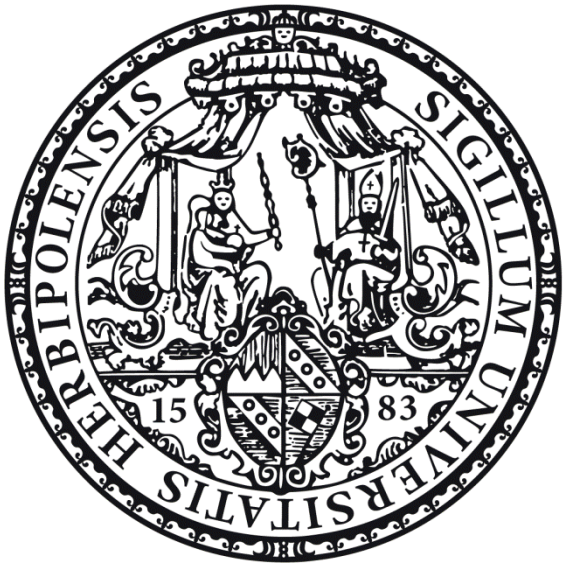

Neuropsychological Endophenotypes of Attention-Deficit/Hyperactivity Disorder

Neuropsychologische Endophänotypen des Aufmerksamkeitsdefizit-/Hyperaktivitätssyndroms

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Summary

Introduction Endophenotypes as a link between heterogeneous phenotype and complex genetics of Attention-Deficit/Hyperactivity Disorder (ADHD) were the focus of the present work. Response inhibition, working memory, response time variability and sensory gating served as candidate endophenotypes, and the previously with ADHD associated genes coding for Catechol-O-Methyl-Transferase (COMT), the Dopamine Transporter (DAT, SLC6A3) and Latrophilin-3 (LPHN3) were examined for their moderating influence on endophenotypes. We investigated medicated (N=36) and unmedicated (N=42) ADHD patients and matched healthy control children and adolescents (N=41) on a range of neuropsychological tasks while simultaneously recording a 21-channel EEG and deriving event-related and topographical parameters corresponding to specific cognitive operations. NoGo-Anteriorization (NGA) based on P300 responses during Go and NoGo trials was the main electrophysiological correlate of response inhibition. Sensory gating described the suppression of the P50 wave to the second of two consecutive stimuli, serving to prevent overstimulation of higher cortical areas. Working memory event-related potential components of interest were indicative of early sensory processing (P100 for target and N100 for non-target stimuli), selection of material (P150), memory retrieval (N300), event categorization (P300 for target stimuli) and updating of working memory contents (P450 for non-target stimuli). Behavioural performance was quantified in terms of omission errors reflecting inattention and false reactions reflecting impulsivity as well as speed and variability of reaction times (RTV).

Results Higher rates of omission errors in unmedicated ADHD patients point towards difficulties with both inattention and working memory. RTV was also more pronounced in patients without the support of medication. At the second measurement, they furthermore displayed longer reaction times and a higher number of commission errors. Early sensory processing was largely intact in ADHD, the only exceptions being in interaction with DAT and COMT. NGA as electrophysiological correlate of response inhibition overall did not prove to be an optimal endophenotype candidate, since it was not yet developed in approximately half of the examined children and adolescents. It was independent of diagnosis; ADHD risk

alleles for DAT conferred lower NGA as well as more variable reaction times across groups. DAT genotype interacted with diagnosis on the level of centroid location in the response inhibition task. While in the homozygous 10 repeat (10R) carriers diagnosis did not moderate centroid locations, having at least one protective Val allele in combination with psychostimulant medication moved centroids to more anterior areas. However, DAT genotype did not manifest in behavioural deficits in this task. In the case of sensory gating, homozygosity for the DAT allele associated with ADHD (10R) generally conferred impairment in sensory gating. ADHD itself only became relevant in participants without genetic risk, where patients without medication struggled most with suppression. In the working memory task, DAT modulated selection of material (P150). While under high load unmedicated patients had delayed responses compared to both other diagnostic groups without genetic risk playing a role, low load conditions showed that the combination of risk genotype and stimulant medication led to latencies even below healthy controls. While among unmedicated patients being in the DAT risk group led to enhanced P100 amplitudes, these patients showed dampened P100 responses compared to other diagnostic groups amplitudes if carrying at least one 9R allele. Carrying the risk genotype also meant tendentially higher target P300 amplitudes in unmedicated patients, whereas without genetic risk, they had the lowest P300 amplitudes reflecting aberrant event categorization and evaluation.

An interesting trend emerged for LPHN3, where carrying all risk variants was associated with higher NGA scores in ADHD patients irrespective of medication. This warrants further study, as the haplotype also exerts a positive influence on sensory gating abilities specifically in patients. At the same time within the genetic risk group, patients without medication had the weakest NGA. However, on centroid level the LPHN3 risk haplotype effected more posterior Go centroids, putatively facilitating response execution, which is supported by a higher number of false alarms. When response inhibition was required (NoGo trials), the risk variants caused unmedicated patients to have more posterior NoGo centroids compared to both their medicated counterparts as well as controls, speaking to differences in inhibition-related brain activation. The LPHN3 genotype produced very different effects on sensory gating in controls and patients. While as expected the ADHD risk SNPs in combination led to

compromised gating, this was reversed in healthy controls where the haplotype was acting in a protective manner with enhanced filtering.
During working memory operations, the risk haplotype showed stronger N300 responses suggesting investment of more resources and thus better retrieval.

While COMT did not exert an influence on NGA directly, carriers of the risk Met allele had more posteriorly located centroids both during response execution and inhibition, and displayed more variable responses in addition to being more prone to false alarms.
On the level of P300 response as the basis of the NGA phenomenon, unmedicated patients produced smaller P300 during successful execution of responses than controls in absence of the risk allele, while with risk Met they had shorter latencies and presumably a greater tendency towards premature behavioural reactions. Carrying the COMT risk allele for ADHD (Met) was associated with higher RTV. Additionally, it brought out impairments in sensory gating, thus making patients without medication less able to filter out irrelevant and potentially interfering information, while they were able to compensate even without medication if they had the protective Val/Val genotype. The influence of COMT on sensory gating seems to be specific for ADHD, as this gene was of no consequence in healthy controls. In the working memory task, Met was beneficial for updating processes as reflected by the P450 amplitude. In ADHD irrespective of medication COMT did not change P450 strength, but for controls this effect was observed.

With regard to longitudinal development, the most striking finding was a universal quickening of responses (latency shortening) with simultaneous reduction in strength (amplitude decrease) that was largely independent of genotype and diagnosis. Reaction times, RTV and error counts were also lower at the second measurement, albeit not across tasks. No developmental effects emerged for NGA. Including COMT genotype in the analysis, higher P150 amplitudes for carriers of the Met allele were only observed at T1, and the time-dependent reduction of amplitude and latency for target components (P100 and P300) were limited to ADHD patients and absent in controls, however P300 responses were weaker in controls than either patient group. This suggests already less resource investment at T1 for the same or better behavioural results.

Zusammenfassung

Einleitung Endophänotypen als Bindeglied zwischen heterogenem Phänotyp und der komplexer genetischer Basis des Aufmerksamkeitsdefizit-/Hyperaktivitätssyndroms (ADHS) besitzen großes Potential als diagnostische Marker. Im Fokus der vorliegenden Arbeit standen Antworthemmung, Arbeitsgedächtnis, Reaktionszeitvariabilität (RTV) und sensorisches Gating als Kandidaten-Endophänotypen, sowie die Untersuchung des Einflusses von genetischen Varianten in den ADHS-assoziierten Genen COMT, DAT und LPHN3. Die Stichprobe im Kindes- und Jugendlichenalter bestehend aus medizierten (N=36) und umedizierten (N=42) ADHS-Patienten sowie gesunden Kontrollen (N=41) wurde in einer Serie neuropsychologischer Tests unter simultaner Ableitung eines 21-Kanal-EEGs untersucht. Abhängige Variablen waren neben Verhaltensmaßen ereigniskorrelierte und topographische EEG-Parameter. Die NoGo-Anteriorisierung (NGA) als elektrophysiologisches Korrelat von Antworthemmung basiert auf der Lage der Feldschwerpunkte (Zentroide) der P300-Peaks in Antwortausführungs- (Go) und Inhibitionstrials (NoGo). Sensorisches Gating beschreibt die Fähigkeit, bei schneller Folge konkurrierender Reize die Weiterleitung des zweiten Reizes zur Prävention einer kortikalen Überstimulation zu unterbinden, was sich elektrophysiologisch in einer gedämpften P50-Amplitude zeigt. Um sowohl frühe als auch späte Auffälligkeiten im arbeitsgedächtnisbezogenen Informationsverarbeitungsprozess erfassen zu können, wurden ereigniskorrelierte Komponenten analysiert, welche frühe sensorische Verarbeitung (P100 und N100), Materialselektion (P150), Abruf von Gedächtnisinhalten (N300), Ereigniskategorisierung (P300) und Aktualisierung der Arbeitsgedächtnisinhalte (P450) reflektieren. Auslassungsfehler dienten als Indikator für Aufmerksamkeitdefizite sowie Falschalarme als Indikator für Impulsivität.

Ergebnisse Unmedizierte ADHD-Patienten zeigten neben variableren Reaktionszeiten mehr Auslassungsfehler, was Hinweise auf Defizite in Bezug auf Aufmerksamkeit, Arbeitsgedächtnis und Zustandsregulation gibt. Zum zweiten Messzeitpunkt waren überdies längere Reaktionszeiten und mehr Falschalarme zu beobachten. Unterschiede in der frühen sensorische Verarbeitung manifestieren nur in Interaktion mit dem genetischen Hintergrund (COMT, DAT). Die NGA erwies sich in unserer Untersuchung als beschränkt geeigneter Endophänotyp, da diagnostische Marker hingegen vor allem im in Frühstadium der Störung

von Bedeutung sind, jedoch bei viele Probanden im eingeschlossenen Altersspektrum keine NGA nachzuweisen war. Im Längsschnittverlauf kristallisierte sich eine übergreifende Beschleunigung (Latenzverkürzung) und Abschwächung der Stärke (Amplitudenreduktion) der elektrophysiologischen Reaktionen im Zeitverlauf unabhängig von Genotyp und Diagnose heraus. Reaktionszeiten, RTV sowie Fehlerzahlen nahmen ebenfalls ab. Es zeigten sich keine Entwicklungseffekte bei NGA. Träger des COMT-Risikoalleles (Met) hatten nur zu T1 höhere P150-Amplituden, und die Abnahme von Latenzen und Amplituden der Targetkomponenten (P100 und P300) von T1 zu T2 blieb beschränkt auf die ADHS-Gruppen, wobei P300-Reaktionen in Kontrollen am schwächsten ausgeprägt waren. Dies deutet darauf hin, dass bereits beim ersten Messzeitpunkt die Investition von weniger Ressourcen in gleicher behavioraler Leistung resultiert.

