. On the other hand, the involvement of the VAN indicates impaired modulation of its activity by relevance in ADHD. Increased neural activation following task-irrelevant novel stimuli has already been found in a patient group in a visual oddball task (Tegelbeckers et al., 2015) and can be linked to increased distractibility by unimportant stimuli.

However, the standard sound on the other hand activated the bilateral PCC, right ACC and right parahippocampus to a greater extent in the comparison group. The cingulate regions fulfill a multitude of different functions from affect regulation to cognitive monitoring (e.g. Leech & Sharp, 2014; Vogt, Finch, & Olson, 1992) and have been frequently associated with ADHD symptomatology before (Bonath, Tegelbeckers, Wilke, Flechtner, & Krauel, 2016; Bush, 2011; Castellanos & Proal, 2012). During passive listening in the current study, the standard sound might have activated these regions in healthy children due to an already established cue function during training. The PCC is connected to the parahippocampal gyrus and both seem to be involved in detecting environmental events that might require behavioral changes or a switch from intrinsic to extrinsic attentional focus (Leech & Sharp, 2014). The ACC is involved in cognitive (for review see Stevens, Hurley, & Taber, 2011) and motor control (Asemi, Ramaseshan, Burgess, Diwadkar, & Bressler, 2015). Jointly, these activations indicate that the standard sound has already implemented an association with the task set in TD children but not participants with ADHD. However, as this task set must not be applied here, activity in anterior and/or posterior cingulate could also reflect control over motoric inhibition.

Moreover, an interesting interaction pattern between sound and group appeared most prominently in the bilateral medial frontal gyri, mid-cingulum, and parahippocampal gyri as well as right precuneus and left angular gyrus, all areas belonging to the default mode network (DMN) (Raichle et al., 2001). Thus, decreased activity following one of the sounds might be interpreted as more conscious evaluation of the stimulus. For children with ADHD the standard sound resulted in less activity of these DMN regions, for the comparison group novel sounds had a deactivating impact. This finding shows once more that DMN activity in ADHD is altered when compared to typically developing peers (Castellanos & Proal, 2012).

So far, investigations of passive auditory processing in ADHD have rarely been conducted. Instead, auditory studies mostly involved task-related concentration on (e.g. as cue or in form of auditory oddball tasks) or inhibition of (e.g. distracting influence) presented sounds. The few experiments regarding passive listening have used ERP recordings and found reduced attenuation in the processing of redundant information in adults with ADHD (Sable et al., 2013) as well as increased evaluation of deviant tones in adolescent patients (Yang et al., 2015) but point to intact mismatch detection (Huttunen, Halonen, Kaartinen, & Lyytinen, 2007; Sable et al., 2013). Our study differed from the former in being the first to identify the underlying anatomy of passive listening in children and adolescents with ADHD. Although the main focus of the current experiment was elsewhere, our findings contribute to the understanding of a basal alteration of neural auditory processing in ADHD. These alterations may not lie in primary auditory cortices but rather default mode network activity and areas related to cognitive control. This is in line with the aforementioned studies in so far that the detection of familiar and novel sounds seemed to be intact in ADHD while a potential exploitation of the standard cue had not yet been established and novel sounds appeared to be of greater interest in the patients.

Main task. When the experimental setup changed and the sounds developed their cueing function within an actual task, group differences in neural activity related to novel sounds vanished whereas the standard sound gained considerably more influence on children with ADHD compared to the TD group. Moreover, the sounds produced significant behavioral facilitation, particularly in children and adolescents with ADHD.

Alerting. During experimental tasks, the positive behavioral effect of alerting cues usually manifests in a decrease in reaction times (Escera & Corral, 2007; Parmentier et al., 2010; SanMiguel et al., 2010a). Accordingly, participants of both groups showed faster responses due to task preceding sounds. In ADHD, however, the alerting benefit of the standard compared to no sound was stronger than in the TD group and reaction time variability (RTV) normalized by the familiar sound in the patients. As RTV is most reliably impaired in ADHD (for review, see Tamm et al., 2012), a particular beneficial effect of the allegedly alerting standard sound in this group is reasonable and has been shown before (Casagrande et al., 2012; Gupta & Kar, 2009; Mullane et al., 2011). This enhanced responsiveness towards alerting cues might be based on a disorder specific reduced tonic alertness which enables a greater improvement by cues (Sergeant, 2000; Zentall & Zentall, 1983).

Interestingly, we previously reported the opposed finding that novel but not standard sounds exert a beneficial effect on RTV in ADHD (Tegelbeckers et al., 2016). However, a numerical trend of improved RTV by standard sounds was also reported there and the more pronounced effect in the current study is probably based on the considerable increase in trials per condition. RTV depends on the individual state of vigilance which is known to decrease over time. Therefore, the effects of standard and novel sounds might have become clearer during the prolonged course of the current experiment. Furthermore, vigilance improves with age which might lead to decreased efficiency of alerting cues (Curtindale, Laurie-Rose, Bennett-Murphy, & Hull, 2007; Mullane, Lawrence, Corkum, Klein, & McLaughlin, 2016; Rueda et al., 2004). As the investigated participants in this study were considerably older than the ones of the behavioral study, the dissimilarities might as well be accounted for by the different age groups.