Diagnoseunabhängig war neben einer höheren RTV die NGA bei Trägern der ADHS-Risikovariante (10R/10R) schwächer ausgeprägt. Die Interaktion von DAT und diagnostischer Gruppe bedeutete auf Zentroidebene, dass nur in Anwesenheit eines protektiven Val-Allels die Stimulanzienmedikation mit einer Anteriorisierung beider Feldschwerpunkte korrespondierte. Während homozygote 10R-Träger generell Beeinträchtigungen im sensorischen Gating zeigten, kam ohne genetisches Risiko die Diagnose zum Tragen, da hier die Gruppe mit unmedizierten ADHS die größten P50-Suppressionsdefizite aufwies. Während der Arbeitsgedächtnisaufgabe modulierte DAT die Materialauswahl (P150). Wiesen unter hohem kognitivem Load die ADHS-Patienten ohne Medikation unabhängig vom Genotyp verzögerte Reaktionen im Vergleich zu beiden anderen Gruppen auf, so zeigten medizierte Patienten mit Risikogenotyp unter niedrigem Load verkürzte Latenzen auch im Vergleich zu gesunden Kontrollen. Während bei unmediziertem ADHD der DAT-Risikogenotyp mit höheren P150-Amplituden und somit verstärkter Ressourcenallokation zur Materialselektion korrespondierte, zeigte diese Gruppe bei Vorhandensein eines 9R-Allels gedämpfte P100-Amplituden im Vergleich zu medizierten Patienten und Kontrollen, was auf abnorme frühe sensorischen Verarbeitung hinweist. Zuletzt bedeutete der DAT-Risikogenotyp für unmediziertes ADHS höhere P300-Amplituden, während diese Gruppe mit dem protektiven Genotyp die schwächsten P300-Reaktionen zeigten. Dies gibt Hinweise auf Beeinträchtigungen bei der Ereigniskategorisierung.

Ein interessanter Trend zeigte sich bei der Analyse der Implikationen des LPHN3-Risikohaplotyps, der bei ADHS medikationsunabhängig mit besserer NGA assoziiert war. Da die Kombination aus Risikovarianten ebenfalls einen ADHS-spezifischen positiven Einfluss auf sensorisches Gating ausübte, sind fortführende Studien zur Funktionalität dieses Haplotyp angeraten. Auf Zentroidebene wiesen Träger des Risikohaplotyps generell mehr posterior gelegene Go-Feldschwerpunkte auf, was die Ausführung von Reaktionen begünstigt und sich entsprechend in einer höheren Anzahl an Falschalarmen niederschlägt. Bei erforderlicher Antworthemmung (NoGo) ging der Risikohaplotyp bei unmedizierten ADHS-Patienten mit mehr posterioren Zentroiden als in den Vergleichsgruppen einher, was für Unterschiede in inhibitionsspezifischer Gehirnaktivität spricht. In Bezug auf sensorisches Gating erzeugte der LPHN3-Haplotyp gegensätzliche Effekte bei Patienten und Kontrollen. Während der ADHS-Risikohaplotyp in der unmedizierten ADHS-Gruppe erwartungsgemäß mit schwächerem Gating assoziiert war, manifestiert er in Kontrollen und medizierten Patienten protektive Eigenschaften in Form überlegener Filterfähigkeiten. Abschließend korrespondiert der Risikohaplotyp bei Arbeitsgedächtnisaufgaben mit höheren N300-Amplituden als Indiz für Ressourceninvestition beim Abruf von Gedächtnisinhalten.

Während sich die NGA als unabhängig vom COMT-Genotyp erwies, lagen die Zentroide bei Probanden mit Met-Allel weiter posterior, sie zeigten darüber hinaus eine variablere und fehleranfälligere Leistung (Falschalarme). Die der NGA zu Grunde liegende Go-P300 war ohne Risikoallel bei unmedizierten ADHS-Patienten schwächer ausgeprägt als bei Kontrollen, wohingegen die Präsenz eines Met-Allels mit verkürzten Latenzen und mehr vorschnellen Reaktionen einherging. Generell bedeutete die mit ADHS assoziierte COMT-Variante eine erhöhte RTV sowie schlechtere Gatingleistung in unmediziertem ADHD, während sie durch das protektive Val-Allele in die Lage versetzte, dieses Defizit ohne Medikation zu kompensieren. Dieser Einfluss von COMT auf sensorisches Gating war spezifisch für ADHS. In Aufgaben, welche das Arbeitsgedächtnis beanspruchen, war die Met-Variante von Vorteil für Aktualisierungsvorgänge (P450), was im Gegensatz zu den Gating-Effekten nur in Kontrollen auftrat.

Preface

Ever since Sir Alexander Crichton remarked upon “mental restlessness” as a pervasive problem throughout the lifespan in 1798 (Crichton, 2008), the idea of a childhood disorder being of relevance in an adult has periodically piqued the interest of the scientific world. Explanations ranged from lack of moral control over a defect in the ego apparatus to minimal brain damage. First reports of what would now be considered rather clear-cut cases of adult Attention-Deficit/Hyperactivity Disorder (ADHD) date back even further to the Elizabethan era (1558–1603), impressively embodied by Robert Devereux, the 2nd Earl of Essex. The long-time favourite of Queen Elizabeth 1st infamously drew a sword on his sovereign in a fit of temper after being reprimanded for an insolent comment that slipped his tongue. Needless to say he ultimately – and literally – lost his head in reward of such unintentional but utterly unacceptable behaviour. His biography reads like a case study for adult ADHD: impetuous and rash, prone to inexplicable but fleeting mood swings, great ambitions thwarted by an inability to approach even simple matters in an organised manner and so on (Strachey, 1971). Charming during one's youth, but considerably debilitating with regard to one's own future and increasingly annoying to others, who are unwilling to tolerate that kind of behaviour in a person considered an adult and thus expected to act like one. While untreated ADHD in a child certainly hampers academic and personal development, it can become positively dangerous in adults as the spectrum of potentially harmful activities at one’s disposal widens, encompassing risky financial decisions, reck- or careless driving, facilitated access to illicit drugs misused for self-medication when not receiving ADHD-specific drugs or engaging in casual relationships (Barkley et al., 2004, Flory et al., 2006, Jerome et al., 2006, Manor et al., 2010).

In light of the serious consequences of a persisting insufficiently treated ADHD alluded to in the first paragraph, it is paramount to accurately diagnose the condition as early as is reasonably possible with methods that are both sensitive and specific for ADHD. However, most of the impairments ADHD children present with unfortunately are rather unspecific, and diagnosis to this point ultimately relies on a clinician’s observation-and symptom based judgement. Diagnostic and treatment-related decisions are additionally complicated by the considerable heterogeneity of ADHD presentations. In the scope of the

present work, the author will venture to explore objectively determinable behavioural, neurophysiological and genetic parameters with regard to their suitability as diagnostic predictors.

The array of neuropsychological tests was selected to tease out impairments in performance and underlying neurophysiological processes by tapping into prefrontally governed executive functions (EFs). Executive functions are a set of abilities at the root of and crucial for goal-directed behaviour, which is why they show great promise in terms of explanatory value for many of the maladaptive ADHD traits. However, deficits in EFs on a behavioural level are found not only in ADHD but also in a range of psychiatric conditions such as autism, oppositional defiant disorder, conduct disorder and Tourette syndrome (Sergeant et al., 2002). Furthermore, seeing that predictors should possess a certain degree of specificity for the state to be predicted, the fact that not every ADHD patient necessarily presents with deficits in any or all of those domains (Seidman, 2006) - possibly due to compensatory mechanisms or confounding environmental variables - raised doubts as to their suitability as diagnostic markers. However, endophenotypes as a link between genotype and phenotype have emerged as promising means to uncover underlying differences in fundamental processes despite overtly similar performance. Employing brain imaging techniques to measure functional correlates of potentially normal behavioural performance of ADHD children and healthy controls in neuropsychological tasks allows for the identification of more basic deficits in information processing and response control as endophenotypes. We recorded a 21-channel electroencephalogram (EEG), allowing us to relate neuronal activity to performance with high temporal resolution. Finally, we were interested in the influence of three genes found to be associated with the broad ADHD phenotype, namely Catechol-O-Methyl-Transferase (COMT), the Dopamine Transporter (DAT, SLC6A3) and Latrophilin-3 (LPHN3) in sample comprising children and adolescents with a clinically diagnosed ADHD (unmedicated or receiving psychostimulant medication) and matched healthy controls.

1 Introduction to Attention-Deficit/Hyperactivity Disorder

1.1 Phenomenology

ADHD affects about 5% of children and adolescents around the globe (Polanczyk et al., 2007) and is thus one of the most prevalent psychiatric disorders of childhood and adolescence. Partly owing to a remarkable genetic component, ADHD has a strong tendency to persist into adulthood (40-65% according to WHO statistics), albeit with a changed phenotype indicative of on-going brain development. The clinical phenotype is extremely heterogeneous and comprises symptoms from the broad domains of age-inappropriate hyperactivity, maladaptive impulsivity, inattention and emotional dysregulation. From childhood and adolescence to adulthood, motor hyperactivity declines while inattention persists (Wilens and Dodson, 2004). Emotional dysregulation emerges as a major issue for adult ADHD patients, manifesting in irritability and unpredictable mood swings. Patients show a compromised ability to deal with stress, partly due to a lack of organizational and emotion regulation skills (Sobanski et al., 2010). The fact that the most readily recognizable feature of the disorder – hyperactivity – attenuates with age has contributed to the long-held notion that there is no such thing as adult ADHD, and that the disorder is solely an affliction of childhood. However, research monitoring the development of neuropsychological profiles of ADHD patients confirmed the persistence of impairments in basic processes underlying cognitive functioning. As the prefrontal cortex (PFC) – the major control instance of human behaviour - matures, inhibitory control increases. So as patients grow older, more sophisticated strategies to conceal the more disrupting impulsive tendencies enter the behavioural repertoire. Still, patients' reports suggest that this formerly externally visible hyperactivity basically becomes internalized in the form of a feeling of restlessness and being driven without purpose.