However, in accordance with the more improved behavioral reaction, participants with ADHD showed more widespread activations than the comparison group during task execution preceded by the standard sound in the left IFG, left inferior and middle frontal gyrus, insula and middle temporal gyrus as well as bilateral STG. This predominantly left-hemispheric activation pattern in the patients overlaps extensively with the previously described areas of the alerting network (Fan et al., 2005) whereas healthy children and adolescent’s activations encompassed comparatively small regions exclusively in the bilateral STG.

This deviation from the expected activation pattern in the alerting network in healthy children and adolescents might be due to ongoing brain maturation (Konrad et al., 2005). If this was the case, the ADHD patients would display a developmental advantage in alerting over their age-matched typically developing peers, but this seems highly unlikely in the light of previous investigation pointing to delayed brain maturation processes in the disorder (Castellanos, 1997; Shaw et al., 2007). Instead, the deviance in activation in the TD group might rather rely on the usage of a sound as an alerting cue compared to the classical investigations using visual cues. It has been argued that the alerting network is served by modality specific brain areas that rely on the relevant primary sensory cortices and further processing pathways (De Santis, Clarke, & Murray, 2007; Langner et al., 2012; Spagna et al., 2015). Moreover, an auditory warning is thought to produce an automatic alerting effect more easily compared to visual stimuli which depend on attention to cause alertness (Spagna et al., 2015; Thiel & Fink, 2007). This effect potentially obviated the involvement of attention related fronto-parietal structures, but only in the TD group. Interestingly, in ADHD the alerting network seems to function less modality specific or to be especially approachable by auditory warning cues. These findings will have to be further clarified in future studies by directly comparing the neural basis of different cue modalities in ADHD.

Orienting. In accordance with the first run, novel sounds produced the expected, orienting related brain activation pattern consisting of the bilateral TPJ and IFG (Corbetta & Shulman, 2002; Petersen & Posner, 2012) also in the context of task execution but here without differentiating between the groups. Furthermore, instead of deteriorating performance by attracting attention away from the task, novel sounds had a beneficial effect on accuracy and reaction times. Thus, we not only found a corresponding activation pattern to the adult ventral attention network (VAN) but also gained insight in the presumably neural basis of novelty-related beneficial effects.

It has been argued that the effect of a task-irrelevant sound on performance consists of an orienting and an alerting component and that facilitation can emerge when orienting costs are smaller than alerting benefits (SanMiguel et al., 2010a). Thus, in direct comparison, novel sounds can be expected to improve performance over standard sounds due to a more pronounced increase in alertness despite eliciting an orienting response. In the current study however, we found no difference in neural activity for the sound conditions in fronto-parietal alerting network areas as well as only a numerical trend of superior accuracy of novel over standard sounds. Therefore, in line with San Miguel and colleagues' (2010) model, we can argue that the alerting effects of both sound conditions were of comparable strength, since both resulted in a similar improvement compared to the no sound baseline. In fact, the alerting effect of a novel stimulus depends on how much it deviates from the context (Schomaker & Meeter, 2015). In our setup, a sound appeared in 2/3 of all trials, novels with the same probability as the standard. Therefore, the salience of the unique sounds in comparison to the repeatedly presented standard sound might have been attenuated compared to previous studies finding the novelty benefit (Ruhnau et al., 2010; van Mourik et al., 2007; Wetzel et al., 2012).

However, as expected, novel sounds elicited a clear neural orienting response, indicating that the VAN reliably detected the unexpected sound. This process had yet no evident distracting impact on performance and this is remarkable as the VAN has been closely related to involuntary attention shifts and the disruption of ongoing behavior, leading to behavioral costs (Corbetta & Shulman, 2002). Also, following the previous argumentation, an increased orienting in the presence of equal alerting should result in distraction when novel and standard sound trials were compared (San Miguel, Linden et al., 2010; Wetzel et al., 2012). However, we argue that there are at least three possible explanations that can account for this phenomenon: first, the orienting response might in itself transport an alerting effect that is independent of the separate network but also based on noradrenergic modulation. Corbetta and colleagues (2008) already proposed a functional connection between noradrenergic locus coeruleus neurons and the VAN as both systems show the same activation pattern with regard to deviance detection. Second, the delay between sound and target might have been long enough to allow for redirection of attention without any behavioral cost. A primary activation of the VAN simultaneously with target presentation might result in a different effect, though. And third, it is conceivable that the role of the VAN is more complex than initially expected. In line with that, VAN activity following sensory stimuli has been shown to depend on task-relevance rather than salience, which contradicts pure bottom-up transfer. Instead, there is accumulating evidence that the function of the VAN rather lies in signaling the transition between two behaviors or tasks (for review see Corbetta et al., 2008 or Vossel, Geng, & Fink, 2014). Thus, depending on the informational value of novel sounds as temporal cues in this experiment, activity in the VAN during task performance might relate to a switch between auditory and visual processing in the form of contextual updating. The effect of task-irrelevant novels might then indeed rely on the neural activity termed “orienting response” but in the way that the task set is re-installed.

However, the brain activity following novel sounds did not differ between participants with and without ADHD. This is in line with previous studies reporting intact orienting responses as well as efficient usage of orienting cues in patients with ADHD in the visuo-spatial domain (e.g. Booth et al., 2007; Huang-Pollock & Nigg, 2003; Mullane et al., 2011; Oberlin et al., 2005). Furthermore children and adolescents with ADHD are not impaired in filtering out irrelevant sounds when engaged in a task (Friedman-Hill, 2010) or can even use these sounds to improve performance (Tegelbeckers et al., 2016; van Mourik et al., 2007). Then again, an enhanced sensitivity to novelty in terms of stronger electrophysiological reactions has nevertheless been reported in ADHD patients: in oddball tasks which either consisted of auditory stimuli (Gumenyuk et al., 2005) or pictures (Tegelbeckers et al., 2015), ADHD patients displayed stronger neural reactions to novel stimuli than TD children. These differences between former and the current study most likely point to a dependency of the context in which novel sounds occur or orienting in general is provoked. Oddball tasks confound novelty processing with a target reaction and thus the former is influenced by executive processes like response selection, execution, and/or inhibition. This makes it difficult to interpret the results in terms of single attentional network contribution (Corbetta et al., 2008). In other words, top-down attentional processes should be significantly more involved in such studies compared to our setup and could be the source of ADHD related problems, rather than bottom-up triggered reactions of the VAN.

Executive Control. Impairments in the ability to suppress interfering information have been frequently reported in flanker tasks in ADHD (see Mullane et al., 2009 for review). In line with that, we also found diminished accuracy in our patient group for incongruent compared to congruent trials but only when no sound preceded the task display. With sound presentation, however, interference control of patients improved to the level of the comparison group, indicating a beneficial, probably alerting effect of the sounds on executive functioning. Such interaction between the attentional networks has been reported before, although studies differ in the type of influence they find: some report a deteriorating effect of alerting cues on executive control (Callejas, Lupianez, &

Tudela, 2004; Fuentes & Campoy, 2008) while others found enhanced executive functioning (Spagna et al., 2015). The former argue, that a speed-accuracy tradeoff might account for the negative effect (Fan et al., 2009) or alerting enhances the processing of information per se and thus increases the influence of distractors as well (Weinbach & Henik, 2012). However, in this study we found no evidence for impairments in executive functioning by alerting sounds in TD children and adolescents as well as patients with ADHD. The former's interference control was not influenced by the sounds at all, possibly because they already performed at ceiling.

Furthermore, brain activity differences for incongruent compared to congruent trials could only be detected for the no-sound condition in both groups. Here, successful interference control in TD participants was accompanied by activity in the left ACC and right IFG, which both belong to the executive network (Fan et al., 2005; Raz & Buhle, 2006) and have been linked to suppression of irrelevant information before (e.g. Berron, Frühholz, & Herrmann, 2015; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Botvinick, Cohen, & Carter, 2004; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Zhu, Zacks, & Slade, 2011). ADHD patients on the contrary showed a deviating activation pattern involving the posterior cingulate and precuneus in addition to middle frontal areas. Thus, impaired interference control in the patient group seems to be based on the failure to activate the appropriate control network and instead recruitment of more posterior brain areas. A similar alteration in activity has already been shown for response inhibition in no-go trials (Vaidya et al., 2005), pointing to a general disorder specific deviation of the executive control network.

However, when sounds were presented, interference control related brain activity normalized for participants with ADHD. This normalization could not be seen by an increase in ACC or IFG activation in the patients but instead in diminished activity in these regions in incongruent trials for TD participants (Fig.19). Interestingly, a similar effect has been shown when the frequency of incongruent trials was manipulated (Botvinick et al., 2004; Vel Grajewska, Sim, Hoenig, Herrnberger, & Kiefer, 2011): the difference in ACC activation between both congruency conditions diminished with a higher frequency of incongruent trials. This has been interpreted as evidence for the monitoring function of the ACC which triggers adjustments in strategic control (Botnivick et al., 2004). This conflict monitoring theory fits our findings in the way that sounds apparently increased alertness and facilitated to focus on task execution, which at the same time rendered conflict monitoring redundant or at least less required.

Furthermore, the sounds inverted the activation pattern for congruent and incongruent trials in several other areas, including the right superior and middle frontal gyrus, right inferior temporal gyrus, putamen and caudate for novel sounds as well as prominently in the thalamus for standard sounds in both groups (Fig.18). These areas have recently been linked to the interaction between alerting and executive control in the classic ANT (Xuan et al., 2016) so that our results further reinforce the idea of an adaptation of activity in dependency of alertness and task demands. However, the question remains why increased reactions to congruent compared to incongruent stimuli should be advantageous. Weinbach and Henik (2011) showed that alerting favors the processing of global information at the expense of local details and argue that this mechanism is useful from an evolutionary perspective: in situations of high alertness and potential danger, it might be important to consider the big picture and react quickly. Although we found no behavioral counterpart, the neuronal activity pattern seems to support the hypothesis of a preferential processing of congruent arrangements under high alertness conditions.