Currently, childhood ADHD (cADHD) is diagnosed according to criteria laid down in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV; American Psychiatric Association) or the International Classification of Diseases 10 (ICD10; World Health Organization). For adult ADHD, tools like Conners' Adult ADHD Rating Scales or the Utah criteria incorporated items pertaining to difficulties with planning, structuring

and organizing, while assessment of the hyperactive domain has been supplemented by a more or less constant feeling of restlessness in absence of the overt motor behaviour observed in children. The phenotypical heterogeneity of ADHD is roughly accounted for by the recognition of three subtypes - the primarily hyperactive subtype, the primarily inattentive subtype and the combined subtype. The relative frequency of those subtypes again differs between clinical and community samples (inattentive type most prevalent in general population, combined type most common in clinic samples), indicating that combined symptoms from multiple affected domains make children more likely to be referred to a mental health expert than primarily inattentive cases (Faraone et al., 1998, Carlson and Mann, 2000). The gender ratio in ADHD is skewed towards males (10:1 in clinically referred samples and 5:1 in non-referred children; (Arnold, 1996, Gaub and Carlson, 1997), but ADHD in girls predominantly manifests in the inattentive subtype, and owing to the nature of this subtype's symptoms it is less likely to provoke disruptive behaviour and social difficulties. Furthermore, they develop less psychiatric comorbidities, and this might ultimately result in a referral bias (Biederman et al., 2002). The traditional view of ADHD as a clinical entity and the diagnostic process is currently under revision. The practical use of diagnosing ADHD as distinct categorical subtypes is currently under debate and the fifth edition of the DSM is going to discard with those subtypes and furthermore account for the symptomatic decline with age by adding symptoms typical of adult ADHD as well as by lowering the number of symptoms required for diagnosis. In contrast to many other clinical entities, ADHD is being viewed as a continuum rather than a category [16-17], hence those suffering from a clinically relevant ADHD are at the extreme end of the distribution of a trait that can to some degree be found in all humans.

In addition to questions directly related to the disorder, an important issue in the study and treatment of ADHD are psychiatric comorbidities, since presentations with an isolated ADHD are rather the exception. Over their lifespan, ADHD patients have dramatically high prevalences of comorbid conduct, mood and anxiety disorders, substance abuse and Cluster B personality disorder, motor tics and learning disorders (Jacob et al., 2007, Halmoy et al., 2009, Wilens et al., 2009).This in combination with

the nature of ADHD prevents afflicted children from realizing their full potential at school in terms of academic achievement (Barkley et al., 2006a). One long-term study on school outcomes for 370 cADHD cases compared with normal controls confirmed that they had tripled grade retention rates and were 2.7-times more likely to drop out of school without a degree (Barbaresi et al., 2007, Biederman et al., 2010a, Biederman et al., 2010b). Naturally, this along with the persistence of the general symptoms is likely to have serious implications for their future paths, probably limiting career options very early on. This is supported by reports of considerably lower rates of employment for individuals diagnosed with ADHD (24 vs. 79% for controls; (Halmoy et al., 2009), and difficulties in the workplace when it comes to job performance (Barkley et al., 2007, Sobanski et al., 2010) or continuity of employment. Furthermore, impaired social cognition (for a review, see (Uekermann et al., 2010), emotion processing (Da Fonseca et al., 2009) and dysfunctional peer relationships (Hoza et al., 2005) put an additional strain on quality of life, which has been found to be lower in ADHD patients (Klassen et al., 2004, Adler et al., 2006).

In the early stages of aetiological research, investigators were keen on identifying one deficit to explain the entirety of ADHD, not taking into account the fact that such an endeavour was very likely to prove futile in such a heterogeneous disorder where no two patients look alike. The following selection of models is merely an illustration of the variety of research inspired by the one-core-deficit idea, and is by no means intended to be comprehensive. Barkley for example proposed that an inhibitory deficit is at the heart of other impairments pertaining to executive functions like working memory, self-regulation of affect, motivation and arousal, internalisation of speech and reconstitution (Barkley, 1997). The self-regulation aspect of Barkley's theory was expanded by Sergeant in his cognitive energetic model, which identified the core problem in ADHD to be inadequate allocation of energetic resources and thereby introduced the concept of an increased variability in attention instead of a linear decline over time (Sergeant, 2000). In an attempt to bring order to the chaos of executive functioning, Zelazo & Mueller (2002) made a distinction between hot executive functions that involve the affective dimension and cool, more abstract EFs

(Zelazo and Müller, 2002). Today, research has embraced the concept of causal heterogeneity and multiple developmental pathways to ADHD (Sonuga-Barke, 2003, Nigg et al., 2005, Sonuga-Barke, 2005), and in accordance with the idea of equifinality in psychopathology aetiologically distinct pathways will ultimately manifest in the clinical picture summarised under the header of ADHD.

1.2 Neuropsychology of ADHD and the concept of endophenotypes

Neuropsychological impairments for both young and older ADHD patients have been reported in a wide variety of tasks assessing executive functions (response inhibition, verbal and spatial working memory and cognitive flexibility), delay aversion and so on (Martinussen et al., 2005, Wåhlstedt et al., 2009, Biederman et al., 2011). However, neuropsychological profiles are as heterogeneous as the phenotypical presentation of the disorder, supporting the notion of multiple pathways in the aetiopathogenesis of ADHD. Data collected from 3734 patients confirmed, on the whole, a performance impairment of medium ES for this population on planning, working memory, vigilance and response inhibition tasks (Willcutt et al., 2005, Bidwell et al., 2007). Bidwell and colleagues (2007) examined a large sample of twin pairs either con- or discordant for ADHD with a battery assessing executive functions (working memory, response inhibition, set shifting and interference control), processing speed and response time variability. They found ADHD children to fare significantly worse than matched control twins on all of the aforementioned variables, with the exception of motivational and delay aversion measures. Even though the co-twin in the discordant pairs showed no clinically relevant signs of ADHD, they had intermediate scores on most tests, meaning that they to some degree had also inherited the ADHD-related disadvantages. It has to be noted though that the outcomes from those kinds of tests do not constitute reliable markers for diagnosis, since they are neither consistently present in every ADHD patient nor do controls always outperform peers with ADHD, furthermore as mentioned before EF deficits are a common finding in many psychiatric disorders and thus lack specificity.

In a meta-analysis by Willcutt et al. (2005) on executive functioning in ADHD, the markers most reliably associated with the disorder were related to response inhibition (SSRT), vigilance (omission errors in CPT), verbal and spatial working memory. If not used singly but in combination, tests of executive functioning can well distinguish ADHD patients from healthy individuals. Combinations of working memory and response inhibition have proven to be particularly useful for the identification of ADHD children (Holmes et al., 2010). ADHD children made more errors of omission and commission in a CPT, had compromised verbal and visuo-spatial working memory as well as reduced cognitive flexibility as indicated by the Wisconsin Card Sorting Test and compromised planning abilities in the Tower of London (Holmes et al., 2010). However, correlations between behavioural output indicating EF deficits and ADHD symptom are typically weak (Willcutt et al., 2005), and problems arise when trying to disentangle neuropsychological profiles of similar psychiatric groups. Geurts et al. (2002) found autistic children to display more generalised EF deficits in direct comparison with an ADHD group, but for example on Stop Signal Reaction time as a measure of inhibitory control. The two clinical groups were equally impaired compared to healthy controls (Geurts et al., 2004).

The endophenotype concept in psychiatric research. Endophenotypes - also known as intermediate phenotype – are latent traits carrying genetic load and associated with behavioural symptoms. As markers of genetic liability they serve as a link between genotype and phenotype; they are thought to underlie behavioural symptoms but to be one level closer to the genetic basis of a disorder and thus more directly reflecting genetic vulnerability (Almasy and Blangero, 2001). One endophenotype can be responsible for multiple overt behavioural symptoms. For example, deficient response inhibition in the case of ADHD can result in blurting out comments, getting up in the middle of a meeting, carelessly crossing the street or interrupting on-going work due to an intruding impulse. Focusing on those intermediate phenotypes allows researchers to select more homogeneous groups of patients and also facilitate the identification of risk genes underlying these more basic deficits. In order for a marker to be considered useful as an intermediate phenotype, it has to fulfil certain criteria: a primary deficit in

the disorder in question, it should still be a dimensional attribute also found in the normal population. An endophenotype has to be a heritable and familial trait and crucially, it needs to be quantitatively measurable, so that ultimately those endophenotypes can predict ADHD the same way blood cholesterol can predict coronary heart disease (Castellanos and Tannock, 2002, Rommelse et al., 2008c). Additionally, mean values of unaffected siblings should lie somewhere between those of patients and those of healthy controls as they share some of their ADHD sibling's genetic background and thus very likely also inherited some of the genetic variants contributing to the disorder. Rommelse and colleagues (2008) confirmed the suitability of executive functions – particularly response inhibition (RI) and working memory - as endophenotypes of the disorder, as they could show that an EF component comprising response inhibition and working memory was compromised in cases and affected siblings to an equal extent and in unaffected siblings at an intermediate level as compared to healthy controls (Rommelse et al., 2008b).

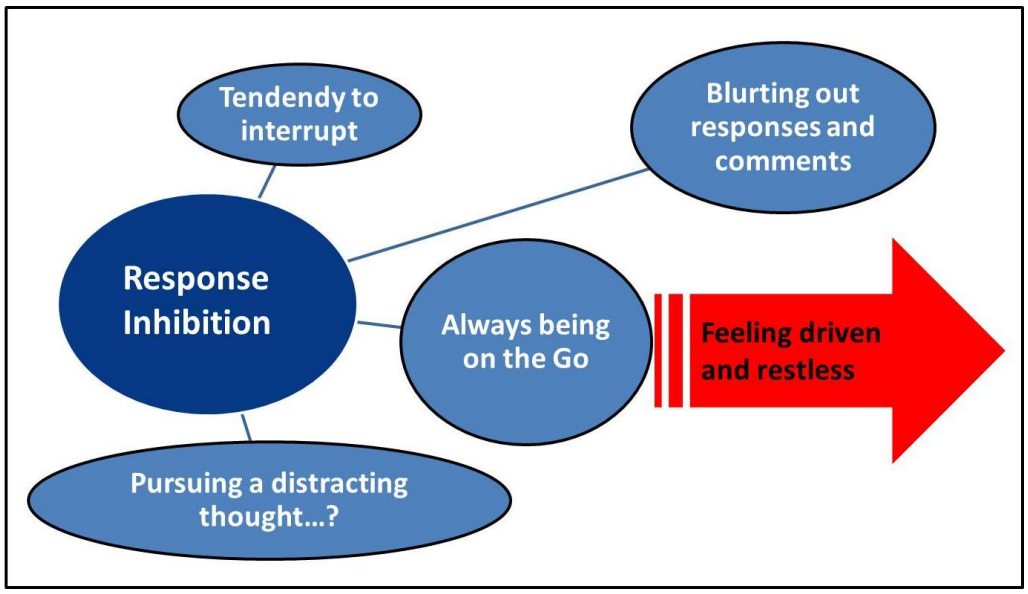

Figure 1: Explanatory value of an endophenotype for multiple behavioural symptoms

Response inhibition for example could just as well be considered an endophenotype if approximated by errors of commission or Stop Signal Reaction Times, without employing more time-consuming electrophysiological methods. However, be it due to the phenotypical diversity according to the 18 symptoms currently used to diagnose ADHD, or the heterogeneous patterns of deficits in

behavioural performance in neuropsychological tests: stable differences are hard to come by when comparing ADHD patients with normally developing individuals. The highly structured nature of a neuropsychological examination in a laboratory might further mask underlying deficits, which under natural circumstances would clearly impact on tasks of daily life. Draeger and associates observed that as soon as the experimenter left the room, a significant deterioration of performance occurred in the ADHD group (Draeger et al., 1986). So even in the face of normal performance in terms of errors rates, this effort to keep up appearances is likely to show in electrophysiological activity preceding or accompanying correct and incorrect responses. Indeed, even in the absence of overt behavioral impairments there are often distinct differences in underlying brain activity in ADHD patients. Despite normal behavioral performance in tests of spatial and verbal working memory and executive functioning, connectivity was enhanced in ADHD adults in one network (right PFC, left dorsal cingulate cortex and left cuneus) and decreased in another (ventrolateral PFC, anterior cingulate cortex (ACC), superior parietal lobule and cerebellum) during a basic activation task (Wolf et al., 2009). Valera et al. (2005) had previously observed lower cerebellar activation during an n-back working memory task, again in absence of behavioral effects (Valera et al., 2005). They furthermore found a gender effect in working memory-related brain activity on top of generally lower prefrontal activity in ADHD patients (Valera et al., 2010). Women did not differ from controls, whereas men had decreased activation in left cerebellar and occipital areas, and enhanced activity in right frontal, temporal and subcortical regions compared with healthy controls. This illustrates the benefits of using imaging techniques during the examination of neuropsychological functioning to gain a deeper insight into the integrity of basal processes and recommends functional parameters as endophenotypes for the study of psychiatric disorders such as ADHD

1.3 Candidate genes

Investigations into structural and functional ADHD neuroanatomy point mainly towards abnormalities in fronto-striatal circuitry (Seidman et al., 2005). As both the PFC and the basal ganglia rely heavily on catecholaminergic neurotransmission, it makes sense to

take a closer look at genes coding for the main modulators of catecholaminergic action in those regions. COMT is expressed mainly in the PFC and degrades catecholamines such as dopamine (DA), norepinephrine (NE) and epinephrine, thus limiting the duration of action in the synaptic cleft. Similarly, the DAT is more abundant in the striatum, where the reuptake of DA and to a lesser extent NE into the neuron via the DAT marks the end of the synapses' active period.

1.3.1 Catechol-O-Methyl Transferase (COMT)

COMT is of critical importance for maintaining the balance of catecholamines and thus the functionality of prefrontal brain areas (Grossman et al., 1992). The gene coding for this enzyme located on Chromosome 22q11.21 has been studied extensively, with much of the published research focusing on the Valine158Methionine-coding single nucleotide polymorphism (SNP) in Exon 3 of the gene, where the change from C to G in the nucleotide sequence of the COMT gene leads to an exchange of amino acid 158 from valine (Val) to methionine (Met). This results in the production of a more thermo-labile and thus less active enzyme and ultimately higher catecholamine availability (Lachman et al., 1996).

Findings regarding functional implications of COMT genotype are heterogeneous. For healthy children and adults, the Met allele seems to be largely beneficial for prefrontally mediated functioning (Malhotra et al., 2002, Gallinat et al., 2003, Diamond et al., 2004, de Frias et al., 2005); others find no link [(Blanchard et al., 2011); meta-analysis by (Barnett et al., 2008)] or the exact opposite pattern, where Val helps performance [22q11 (Baker et al., 2005); ADHD (Bellgrove et al., 2005)]. It has been proposed that the Val allele mainly confers an advantage in terms of cognitive flexibility (Bilder et al., 2004). A recent study by Dumontheil et al. (2011) suggests developmental changes in the impact of COMT on cognitive tasks, since they found the beneficial influence of the Met allele first manifesting around the age of 10 (Dumontheil et al., 2011). Gender has also been implicated as a potential moderator, with the positive relationship between different cognitive functions and COMT

genotype (or rather number of Met alleles) only manifesting in males (Barnett et al., 2007).

In ADHD, having the normal Val allele with its quick degradation of catecholamines has been hypothesized to contribute to the often reported hypo-dopaminergic state in ADHD. Impaired sustained attention in ADHD children with at least one Met alleles has been described (Bellgrove et al., 2005), while others find no behavioural difference on measures of working memory and different measures of response inhibition (Mills et al., 2004). Interestingly, the Val allele which has been found to be more frequent in childhood ADHD also confers a more favourable response to Methylphenidate (MPH) than Met/Met patients in terms of symptom severity (Kereszturi et al., 2008). The nature of the relationship between COMT and ADHD is also far from clear. While some studies find an association of the Val158Met polymorphism with ADHD (Eisenberg et al., 1999, Qian et al., 2003, Palmason et al., 2010) and higher ADHD scores in Met carriers (Palmason et al., 2010), others cannot confirm those results (Hawi et al., 2000, Bellgrove et al., 2005, Turic et al., 2005). A recent meta-analysis by Cheuk and Wong (2006) found no association between COMT Val158Met polymorphism and ADHD, although the authors acknowledge there was considerable clinical heterogeneity between studies, which might have biased the pooled results (Cheuk and Wong, 2006). This casts serious doubt on a direct association between the polymorphism and the disorder, it seems far more likely that having a certain genotype in combination with ADHD related structural and functional alterations has an additive effect and might provoke more serious impairment in ADHD patients compared to healthy individuals.

1.3.2 Dopamine Transporter 1 (DAT)

The gene coding for the DAT is located on Chromosome 5p15.3 (Kawarai et al., 1997), and it is mainly expressed and influencing dopaminergic neurotransmission in the striatum and cerebellar vermis and to a much lesser degree in PFC (Ciliax et al., 1999, Durston et al., 2005, Scherk et al., 2009). The most commonly studied polymorphism is a variable number tandem repeat of 40bp in the 3' untranslated region (3'UTR). In

human populations the reported number of repeats ranges from 3 to 13, with 9R and 10R alleles emerging as the most common alleles (Mitchell et al., 2000). The 9R allele is associated with lower gene expression and thus reduced transporter activity and more DA in the synaptic cleft (Heinz et al., 2000, Mill et al., 2002). Especially motor inhibition requires basal ganglia and PFC to work in concert (Chambers et al., 2009). The PFC requests an increase of behavioural control by top down commands, and DA then acts as an executive messenger, translating the PFC commands into inhibitory signals to motor areas in the cortex (Mink, 1996). DAT is the main target of psychostimulant drugs used for the treatment of ADHD, which presumably exert their effect by increasing catecholaminergic stimulation of α2-adrenoreceptors and D1 receptors (Arnsten and Dudley, 2005, Gamo et al., 2010). Striatally, methylphenidate blocks the DAT and thus the reuptake of DA, hereby influencing both cognitive and motor behaviour via the direct and the indirect pathway through D1 and D2 receptors (Volkow et al., 2001). In the PFC, effects on executive functions are likely to be mediated by raising DA and NE through a comparable blockage of the NE transporter (NET), which is more abundant there and MPH also possesses an affinity for (Bymaster et al., 2002).

Indications for the gene's involvement in the aetiopathogenesis of ADHD come from several lines of evidence. In addition to hints from the mechanisms of action of stimulant drugs commonly used for the treatment of ADHD (Faraone et al., 2004, Volkow et al., 2005), genetic association studies link the above-mentioned VNTR to the disorder, although - similar to COMT - findings regarding the association of DAT with ADHD are heterogeneous]for an overview, see the meta-analysis by (Rommelse et al., 2008a)]. As a model organism, DAT knockout mice display a pronounced motorically hyperactive phenotype, thus supporting the gene's involvement in ADHD pathogenesis (Gainetdinov and Caron, 2000). Interestingly, there seem to be developmental effects, as the risk allele changes with age. The 10R allele is considered a risk allele for childhood ADHD [meta-analysis by (Faraone et al., 2005)], and carrying two copies of the 10R allele confers an increased risk for impaired cognitive functioning in this age group (Loo et al., 2003, Cornish et al.,

2005), although there are also reports in the opposite direction (Barkley et al., 2006b, Karama et al., 2008). For adult ADHD, the 9R allele and the 9/9 genotype seem to be the risk variants, interfering with optimal performance (Franke et al., 2010). Cheon et al., (2005) reported homozygous 10R carriers to respond less favourably to MPH. Left caudate volumes were smaller for the 10/10 genotype and in ADHD subjects, but the two factors did not interact (Cheon et al., 2005). This structure is crucial for inhibition (Shook et al., 2011), speaking to the role of DAT in response control. Cornish and colleagues (2005) found homozygous carriers of the DAT 10R allele to have higher ADHD scores and performance impairments in tasks requiring response inhibition and selective attention, but not working memory. High scorers were generally out-performed by low scorers in tasks on attention, inhibition and working memory.

Age differences between samples might partly explain inconsistent findings concerning the connection between DAT and ADHD. Further contributing to practical ramifications of DAT genotype might be the nature of the task. More cognitive (prefrontal, executive) tasks are largely independent of DAT genotype, while those involving a motor response are more influenced due to involvement of striatum. Also, the relatively low frequency of 9R makes pooling of 9/9 and 9/10 probands necessary, and this might obscure some effects.

1.3.3 Latrophililin-3 (LPHN3)

Latrophilin-3 (LPHN3) is a member of a large family of adhesion G-protein coupled receptors (adhesion GPCR). It possesses seven trans-membrane domains and a large extracellular site (Sugita et al., 1998). While LPHN 1 and LPHN2 bind latrotoxin – the venom of the black widow spider – with differing affinity, the exact function of LPHN3 as well as its endogenous ligand remain elusive. Putative functions include the negative regulation of axonal growth and protection against oxidative stress. It is presumably involved in processes of cell adhesion, synaptic plasticity and signal transduction. The protein is predominantly expressed in cerebral cortex, cerebellum, amygdala and caudate nucleus, but has also been found in putamen, hippocampus, corpus callosum, frontal and temporal lobe, occipital pole (Arcos-Burgos et al., 2010).

In addition to being heavily in expressed in the striatum, LPHN3 is associated with changes in dopaminergic brain circuitry, as animals models recently were able to demonstrate. (Wallis et al., 2012) succeeded in generating a LPHN3 knock-out mouse model. These animals – aside from a pronounced phenotypical hyperactivity – displayed elevated levels of DA and serotonin (5-HT) in the dorsal striatum, furthermore receptors and transporter molecules for those neurotransmitters were altered, indicating a profound interaction of LPHN3 and the dopaminergic system. Also, the animals lacking LPHN3 showed a heightened sensibility to the stimulating effects of cocaine. The more ecologically plausible zebrafish knock-down model (Lange et al., 2012) sheds some light on potential changes occurring in humans with the less active LPHN3 haplotype. Even in this intermediate state, the decreased levels of LPHN3 interfere with dopaminergic architecture in the central diencephalon in the form of more sparsely distributed and spatially misplaced DA-positive neurons. Drugs commonly used for the treatment of ADHD are capable of an effective phenotypical rescue of the motorically hyperactive animals. The authors speculate that the variants of the gene leading to a decrease in LPHN3 levels might contribute to the hyperactive phenotype, whereas different variants might be involved in the pathogenesis of Parkinson's disease. The connection between ADHD and LPHN3 has first been described by Arcos-Burgos et al. (2004) in a genome-wide linkage study on a Columbian population isolate (Arcos-Burgos et al., 2004). In this population, the highly prevalent ADHD was linked to a risk variant in the region around the LPHN3 gene, which could be mapped to a locus at 4q13.2 in subsequent investigations. This finding has since been replicated in European and US samples (Arcos-Burgos et al., 2010, Ribases et al., 2011). The authors identified a risk haplotype comprising 3 SNPs - rs6551665 (G), rs1947274 (C) and rs2345039 (C) – belonging to a common linkage disequilibrium (LD) block. In a region-of-interest analysis of brain chemistry using Proton magnetic resonance spectroscopy (1H-MRS), the risk haplotype carriers displayed decreased activity in left lateral and medial thalamus as well as the right striatum, and an increase in the cerebellar vermis (Arcos-Burgos et al., 2010). Interestingly, one of the risk SNPs comprising the risk haplotype (G allele for rs6551665) was also associated with better response to stimulant medication.