Conclusion. In summary, the current study is the first to shed light on the neural basis of the influence of unique/novel and familiar/standard sounds in children and adolescents with ADHD and a typically developing comparison group. The current setup allowed investigating the influence of sounds during passive listening as well as during task performance in general and in interaction with executive control. Overall, we found the expected impaired performance in children and adolescents with ADHD in all relevant behavioral measures. Additionally, during task performance, the patients showed alterations in brain activation patterns associated with alerting by standard sounds and interference control, but not orienting following novel sounds. However, when not engaged in a task the ADHD group had significantly stronger reactions following novel sounds than the comparison group.

This finding concerning the neural processing of novel sounds contributes fundamentally to bridging the gap between the observed enhanced behavioral distractibility in ADHD and missing evidence for this symptom in cognitive tasks (Huang-Pollock & Nigg, 2003). Apparently, top-down modulation of the VAN can function regularly in children and adolescents with ADHD under certain conditions but is diminished in other situations. We think that our participants were highly motivated to perform the task as successfully as possible and were furthermore impressed by the extraordinary surrounding of the fMRI. In everyday situations, these conditions might be different, leading to increased responses in the manner of the passive listening run. Moreover, the novel sounds were not completely distracting but contained temporal information about the subsequent target. In a setup without such a cue function, a TD group might differ from patients with ADHD in their neuronal orienting reaction.

However, the activation of the ventral orienting network in both groups was not accompanied by behavioral cost as previously assumed (SanMiguel et al., 2010a; Wetzel et al., 2012). Instead both sounds had beneficial effects on task performance and most interestingly even normalized brain activity associated with executive control in children and adolescents with ADHD. These effects are promising with regard to the search for optimized learning and working conditions in ADHD patients. Their particular benefit is most likely based on an underlying deficit in alertness which increases their sensitivity for the influence of sounds.

6 General Discussion

6.1 Summary

Successful goal-directed behavior is based on the ability to select and process relevant information while inhibiting distracting stimuli. At the same time, the attentional system has to be able to detect a potential danger or other changes in the environment requiring adaptation of the current behavior. To achieve this balance, the human attentional system works via two parallel streams: top-down control maintains task-related demands whereas bottom-up signaling can disrupt ongoing processes in favor of environmental requirements.

In healthy awake individuals these processes work more or less effortlessly together, underlying typical occasional fluctuations by boredom, fatigue or motivational problems. However, certain psychiatric conditions, most notably ADHD, are characterized by impairments in either or both attentional control processes in everyday life. At present, there has been accumulating evidence for deficits in top-down attentional control in ADHD in various tasks (e.g. Bush, 2010; Jonkman et al., 2000; Rubia, 2011) whereas the functioning of the bottom-up attentional stream received comparatively little interest. Therefore, this thesis aimed to close the gap and provide insight into the processing of unique, unexpected, and thus novel stimuli in children and adolescents with ADHD. To do so, patients with ADHD were compared to age-matched TD children and adolescents in their neuronal detection of visual novelty (Experiment 1), the behavioral consequences of auditory novelty (Experiment 2) and the neuronal effects of novel sounds on three attentional networks (Experiment 3).

First of all, there is an ongoing debate about the strength of ADHD-related impairments in cognitive tasks as some studies failed to find group differences and meta-analysis report only small effect sizes (e.g. Huang-Pollock & Nigg, 2003; Willcutt, 2014). Our findings of considerable differences between the groups in all of the three conducted studies indicate that tasks incorporating novel stimuli are suitable to tap into ADHD-related deficits. However, these behavioral differences became more pronounced when difficulty increased as observable in more impaired performance in ADHD patients in the flanker task compared to the relative simple oddball task. Interestingly, the latter nevertheless revealed alterations in brain activity that clearly distinguished TD participants from participants suffering from ADHD, indicating altered neuronal processing despite similar outcome. This emphasizes the need to investigate the underlying neural basis during tasks performance in greater detail to identify not only deficits and possible alterations in neural activity but also to detect unimpaired functioning or neural compensation as all of these aspects are of high clinical relevance and contribute to a better understanding of the disorder.

Besides finding general ADHD related alterations during the experimental tasks, the main focus of the presented work was on the processing of novelty and its influence on performance in ADHD patients. First, the studies revealed increased neural activity following novel stimuli in the patients compared to TD participants when they were engaged in an oddball task as well as during passive listening. Both situations have in common that further processing of the novel stimulus was unnecessary and inefficient. In the oddball task, novel pictures required the frequent response of the left hand and during passive listening, the sounds required no reaction at all. When the novel sounds, on the other hand, were embedded in an actual task, the neural response of ADHD patients matched the comparison group’s brain activity. Taken together, these findings indicate that the bottom-up orienting response by the VAN remains intact in children and adolescents with ADHD and cannot account for their increased distractibility. If this was the case, we would have found enhanced responses following novel stimuli in the patients in all situations. Instead, the modulation and particularly inhibition of the orienting network by higher-order executive areas seems to be disturbed.