1.4 Candidate Endophenotypes

1.4.1 Response Inhibition

1.4.1.1 Behavioural Correlates of Response Inhibition

The capability for response inhibition describes the successful interruption of prepared responses, requiring an active suppression of behaviour. This marker meets the aforementioned endophenotype criteria, as quantitatively measurable correlates of response inhibition deficits are associated with the disorder in ADHD patients (Wodka et al., 2007) and it has also been found to be compromised in unaffected siblings (Slaats-Willemse et al., 2003, Bidwell et al., 2007). Furthermore RI possesses a distinct genetic component (Goos et al., 2009). A number of meta-analyses [(Schachar et al., 1995, Oosterlaan et al., 1998, Willcutt et al., 2005) on the whole confirm a higher prevalence of inhibitory deficits in ADHD samples, however not all patients showed this particular difficulty. The two major tasks for the study of response inhibition are the Continuous Performance Test (CPT) and the Stop Signal Task (SST) and variants thereof. As the SST however presents with some theoretical and methodological issues and furthermore could not be analysed with regard to electrophysiological correlates of prefrontal functioning, a Go/NoGo paradigm was chosen to assess response inhibition. The CPT as a response inhibition task is very well suited for the examination of ADHD, as it very basic, has high explanatory value as an endophenotype for many behavioural symptoms and provides access to both dimensions of ADHD by means of errors of impulsiveness (errors of commission; False Alarm) and inattention (errors of omission; Miss) as well as response time variability (RTV; operationalized by the standard deviation of reaction times). The task has proven to be particularly sensitive in identifying ADHD cases compared to healthy children and adolescents. In a recent meta-analysis, the majority of studies on CPT performance in ADHD found patients to perform worse than controls - mainly manifesting in increased errors of commission, as this is the most direct indicator of a lack of inhibitory control (Willcutt et al., 2005). Pre-school children aged 3 to 7 years were classified into a high- and a low-risk group for ADHD and tested with a combined CPT –Go/NoGo task. High-risk children made more errors of both types in the CPT, and frequency of errors as well as mean RT and RTV was negatively related to

age. Furthermore, mean and variability of reaction times was higher in the risk group (Berwid et al., 2005). Generally, more errors of commission as indicators of impulsivity and omission as the consequence of inattention (Barkley et al., 2001, Fallgatter et al., 2004, Berwid et al., 2005, Wodka et al., 2007), longer reaction times and more variable responses have been reported in ADHD populations (Banaschewski et al., 2003, Fallgatter et al., 2004, Berwid et al., 2005, Wodka et al., 2007). It has to be noted however, that results are not unequivocal, and a number of studies could not confirm the aforementioned behavioural deficits in ADHD (Fallgatter et al., 2004, Lawrence et al., 2005).

MPH can successfully counteract the impact of ADHD on error rates in a variety of tasks, particularly the rate of false alarms as a correlate of impulsivity [(Broyd et al., 2005, Lawrence et al., 2005); for a review on stimulant effects specifically on CPT outcome, please see (Riccio et al., 2001)]. The beneficial effect of psychostimulants on ADHD related impulsivity seems to be somewhat specific when distinguishing between different kinds of the broad impulsivity construct. DeVito and colleagues (2009) found ADHD children to improve under stimulant medication in terms of impulsivity when it is defined as inhibition of prepotent motor responses, but medication did not influence reflective impulsivity in terms of rash decision-making without evaluating all available information (DeVito et al., 2009). If errors of commission are viewed as indicative of action impulsivity, then the unmedicated ADHD group should be outperformed by their medicated counterparts as well as healthy children.

1.4.1.2 EEG correlates of Response Inhibition

The most commonly studied event-related potential (ERP) components in response inhibition paradigms are the negative fronto-central N200 (200-300 ms) and the positive centro-parietal P300 (300-700 ms). Additionally, the CPT as a Go/NoGo task allows for the assessment of an electrophysiological correlate of prefrontal inhibitory functioning – the NoGo-Anteriorization or NGA (Fallgatter et al., 1997).

1.4.1.2.1 Event-Related Potentials

The origins of both N200 and P300 have been traced back to the anterior cingulate cortex or ACC (Strik et al., 1998, Bekker et al., 2005). The proposed functions of the P300 range from orienting and perceptual evaluation to closure and resource allocation (Brandeis et al., 1998), and the target P3b plays a role in event categorization (Kok, 2001). Both have been presumed to reflect inhibitory effort, and the debate particularly regarding the role of the frontally maximal N200 is on-going [inhibition (Lavric et al., 2004); conflict monitoring (Nieuwenhuis et al., 2003, Donkers and van Boxtel, 2004)], however especially the NoGo-P3 seems to reflect inhibitory effort (Tekok-Kilic et al., 2001, Freitas et al., 2007), as this component has been proven to be more susceptible to manipulations of probability of inhibitory demands than the N2 (Smith et al., 2007). However, since N2 amplitudes have been found to be higher for NoGo compared to Go trials, it no doubt is involved in the inhibitory process in some form (Johnstone and Clarke, 2009). Indeed, Pliszka et al. (2000) found the N2 amplitude to be strongly correlated with inhibitory performance, and greater amplitude for successful as compared to failed inhibitions for N2 and NoGo-P3 only in controls underlines these components' importance in response control and the suppression of unwanted reactions (Pliszka et al., 2000). The increase in N2 amplitude for successful inhibitions was only present in control subjects, indicating abnormal preparatory processes in ADHD (Liotti et al., 2007).

Response inhibition (NoGo) trials normally elicit higher N2 amplitudes than response execution (Go) trials. In healthy subjects, no latency differences between Go and NoGo-N2 emerged (Johnstone & Clarke, 2009). However, the magnitude of N2 responses is related to being a good vs. bad inhibitor in terms of errors of commission (Falkenstein et al., 1999). Groom and colleagues (2010) confirmed previous reports of higher amplitudes for both inhibition- associated components (N2 and P3) during NoGo (inhibition demanding) as compared to Go trials (Groom et al., 2010, Fisher et al., 2011). They furthermore compared electrophysiological correlates of response control between ADHD patients and healthy controls, and found the magnitude of N2 and P3 to be diminished in patients in both conditions.

Methylphenidate was able to normalize amplitudes of both components in the ADHD group, and furthermore added motivational incentives were also beneficial for electrophysiological response. N2 amplitudes are lower in ADHD compared to controls (Johnstone & Clarke, 2009). This less strong N2 response in patients has been found numerous times (Strandburg et al., 1996, Overtoom et al., 1998, Pliszka et al., 2000, Bokura et al., 2001, Johnstone et al., 2001, Broyd et al., 2005, Liotti et al., 2007, Wild-Wall et al., 2009), but there are also contradicting reports of an increase in N2 amplitudes in the ADHD population [adults (Prox et al., 2007) and children (Rubia et al., 2005)]. ADHD patients have been found to show a delayed N2 when inhibition is required compared to trials requiring a response (Johnstone & Clarke, 2009), however there are also reports of shorter latencies for NoGo compared to Go in this population (Smith et al., 2004).

In NoGo trials in a study by Fisher et al. (2011), ADHD was associated with longer latencies for N2 and P3, with lower P3 amplitudes and more errors of commission in comparison to controls. During the Go condition, patients missed more targets and had greater N2 responses compared to controls. During a cued CPT, the increase of N200 amplitudes from Go to NoGo was greater in ADHD, and they also showed shorter NoGo-N200 latencies (Smith et al., 2004). Frontal N2 and posterior P3 amplitudes to target stimuli were diminished in ADHD, and stimulant medication administered for a second experimental session had a normalising effect on ERPs during a cued CPT. Reaction times during Go trials did not distinguish between groups, and differences in error rates during the first session were remedied by methylphenidate as well (Lawrance et al., 2005, see also Fallgatter et al., 2004 for diminished NoGo-P3). A subsequent study by the same group found the same effects on N2 and P3, but distinguishing between types of errors revealed that methylphenidate selectively diminished false alarms, while a higher rate of omission errors persisted (Broyd et al., 2005).

In healthy individuals, P3 amplitudes are higher in NoGo compared to Go trials (Fisher et al., 2011; Groom et al., 2010). Summing up the vast P300 literature,

a review on P300 in childhood ADHD largely describes longer latencies and higher amplitudes as characteristic of the disorder (Barry et al., 2003), while in adult ADHD a recent meta-analysis reported diminished amplitudes in patients (Szuromi et al., 2011). Electrophysiological studies using versions of the CPT have reported generally reduced P300 amplitudes in ADHD children (DeFrance et al., 1996, Strandburg et al., 1996, Overtoom et al., 1998). Differentiating between response inhibition and execution trials, ADHD patients have lower P3 amplitudes for both conditions (Broyd et al., 2005; Fallgatter et al., 2004; Fisher et al., 2011; Groom et al., 2010; Lawrance et al., 2005). Contrary to normally developing control children, patients suffering from ADHD did also show deficits in their allocation of processing energy, as the usual habituation of P300 strength to standard stimuli was absent in ADHD (Karayanidis et al., 2000) and there was a less clear amplitude difference between targets and standards. This could be interpreted as investing an unnecessary amount processing capacity and energy, possibly due to difficulties with distinguishing in terms of relevance. Research on P300 latencies is less consistent. Some studies find faster responses in unmedicated ADHD (Taylor et al., 1997), while others report delayed P300 peaks that could also be counteracted with stimulant medication (Strandburg et al., 1996, Sunohara et al., 1999).

1.4.1.2.2 Topographical parameters: NoGo-Anteriorization

NGA describes a shift in the positive electrical field of the brain during the P300 window from posterior to more anterior areas whenever a prepared motor response has to be inhibited (NoGo condition) as compared to executed (Go condition). A coordinate system ranging from 1 to 5 is superimposed onto the topographical brain maps and the weighted centroid location for Go and NoGo along this axis is calculated. By subtracting the location of the NoGo centroid from the Go centroid, the resulting NGA constitutes an individual quantification of the magnitude of this shift for each participant. Higher NGA values signify better the inhibitory control from the PFC. Fallgatter and colleagues established this topographical parameter as an electrophysiological correlate of prefrontal response control (Fallgatter et al., 1997, Fallgatter and Strik, 1999) and have shown the NGA

to possess great long-term reliability and intra-individual stability (Fallgatter, 2001, Fallgatter et al., 2002a). As it appears to be largely independent of gender and age (Fallgatter et al., 1999), impairments in NGA could be a promising marker for monitoring executive dysfunction during the course of a disorder. Source localization via functional Magnetic Resonance Imaging (fMRI) and Low Resolution Electromagnetic Tomography (LORETA) traced the origins of the NGA or rather the activation during the NoGo condition back to the anterior cingulated cortex (ACC) (Fallgatter et al., 2002b, Ford et al., 2004).

NGA in ADHD In a study by Fallgatter et al., (2004) looking into inhibitory mechanisms in ADHD, only affected boys (N=16; aged 7-11) and healthy male controls (N=19; aged 8-11) were included. The authors observed a dampened central NoGo P3 for the ADHD group, which corresponded to lower ACC activation during inhibition trials. Behaviourally, ADHD children had longer reaction times and made more omission errors, but did not differ in the number of false alarms. Controls had higher fronto-central P3 amplitudes during NoGo compared to Go, and higher parietal P3 amplitudes during Go- compared to NoGo-trials. ADHD children displayed higher Go amplitudes both at Cz and Pz with generally longer latencies. Regarding the N2, no group effects on amplitude were found, but this peak is more negative during Go-trials and the difference between conditions is most pronounced at Cz. Longer latencies in ADHD group could only be observed during NoGo trials at Cz.

Banaschewski et al. (2004) reported on a sample aged 8 to 14 with assessed with a cued CPT, where ADHD children showed most pronounced problems in the cue condition (to the warning stimuli). Strikingly, the expected anteriorization of brain activity for NoGo could only be found in the hyperkinetic group (Banaschewski et al., 2004). It has to be noted though that no NGA as such was calculated. The inhibitory NoGo-P300 shows earlier maturation in control children, whereas this component emerged later in the young ADHD patients. However the target P300, which normally decreases in amplitude with age, showed the opposite pattern in

ADHD and thus speaks more to a deviation from normal development in terms of response execution (Doehnert et al., 2010). The authors followed a small group of ADHD patients (N = 11, age at baseline Ø 10.9 years) diagnosed in childhood over the course of 11 years (Doehnert et al., 2012) and assessed them at four time points (baseline, T2 = 1.1 years, T3 = 2.4 years and T4 = 11 years) with a CPT / Go-NoGo paradigm, looking both at preparatory and inhibition-related processes. The absence of group by time interactions suggest that none of the parameters deviated from the typical developmental trajectory, the direction of change over time was the same for ADHD and controls. Behavioural parameters (RT, RTV, errors of omission) and preparatory potentials (Contingent Negative Variation CNV, Cue P300) decreased over time, with ADHD patients having higher RTV and lower Hit rate and magnitudes of Cue-P300 and CNV at single measurement points. Interestingly, the CNV was the only marker to be consistently diminished, lending support to its suitability as a stable candidate endophenotype present even in patients no longer meeting full ADHD criteria. NoGo global field power amplitude decreased with age, but was higher in ADHD compared to controls at T3. Adult ADHD patients present with decreased NGA and GFP amplitudes and a less substantial increase in fronto-central P300 from Go to NoGo compared to controls, however one has to bear in mind that the probands were out-patients of the forensic section all diagnosed with a personality disorder and an incidental and not conclusively verified cADHD (Fallgatter et al., 2005).

A reduced NGA has been observed in other clinical populations as well (Fallgatter and Muller, 2001, Fallgatter et al., 2003) and thus is not specific for ADHD. MPH has a normalising effect on P3 amplitudes, which were diminished in ADHD boys following both Go and NoGo stimuli (Seifert et al., 2003). Interestingly, the NGA has proven clinically useful as it shows a predictive value for medication response in schizophrenia, facilitating treatment decision. A good initial NGA corresponded with a more favourable response to typical antipsychotic medication, whereas a low initial NGA predicted a better response to atypical antipsychotics (Ehlis, 2008). So this parameter might have clinically highly relevant implications which warrant

following up patterns of impairment and interactions with additional risk factors such as genotype of catecholaminergic genes.

1.4.1.3 Genetic Modulation of Response Inhibition

COMT A study by Fallgatter et al. (2009) on adult ADHD observed that subjects with Val/Val genotype had smaller NGA values irrespective of diagnosis (ADHD vs. controls), but patients per se did not differ from controls in NGA. Upon closer inspection of an interaction of diagnosis and COMT, the genotype effect was limited to the patient group with better NGA for Met/Met carriers, while COMT did not play a role for healthy controls. Both centroids were located more anteriorly for ADHD patients and homozygous Val carriers, however in the ADHD group, only Go centroids were located more anteriorly for Val/Val. Surprisingly, testing more subjects and re-analysing the data only confirmed more anterior centres for the positive brain electric field for NoGo and patients, respectively. None of the interactions or the effects involving COMT genotype could be replicated. The authors could not identify any sample characteristics differing between the preliminary and the final sample (Fallgatter et al., 2009).

In a group of schizophrenic patients examined by Ehlis et al. (2007), Met/Met carriers showed increased NoGo amplitudes and NGA values compared to Val/Met, while performance outcome was the same for all genotype groups. There was a clear dosage effect for the disadvantageous Val allele, as the small Val/Val group - included for exploratory analyses - showed a further decrease in NGA and NoGo-P3 amplitude compared to Val/Met. For amplitude and latency comparisons, the P300 peaks at Cz (NoGo) and Pz (Go) were used. Differences between genotype groups were found exclusively in the NoGo condition, making dysfunctions during the inhibition process the basis for NGA differences. Only high doses of the favourable Met allele seemingly permitted for the formation of a stable NoGo potential (Ehlis et al., 2007). The influence of COMT genotype on prefrontal functioning follows an inverted U-Shape, where for healthy individuals the heterozygous (Val/Met) genotype is at the apex of the curve and thus has

optimal prefrontal catecholaminergic metabolization for a range of cognitive tasks. The extent of the genotype influence however depends hugely on baseline functioning. So while in healthy controls the added benefit of the Met allele might be limited, it may elevate prefrontal catecholamine levels of psychiatric populations with known catecholaminergic pathology into the lower end of the normal spectrum. Healthy Val homozygotes on the other hand show performance impairments, which can be remedied by amphetamine administration (Mattay et al., 2003).

DAT According to Loo et al. (2003) performance in a vigilance task (CPT) was better for carriers of at least one 9R allele compared to 10/10 carriers regardless of ADHD status in a sample of children. Furthermore, the authors reported more errors of commission for 10R carriers, indicating deficient response control on a behavioural level. Among ADHD adolescents, the 10/10 group displayed higher activity related to inhibition in left striatum, right dorsal premotor cortex and bilaterally in the temporo-parietal junction in a response inhibition task despite identical behavioural performance (Bedard et al., 2010), which suggests they were able to compensate potential underlying deficits through an increase in effort, or rather: they had to activate more strongly to keep up with the non-risk genotype group. Dresler et al. (2010) confirmed lower NGA values in adult ADHD patients to be tied to the 9R allele, with no genotype effect emerging in healthy controls (Dresler et al., 2010). However seeing that the risk genotype switches from 10R in cADHD to 9R in adult ADHD, this could also be the case for the relationship with this electrophysiological marker of inhibitory functioning. Previous studies looking into the relationship between the DAT VTNR and P300 elicited in in a conflict processing or an auditory oddball task (Tsai et al., 2003, Han et al., 2010) did report no association between genotype and event-related potential.

LPHN3 A pilot study by Fallgatter et al. (in press) classified subjects into a high- and a low-risk group according to a haplotype comprising four SNPs

(rs2305339 - rs734644 - rs1397547 - rs1397548; risk haplotype: A-G-C-C). ADHD subjects carrying two copies risk haplotype showed smaller NGA due to a more anterior Go centroid. Behaviourally, these individuals committed more errors of inattention (miss), but no differences in false alarms or reaction times emerged.

1.4.2 Working Memory

Working memory describes the ability to temporarily hold information online and manipulate it for later use in the absence of external cues (Baddeley, 1992, Goldman-Rakic, 1996). This makes working memory a prerequisite for almost any kind of cognitive operation, whether it is to discriminate between response inhibition and executions cues, or adjusting current behaviour for the attainment of a future goal.

Baddeley & Hitch (1974) proposed one of the most influential models of working memory to date (Baddeley and Hitch, 1974). According to this model, working memory comprises separate storage systems with severely limited capacity depending on the modality of the stimulus to be encoded. Speech-based information is stored by means of circulation in the so-called phonological loop, thus keeping it active. Visual information is transferred to a visuo-spatial sketchpad, where it also can be manipulated. The integration of different modalities and orchestration of working memory operations is provided by a central executive. This central executive in turn has its own short-term storage, where information can be combined. In 2000, the authors introduced the episodic buffer as the central executive's storage component (Baddeley, 2000). Both contents from long-term memory as well as information from phonological loop and visuo-spatial sketchpad can be downloaded into this store in order to be manipulated and updated, making the episodic buffer a temporary interface between the working memory slave systems.

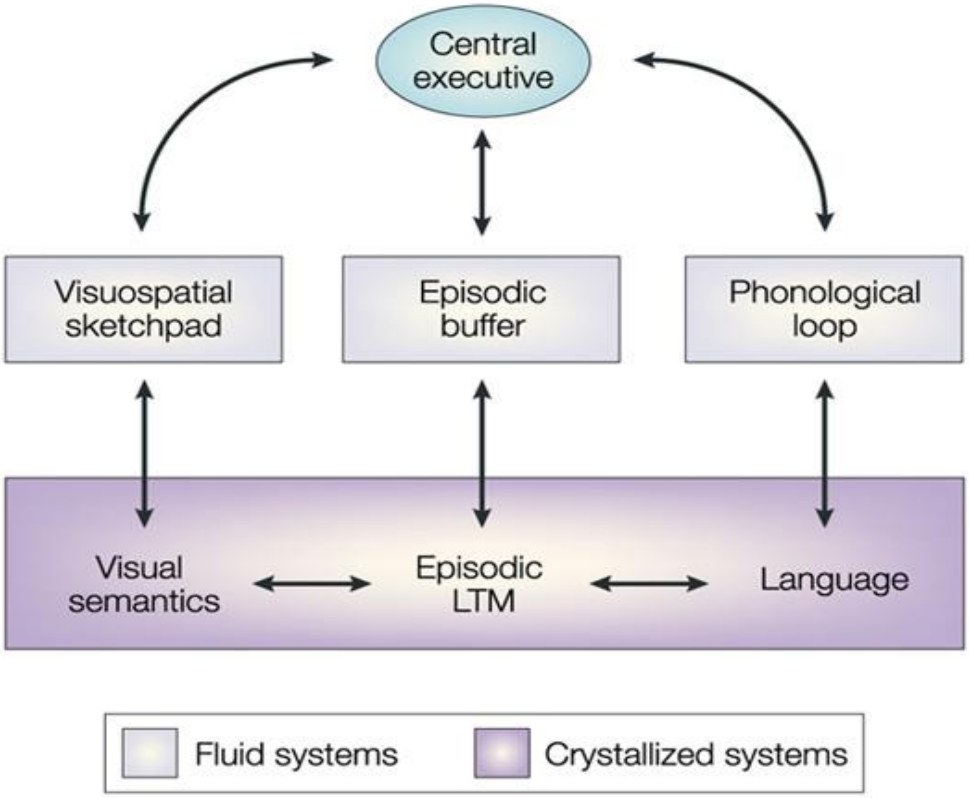

Figure 2: Modified model of working memory (Baddeley, 2000)

Both tonic and phasic DA levels in striatum and PFC are involved specific aspects of working memory. Hazy et al. (2006) proposed a computational model according to which phasic striatal DA release mediates the updating of working memory upon presentation of new material, and tonic DA levels in the PFC are crucial for the maintenance of information within the network e.g. holding information on-line during delay periods of a task [(Hazy et al., 2006), see also (Bilder et al., 2004)]. The n-back task taps into verbal and spatial working memory processes (Meegan et al., 2004) and activates a working memory network comprising dorsolateral (DLPFC) and ventrolateral PFC (VLPFC) dorsal cingulate, lateral premotor cortex, medial premotor cortex, PFC, frontal poles and medial and lateral posterior parietal cortex (Owen et al., 2005).