Furthermore, in ADHD, the same brain areas processing novel stimuli were also involve when rare, familiar stimuli were presented. For TD children and adolescents on the other hand, the repeatedly presented stimulus caused activity of relatively small magnitude. This pattern of altered salience processing in ADHD occurred not only in the oddball study but also for standard sounds in the flanker study (Fig. 20) so that the mutual finding in both studies points toward a deficient modulation of bottom-up processing independent of stimulus modality. Apparently, adaptive down-regulation of orienting responses following the repeated presentation of the same stimulus does not take place and might account for the increased distractibility in the patients.

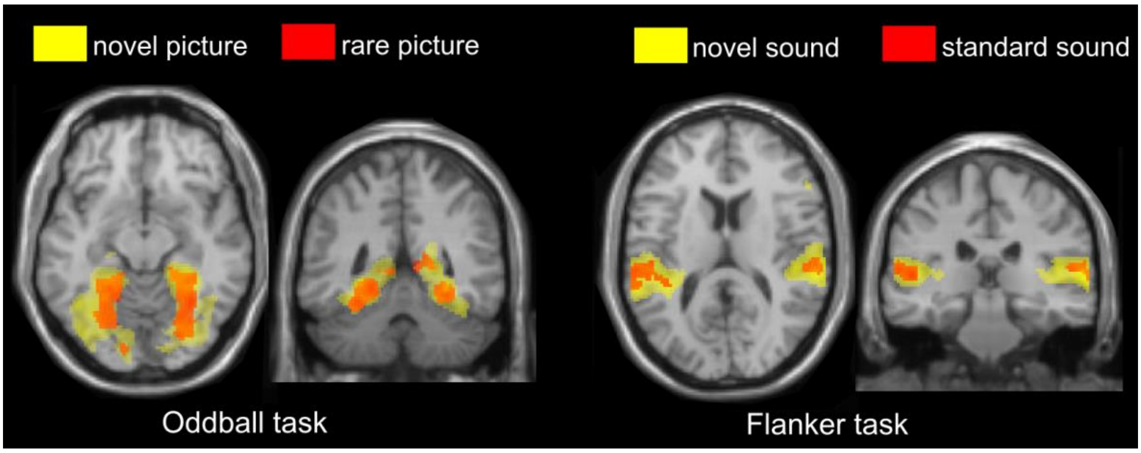


Fig. 20 Overlap in brain activity between novel and familiar stimuli in the ADHD group for the visual (oddball) and auditory modality (flanker)

However, most interestingly this enhanced neural response following repeatedly presented stimuli was accompanied by behavioral facilitation. The beneficial effect of standard sounds as well as novel sounds in the patient group was considerably stronger than in the healthy comparison group. Moreover, in the oddball task, we surprisingly failed to find group differences in performance although these are most robustly reported (Jonkman et al., 2000; Stevens et al., 2007; Tamm et al., 2012). Having seen the beneficial effects of novelty on performance, one might speculate in retrospection that embedding the novel pictures might have increased alertness in this set-up as well and thus enabled the patients to show normal performance. Future studies will have to clarify whether such spill-over effects of novelty exist.

In summary, although we found evidence for altered DMN activity particularly during passive listening, most of the differences between the groups can be accounted for by deficient regulation of the orienting network. Maybe this regulation depends on the general alertness of the individual in the way that the orienting response has to “wake up” the system when it is not alert but is not required when alertness is high (enough). In this regard, the greater improvements in performance as well as the stronger neural activity following both sounds in the ADHD group also fit the assumption of an underlying deficit in alertness.

6.2 Limitations and Outlook

Although all of the presented studies were carefully planned and interpreted, several limitations need to be considered. First of all, participation in all studies was voluntary which possibly resulted in a sample of highly cooperative and motivated individuals. Thus, attentional performance and the effort to perform well might exceed the usual behavior in school settings, for instance. Furthermore, participants with extensive movements in the fMRI scanner and lower-than-average performance were excluded but these might in fact be the particular “hard cases” with the most pronounced impairments. This selection bias potentially limits the generalizability of results and can only be overcome by replication studies with large sample sizes. In these, it would also be interesting to analyze the influence of novelty on the different subtypes of ADHD: it might be possible that novelty has an increased alerting effect on predominately inattentive children while the slowing of reaction times is particularly beneficial for patients suffering from enhanced impulsivity.

Moreover, the choice of fMRI to display brain activity during novelty processing has certain limitations, both methodologically and in the conclusions that can be drawn. Although the spatial resolution is high, temporal resolution lacks precision so that we for instance could not disentangle effects of orienting and reorienting between the sounds and task display, respectively. It would be interesting to further investigate group differences in these processes using EEG or a combination of EEG and fMRI. Furthermore, the minimum age of children taking part in fMRI studies is limited to 11 years by the local ethics committee. Although an amendment of this limitation might be possible, the scanning of younger children would be increasingly complicated in light of the already enhanced motion artifacts in children above the age of 11. However, the evidence for age-effects in the oddball study as well as performance differences in the behavioral and fMRI flanker study point to a potential developmental modulation of novelty-related effects. Younger children with ADHD might differ in their orienting responses or alerting benefits from TD children especially during task performance. Thus, further EEG investigations or measuring the pupil diameter might contribute to a better understanding of the development of novelty processing, both in children with and without ADHD.