1.4.2.1 Behavioural Correlates of Working Memory

Working memory performance is a primary deficit in ADHD (Martinussen et al., 2005; Willcutt et al., 2005), and unaffected siblings are impaired on an intermediate level

(Bidwell et al, 2007), it is heritable [43-49 %; (Ando et al., 2001)] and can be translated to quantitative measures. Different aspects of working memory have been found to be compromised in ADHD on a behavioural level (Martinussen et al., 2005, Keage et al., 2008) and in terms of underlying electrophysiological correlates (Barry et al., 2003; Keage et al., 2008). ADHD children might not have a generalized impairment in verbal or spatial working memory, but instead have difficulties pertaining to functions of the central executive that becomes especially relevant when faced with more complex tasks e.g. requiring switching between modalities (Karatekin, 2004). Behavioural abnormalities reflected by errors and reaction times during working memory operations can successfully be countered with psychostimulants (Kempton et al., 1999, Mehta et al., 2004). Importantly, working memory and response inhibition do not seem to represent aspects of one integrated phenotype, but it has been argued that inhibitory problems might be a consequence of working memory impairments (Schecklmann et al., 2012), although working memory has been found to be the link between abnormal performance in the Stop Signal Task and ADHD (Alderson et al., 2010). Working memory relies heavily on the integrity and the interplay of fronto-striatal regions as well as the cerebellum (Bunge et al., 2001, Gottwald et al., 2003, Kondo et al., 2004, Lewis et al., 2004).

DA and NE are potent modulators of working memory functioning (Arnsten, 2001, Goldman-Rakic et al., 2004), and they are the main agents of neuronal activity in frontal and striatal regions subserving working memory. Conversely, structural and functional abnormalities in those transmitter systems as well as fronto-striato-cerebellar pathways are intricately implicated in the aetiopathogenesis of ADHD (Seidman et al., 2005). The relationship between DA levels and prefrontally based functions follows an inverted U-shape, making those functions susceptible to both too high and too low doses of the transmitter (Arnsten, 1997, Vijayraghavan et al., 2007). Hence, working memory impairments in ADHD may be explained in terms of catecholaminergic dysregulation of in fronto-striato-cerebellar networks (Levy and Swanson, 2001). Improvement of working memory performance can be achieved via the administration of drugs with DA-agonistic effects (Mehta et al., 2004). As a

consequence, genes involved in Dopaminergic and noradrenergic neurotransmission in those areas are likely to exert an influence on performance and neurophysiological correlates in a working memory task. A recent observation of additive effects of COMT and DAT for working memory underlines the importance of these regions' interaction (Caldu et al., 2007). Importantly, no individual effects of COMT or DAT on performance or brain activation could be found

1.4.2.2 EEG correlates of Working Memory

In venturing to explain the above-mentioned error-proneness of ADHD patients in working memory tasks, EEG is an excellent tool, since its high temporal resolution allows researchers to identify the stage at which differences first arise. It allows for the attributions of performance deficits indicated by errors to either early more sensory processes involved in stimulus perception and discrimination, or late more cognitive processes such as allocation of processing capacity or attention. To this end, early and late ERP components during target- and non-target trials were used for analysis. In response to non-target stimuli indicating a need for updating processes, we studied N100, P150, N300 and P450. Target trials were examined for differences in P100 and P300 amplitudes and latencies.

1.4.2.2.1 Non-Target related ERP components in ADHD

The frontally maximal N100 indicates early stimulus discrimination (Vogel and Luck, 2000). The fronto-central P150 is a sign of fronto-central networks preparing for impending change (Clark et al., 1998). The N300 peak at frontal and central sites is evoked when retrieving content from long-term storage (Friedman, 1990). The P450 describes a specific non-target evoked centro-parietal P300 response, observed when transferring information to the respective working memory store and thus updating working memory content (Clark et al., 1998). In addition to that function, it seems to be involved in the process of comparing the new stimulus with the preceding one (Watter et al., 2001).

Previous research looking into working memory updating related ERPs reports delayed frontal N100 and P150 responses in ADHD samples compared to controls when a stimulus necessitates updating of working memory content. Those early components can be indicators of impairment on a more basic perceptual level. Longer N300 frontal latencies (Karayanidis et al., 2000) and decreased amplitudes over central regions were present in ADHD (Sartory et al., 2002). Furthermore, ADHD patients exhibit prolonged P450 latencies (Strandburg et al., 1996) and they did increase P450 from frequent to rare stimuli to a greater degree than healthy controls (Karayanidis et al., 2000).

Keage and colleagues (2008) were the first to comprehensively assess electrophysiological responses of ADHD patients in non-target trials requiring only updating of working memory without demands for a motor response. Without medication, numerous differences between combined type ADHD children and adolescents and matched controls emerged. Central P450 amplitude attenuation was observed in unmedicated ADHD patients of both the young and adolescent age group in comparison with healthy controls, and this was completely remedied by psychostimulants. This marker only remained significantly impaired in the inattentive sub-sample, which indicated different underlying deficits in this particular symptom group. As the only direct effect of medication on EEG parameters within the ADHD sample, in the children group medication effected a depression of P450 amplitudes. Surprisingly, no other direct influences of psychostimulants on ERPs were observed despite previous reports of normalizing effects (e.g. Seifert et al., 2003; Sunohara et al., 1999). The most robust finding was the amplitude attenuation of the P450 component, which was present across age groups and ADHD subtypes. This could speak to those children being less well able to integrate newly relevant information into the working memory image. Interestingly, no differences between the inattentive and the combined subtype were observed in terms of electrophysiological or behavioural parameters, which the authors interpreted as supporting evidence for the two subtypes lying on the same continuum instead of constituting two separate clinical entities.

Behaviourally, combined type ADHD came with a greater number of errors of commission and omission in children and additionally higher RTs and RTV in adolescents. Stimulants only influenced behaviour in the combined subgroup across the age spectrum, ameliorating RTV and omission errors, whereas it had no effect on inattentive ADHD. The lack of deviation from normal controls with regard to N100 and P150 as correlates of early stimulus processing is in line with a majority of the literature [e.g. (Sergeant and van der Meere, 1990, Lopez et al., 2006).

Taking into account potential developmental effects, arousal may be affected differently across the lifespan according to observations regarding hyper-arousal in cADHD and hypo-arousal after entering adolescence (Satterfield et al., 1984). This could be related to vigilance regulation, which has been found to be compromised in ADHD. Specifically the stability of vigilance states over time is affected (Sander et al., 2010) in all subtypes, which is in line with the variability of responses discussed previously.

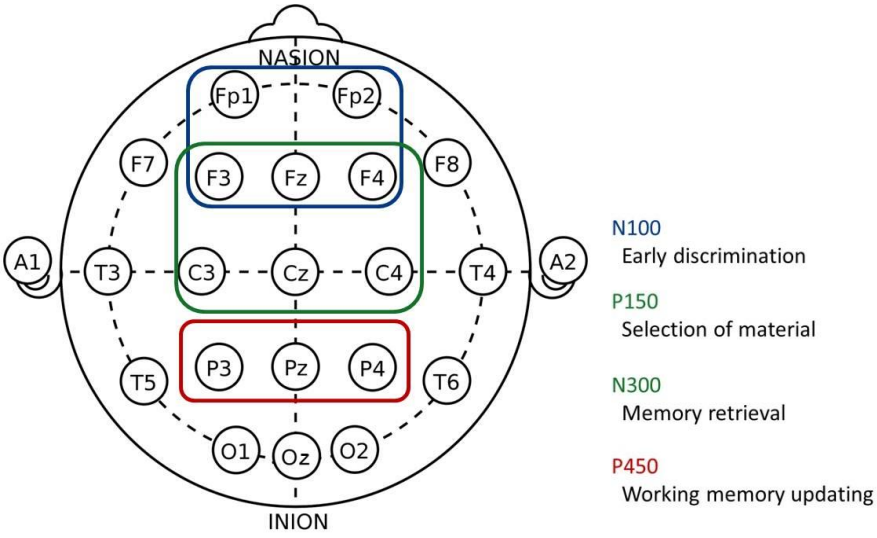

Figure 3: Scalp distribution of non-target components during working memory task

1.4.2.2.2 Target ERP components in ADHD

To mirror the examination of both early and late processes performed with non-target trials, we analysed the more perceptually based visual P100 at occipital sites along with the previously described parietal target P300. Abnormalities in early

ERP components pertaining to the integrity of the visual system in ADHD have been observed in a variety of tasks. As a correlate of early visual processing, Kemner and colleagues (1996) reported that while the strength of P100 responses to novel stimuli was intact in ADHD, standard and deviant stimuli elicit lower P100 amplitudes in ADHD compared to controls (Kemner et al., 1996). Altered P100 emerged for ADHD subjects in a variety of tasks, although the direction is not clear [e.g. reduced amplitude in visual search (Woestenburg et al., 1992), increased amplitudes in stimulus-response compatibility task (Yong-Liang et al., 2000)]. Nazari et al. (2010) observed lower amplitudes of visual P100 specifically in NoGo trials of a cued CPT and longer latencies in both Go and NoGo for ADHD compared to controls. Investigating behavioural implications of P100 timing and strength, correlational analyses showed that in the total sample, P100 latency was positively correlated with errors of omission and commission. Further significant relationships with performance parameters were limited to healthy controls, where positive correlations of P100 amplitude with RTV and errors of commission as well as a negative relationship with number of hits were reported. In controls, higher amplitudes were associated with a greater error-proneness, and a decrease in P100 strength was linked to better attentional focusing and less errors. These two factors were however uncoupled in the ADHD group, implying that ADHD patients don't benefit from lower P100 amplitudes in terms of performance the way healthy individuals do (Nazari et al., 2010). Regarding the timing of this early visual response, delayed occipital P100 (Yong- Liang et al., 2000) along with later N200 have been found in a cued CPT (Nazari et al., 2010). As a putative mechanism behind these deficits an impaired capacity for focusing attention in ADHD has been postulated.