Moreover, to better understand the beneficial effects, it will be crucial to examine how children's brains process novel, unexpected stimuli that are not indicative of the upcoming target but truly task-irrelevant. To do so, the auditory cued flanker task has to be modified with a variable sound target interval and trials with simultaneous presentation of sound and target have to be introduced. In this context it will also be interesting to see whether the presentation of novelty "spills over" on general alertness and has the ability to improve task performance over a certain period of time or whether the effect is limited to the following trial only. If general alerting effects exist, it would be necessary to identify how many novel sounds need to be introduced over the course of an experiment to improve performance.

Furthermore, the influence of novel sounds on different types of cognitive tasks requires further investigation. Especially learning in the context of novelty is supposed to be more efficient than without (Fenker et al., 2008), an effect that would be interesting to replicate in children with ADHD as they are assumed to suffer from memory deficits as well. But also response inhibition in stop-signal tasks or go-nogo paradigms might benefit from novel sounds due to the prolonged reaction times they cause.

On the other hand, studies need to identify the mechanisms leading to facilitation versus distraction and in doing so the focus has as well to be put on individual differences. We found no evidence for a distracting influence of sounds in the group mean, but exploratory insight into the data revealed a high inter-individual variability of novelty related behavioral effects (Fig. 21). Furthermore, task difficulty and the baseline alertness level might play an important role. If the optimal level of alertness is the peak of a U-shaped function (Zentall & Zentall, 1983), increasing alertness could also lead to diminished performance in certain individuals or under certain conditions. These questions might as well be addressed via concurrent recording of heart rates and/or pupil diameter as additional measures of the alerting state.

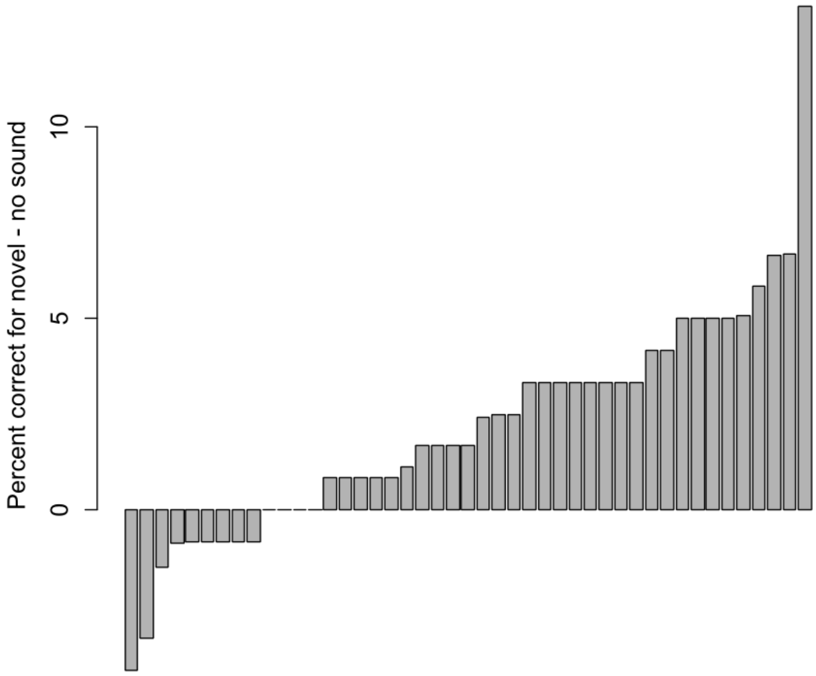


Fig. 21 Individual differences in accuracy improvement in trials with preceding novel sound compared to no-sound baseline (Experiment 3)

In summary, it is a promising approach and of high clinical relevance to examine the effects of novelty on ADHD, not only in terms of potential therapeutic assistance but also to improve our understanding of disorder-specific impairments and preservations. In light of the evolutionary significance of novelty detection for survival it seems logical that this basic mechanism is intact in the developmental disorder ADHD. From here, we can aim to identify the node(s) in the information processing sequence or network that are deficient in the disorder and begin to think of possibilities to make use of the intact mechanisms. Results of upcoming research on this topic may lead to adapted and optimized learning as well as working conditions. For instance, it is conceivable that technical devices will be able to monitor alertness concurrently and produce alerting sounds when necessary. But until then, the open questions need to be addressed.

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8 Appendix

8.1 Supplementary tables of Experiment 3

Table S1	Passive listening: Activation peaks of t-tests per group for the comparison of both sound conditions against baseline and against each other
Table S2	Main task: Activation peaks of t-tests per group for the comparison of both sound conditions against baseline and against each other
Table S3	Main task: two-sample comparisons for standard and novel sounds

Table S1 Passive listening: Activation peaks of t-tests per group for the comparison of both sound conditions against baseline and against each other

	ADHD					TD				
	k	MNI (mm)			Z	k	MNI(mm)			Z
Novel > No Sound										
R superior temporal gyrus	3008	66	-24	8	6.18	127	48	-10	-6	3.92
middle temporal gyrus		62	-32	4	6.17		62	-2	-8	4.04
		50	0	-16	5.70		54	-10	0	3.52
R superior frontal gyrus						232	64	-34	8	3.86
							48	-30	6	3.71
							56	-22	8	3.64
L superior temporal gyrus	3302	-60	-30	8	6.17	390	-56	-32	14	4.18
		-54	-24	6	6.07		-52	-24	2	3.94
							-56	-30	6	3.75
middle temporal gyrus		-54	-44	6	5.92					
L superior temporal gyrus						49	-54	2	-8	3.68
							-48	-4	-4	3.42
middle temporal gyrus							-48	-2	-14	3.20
L superior temporal pole						15	-46	10	-18	3.47
R inferior frontal gyrus	294	50	18	20	4.26					
		54	28	10	3.98					
L inferior frontal gyrus	164	-48	32	-4	4.37					
R parahippocampal gyrus	39	30	-4	-30	4.03					
L cingulate gyrus	25	-8	18	46	3.55					
medial frontal gyrus		-6	12	52	3.23					
SMA		-2	8	58	3.21					
L lingual gyrus	15	-18	-84	-16	3.55					
R cerebellum	33	30	-52	-30	3.50					
		24	-46	-32	3.50					
L medial frontal gyrus	11	-4	28	44	3.47					
R brainstem	15	14	-24	-20	3.47					
L superior frontal gyrus	13	-14	54	24	3.32					
Standard > No Sound										
R middle temporal gyrus	39	66	-32	0	3.86	13	48	-8	-4	2.38
superior temporal gyrus		66	-24	8	3.57	56	56	-16	6	3.88
transverse temporal gyrus							56	-20	10	3.71
L superior temporal gyrus	106	-62	-24	-4	4.14					
middle temporal gyrus		-62	-16	-6	3.74					
		-54	-16	-8	3.38					
L superior temporal gyrus	19	-64	-42	10	3.52					
R anterior cingulate						33	4	30	0	4.15
L superior frontal gyrus						17	-14	68	10	3.61
R superior temporal gyrus						11	62	-4	-2	3.56
L middle frontal gyrus						10	-28	36	-8	3.50
Novel > Standard										
L superior temporal gyrus	343	-48	-26	4	4.75					
		-48	-10	-2	3.57					
		-48	-18	-4	3.48					
L middle temporal gyrus	126	-64	-40	6	4.57					
superior temporal gyrus		-64	-30	14	4.07					
R superior temporal gyrus	698	66	-40	12	4.47					
		48	-20	0	4.47					
		52	-30	4	4.41					
L lingual / fusiform gyrus	33	-20	-88	-10	3.94					
L intraparietal	15	-30	-78	44	3.50					
R angular gyrus	10	40	-64	46	3.35					
L angular gyrus	25	-34	-58	36	3.25					
R precuneus/cingulate gyrus	28	2	-48	38	3.33					

Standard > Novel					
R brainstem	26	10	-34	-24	4.15
L anterior cingulate	21	-16	40	4	3.96
R precuneus	119	18	-50	48	3.93
		8	-54	48	3.42
L medial frontal gyrus	69	-16	58	6	3.86
L inferior parietal gyrus	139	-24	-44	50	3.59
precuneus		-14	-52	50	3.43
R precentral gyrus	11	40	-18	56	3.33

Table S2 Main task: Activation peaks of t-tests per group for the comparison of both sound conditions against baseline and against each other

	ADHD					TD				
	k	MNI (mm)			Z	k	MNI(mm)			Z
Novel > No Sound										
R superior temporal gyrus	2761	66	-26	8	5.71	3521	58	-18	8	6.42
		64	-34	6	5.65		62	-26	10	5.85
		46	-6	-12	5.45		56	-6	-6	5.82
L superior temporal gyrus	2876	-58	-30	12	5.33	3329	-44	-14	-8	6.03
		-60	-42	12	5.20		-42	-20	-2	5.76
		-45	-16	-4	5.07		-52	-24	4	5.66
L middle temporal gyrus						12	-56	-64	16	3.35
R inferior frontal gyrus	79	54	32	2	4.45					
L inferior frontal gyrus	26	-26	20	-24	4.34	247	-44	28	-14	4.40
		-20	10	-22	3.46		-30	28	-18	3.66
middle frontal gyrus							-30	36	-14	3.43
R parahippocampal gyrus	148	22	-12	-28	4.36					
fusiform gyrus		34	-6	-34	4.27					
hippocampus		30	-14	-22	3.91					
L subcallosal gyrus						20	-4	24	-12	3.72
Standard > No Sound										
R superior temporal gyrus	278	66	-34	6	4.16	46	64	-10	4	3.67
		54	-18	4	3.84		60	-18	8	3.53
		52	-8	0	3.77					
L superior temporal gyrus	299	-62	-30	10	4.14	19	-56	-32	14	3.48
		-54	-28	6	4.07					
		-64	-38	12	3.64					
L middle temporal gyrus	38	-64	-48	-4	4.11					
L superior temporal pole	37	-42	0	-20	4.00					
L middle frontal gyrus	153	-32	20	22	3.87					
		-40	14	34	3.76					
		-20	16	22	3.41					
L inferior frontal gyrus	13	-18	44	-6	3.68					
R middle temporal gyrus	20	42	-4	-20	3.66					
L insula	20	-36	-22	0	3.63					
R parahippocampal gyrus	11	30	-22	-22	3.41					
Novel > Standard										
R superior temporal gyrus	1238	66	-24	8	4.90	5168	66	-24	10	6.98
							58	-20	4	6.79
middle temporal gyrus		62	-34	-4	4.40		62	-32	2	6.92
L superior temporal pole	119	-40	4	-20	4.53					
L middle temporal gyrus		-64	-34	8	4.02	4764				
superior temporal gyrus		-52	-34	10	3.75		-52	-30	8	6.89
							-52	-22	4	6.17

L middle temporal gyrus		-56	-8	-8	3.81					
superior temporal gyrus		-44	-14	-6	3.51					
		-56	0	-10	3.40					
L parahippocampal gyrus						45	-16	-12	-14	3.69
hippocampus							-26	-14	-12	3.52
R inferior frontal gyrus	28	54	34	4	3.56	405	46	12	24	4.98
							54	16	26	4.47
							54	18	18	4.45
R inferior frontal gyrus						85	50	28	-6	4.30
L inferior frontal gyrus						43	-58	24	18	3.76
R precentral gyrus						106	24	-26	52	3.87
							32	-22	52	3.67
L paracentral lobule						70	-6	-28	50	3.38
							-12	-34	52	3.33

Table S3 Main task: two-sample comparisons for standard and novel sounds

	ADHD > TD					TD > ADHD				
	k	MNI (mm)			Z	k	MNI (mm)			Z
Standard > No Sound										
L insula	213	-32	-14	6	3.89					
		-40	-14	14	3.73					
claustrum		-34	-6	8	3.53					
R precentral gyrus	24	14	-34	72	3.73					
L middle frontal gyrus	40	-34	20	24	3.72					
L middle occipital gyrus	12	-54	-74	4	3.69					
R middle temporal gyrus	10	44	-18	-16	3.56					
L superior temporal gyrus	11	-54	-28	4	3.54					
R paracentral lobule/medial frontal gyrus	17	8	-28	60	3.46					
	10	2	-30	68	3.30					
Novel > Standard										
R middle temporal gyrus						75	58	-40	-10	4.46
							58	-30	-14	3.17
R inferior temporal gyrus						12	44	-12	-16	3.63
L inferior temporal gyrus						27	-48	-22	-18	3.76
R precentral gyrus						28	16	-34	70	3.88
R SMA/medial frontal gyrus						12	8	-18	70	3.56
R paracentral lobule						44	22	-30	52	3.48
							12	-28	54	3.37
L paracentral lobule						98	-14	-30	52	3.68
							-24	-22	52	3.52

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CURRICULUM VITAE

PERSONAL INFORMATION

Name: Jana Tegelbeckers
Birth Date: 13.06.1986
Birth Place: Prenzlau, Germany
Nationality: German

EDUCATION

05/2011 – 06/2016
PhD in Psychology / Clinical Neuroscience
Otto – von – Guericke University Magdeburg, Dept. Child and Adolescent Psychiatry

10/2005 – 03/2011
Diploma in Psychology
Otto – von – Guericke University Magdeburg
(final grade: 1.3)

09/1996 – 03/2005
Abitur
Wilhelm – Raabe – Gymnasium, Magdeburg
(final grade 1.0)

WORK EXPERIENCE

01/2012 – current
Research assistant
Project “Neurobiology of motivated behavior”, SFB 779, TP A03, Dept. Child and Adolescent Psychiatry Magdeburg

2011 – 2012
Seminar - Instructor
Otto – von – Guericke University Magdeburg, Dept. Experimental Psychology
Summer Term: Cognition
Empirical-Experimental Training I
Winter Term: Perception
Diagnostic Methods I: Interview and Observation

2008 – 2011
Student research assistant
Otto – von – Guericke University Magdeburg, Dept. Experimental Psychology

EIGENSTÄNDIGKEITSERKLÄRUNG

Hiermit erkläre ich, dass ich die vorliegende Dissertation zu dem Thema

Novelty and ADHD

How unexpected stimuli influence neural processing and behavioral performance in children and adolescents with and without attention deficit hyperactivity disorder

selbstständig verfasst und nicht bereits als Dissertation verwendet habe. Die benutzten Quellen und Hilfsmittel habe ich vollständig angegeben.

Weiterhin erkläre ich, dass ich weder diese noch eine andere Arbeit zur Erlangung des akademischen Grades doctor rerum naturalium (Dr. rer. nat.) an anderen Einrichtungen eingereicht habe.

Magdeburg, den 13.06.2016