Gomarus et al. (2009) reported P300 amplitude to be inversely related to working memory demands in healthy volunteers, indicating that an increase in load and thus difficulty is accompanied by a decrease in amplitude (Gomarus et al., 2009). Kok and colleagues (2001) provided an overview of the literature and discussed various explanations for this relationship with regard to working

memory operations (Kok, 2001). This modulation by load was absent in patients suffering from schizophrenia, another psychiatric disorder prominently featuring a dysregulation of Dopaminergic neurotransmission and fronto-striatal pathways (Gaspar et al., 2011). Overall, studies frequently report lower P300 amplitudes in ADHD (see Barry et al., 2003 for a review).

Sunohara et al. (1999) investigated working memory components in a sample of ADHD children aged 10-12 and matched controls. ADHD children performed the task multiple times under different MPH doses (placebo – low - high) to allow for direct comparisons of pharmacological effects within subjects. The paradigm used for this study was a modified CPT (double task) that basically functions like a 1-back task, where repeated letters are the signal for a motor response. During successful response execution trials, controls had longer N2 and shorter P3 latencies than unmedicated ADHD patients, whereas those parameters were normalized in the medicated patient group. Interestingly, latencies of N2 and P3 were correlated in unmedicated patients, but this relationship lost strength with increased MPH dosage and was completely absent in optimally medicated ADHD children and healthy controls. No amplitude effects were evident on P2, N2 or P3.

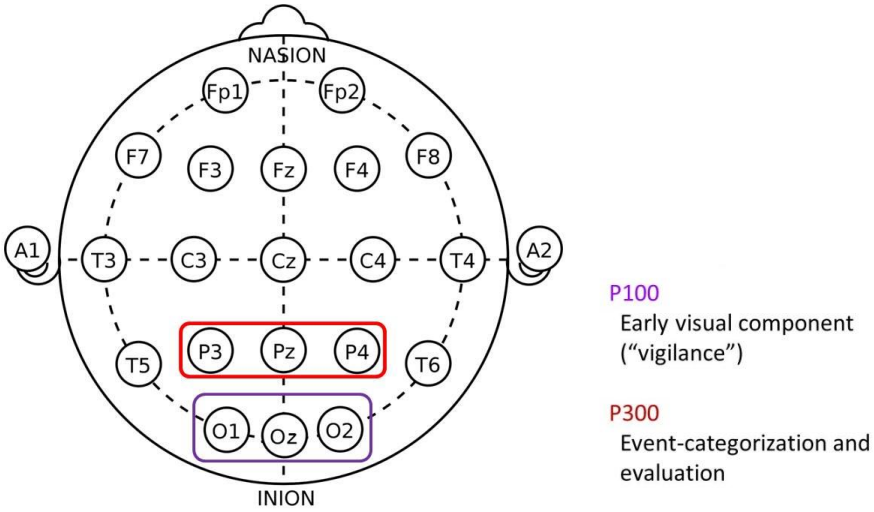

Figure 4: Scalp distribution of target components during working memory task

1.4.2.3 Genetic Modulation of Working Memory

COMT Taking into account the anatomical distribution of COMT, this gene is expected to exert a bigger influence on tonic aspects of working memory and the maintenance of information (Bilder et al. 2004). Behaviourally, COMT genotype did not modulate performance on an n-back task with varying load level in healthy adults (Blanchard et al., 2011). This was also observed in a simple n-back task; however in this case COMT in combination with DAT did affect performance and brain activation (Caldu et al., 2007). The gene seems to predominantly have an effect on more complex operations that require both storage and manipulation of working memory content in a study comparing different working memory tasks (Bruder et al., 2005). Comparing schizophrenia patients and their unaffected siblings with matched controls, homozygous Met carriers' n-back performance was superior to that of individuals with the Val allele. This effect was independent of load or diagnostic group, and siblings showed an intermediate degree of impairment (Goldberg et al., 2003). COMT genotype furthermore predicts working memory related brain activation (Egan et al., 2001), as increasing number of Met alleles corresponding to attenuated task related activity during the n-back in DLPFC. In healthy children and adolescents, the met allele boosted working memory performance and related activity in right inferior frontal gyrus and intraparietal sulcus (Dumontheil et al. 2011). The Met/Met genotype showed more focused activity when engaging working memory networks indicated more efficient resource allocation (Bertolino et al., 2006). Being homozygous for the met allele meant lower working memory-related activity and connectivity within the DLPFC and higher activity and connectivity in the VLPFC compared to the other genotype groups (Sambataro et al., 2009). Finally, Yue et al. (2009) directly assessed the functional relationship between COMT genotype and event-related potentials in a 3-back task in healthy adults. Homozygous Val-carriers had better behavioural performance, higher P300 amplitudes and shorter latencies then subjects carrying at least one Met allele. The authors interpreted this finding a suggestive of superior updating ability and concurrent deficient maintenance of working memory content associated with the Val allele. Heterozygous genotypes corresponded to worst performance as

well as weakest and most delayed P300 responses. Behavioural outcome was furthermore correlated with P300 amplitude at parietal sites (Yue et al., 2009). The beneficial effect of the met allele on working memory manifests around the age of 10 (Dumontheil et al., 2011), which suggests that in the present study most subjects should already show a genotype effect for COMT.

DAT Normally (i.e. in healthy children), when dealing with high working memory loads, performance and fronto-striatal pathways activation are superior with 9R allele compared to 10/10, whereas DAT genotype does not play a role for low load tasks (Stollstorff et al., 2010). In contrast to this, DAT and COMT genotypes – separately or combined - had no behavioural effects on performance in a spatial n-back even with high loads (Blanchard et al., 2011). One study performed by Karama et al. (2008) investigating working memory in childhood ADHD with regard to DAT genotype found the opposite pattern, namely an advantage of being 10/10 (Karama et al., 2008). It has to be considered thought that the paradigms used in this study taps into other functions besides working memory and might thus be influenced in a different way by Dopaminergic genes. However, it fit with functional findings that brain activity in the working memory network is more focused in homozygous 10R carriers of the DAT variable number tandem repeat (Bertolino et al., 2006). In adults, using the same set-up and load condition no DAT influence on working memory have been observed (Bertolino et al., 2006, Bertolino et al., 2009), but maturation of the brain might mean those are no longer equally demanding as they are for children. Thus, the importance of DAT for working memory performance (until 2-back) should decrease with age. In healthy adult volunteers (18-22, males and females) there were additive effects of COMT and DAT on brain functioning during working memory task (fMRI during n-back), where having the Val allele (COMT) plus the 9R allele (DAT) was associated with higher brain activation despite equal performance. Individually, the 10R carriers had faster RTs and more false alarms and the Val allele corresponded to more false alarms and perseverative errors (Caldu et al., 2007).

1.4.3 Sensory Gating

Sensory gating describes the pre-attentional filtering of incoming sensory input to prevent an overload of higher cortical areas due to concurring or excessive stimulation. If presented with two stimuli in short temporal succession, processing of the second stimulus is blocked to ensure adequate processing of the initial stimulus. Especially the acoustically evoked P50 as a very early component appears to be beyond psychological control mechanisms, as increasing the relevancy of the second stimulus did not alter the suppression of the second P50 wave (Jerger et al., 1992). It is largely independent of pre-stimulus alertness and gender (Cardenas et al., 1997, Lijffijt et al., 2009b). P50 amplitudes vary with stimulus intensity, however anything short of startle-evoking intensities do not influence the gating ratio (Griffith et al., 1995). This makes it a relatively pure indictor of the fundamental neuronal rather than higher order psychological foundations of information processing and thus speaks for the suitability of this parameter as an endophenotype in its own right. Still, the pre-attentional nature of the P50 has been called into question, as without further instruction wakeful alertness as indicated by pre-stimulus beta-power did not influence gating (Cardenas et al., 1997), whereas explicit directions to attend to the first or the second stimulus could shape the amplitudes and the ratio of those components in a sample of schizophrenic patients (Yee et al., 2010). Furthermore, special physiological states such as pain or (Johnson and Adler, 1993) or stress (Yee and White, 2001) modulate sensory gating. However, these constitute extreme situations with high evolutionary significance, putting the whole organism in a state of alert. In this context it makes sense to lower the bar for stimuli to be passed on to higher cortical areas, as they warrant heightened scrutiny for potential significance relating to the source of the stress or pain, respectively. Using a variant of the CPT with healthy participants, Lijfijt et al. (2009) described that P50 suppression was negatively related to errors of commission, and stronger gating resulted in longer reaction times. Good N100 gating also contributed to performance. The efficiency of this control mechanism proved to be diminished in a range of psychiatric conditions such as bipolar disorder, schizophrenia, post-traumatic stress disorder or panic disorder (Ghisolfi et

al., 2006, Karl et al., 2006, Patterson et al., 2008, Lijffijt et al., 2009c). A deficit in this domain would consequently lead to the flooding of higher cortical areas with irrelevant information, thus potentially contributing to the ADHD associated distractibility and disorganisation.

Olincy and colleagues (2000) were the first to compare a sample of 16 unmedicated adult ADHD patients to a matched group of healthy controls in terms of P50 sensory gating (Olincy et al., 2000). Neither conditioning or testing amplitudes nor the P50 ratio could distinguish between the two groups, however the P50 difference score was greater for controls indicating better sensory gating at p = .050. None of the reported markers were correlated with ADHD symptom severity. A lack of suppression was observed in 25 % of patients, but this was not statistically different from the 10% of non-suppression seen in healthy probands. Feifel and colleagues (2009) confirmed intact gating in a prepulse inhibition paradigm, again in an adult ADHD population (Feifel et al., 2009). In contrast to this, ADHD children and adolescents had compromised P50 suppression compared to a matched control sample (Durukan et al., 2011). The observed differences in P50 gating ratios were attributable to altered testing responses, as those were found to be both delayed and of higher in amplitude in ADHD children, whereas reactions to conditioning stimuli were identical. Administering MPH to the same group before a second session led to a decrease in amplitude and latency of testing responses, furthermore conditioning responses were also speeded up. Unfortunately the authors did not report on comparisons between the medicated ADHD sample and controls, but by visual inspection all parameters seem to have been returned to normal levels. Conversely, prepulse inhibition in a young sample with ADHD was impaired and could again be remedied by stimulant administration (Hawk et al., 2003). A possible explanation for the discrepant observations in young vs. adult populations could be that sensory gating improves with age (Marshall et al., 2004, Brinkman and Stauder, 2007), suggesting a development effect especially in ADHD patients who are characterised by a delay in cortical maturation (Shaw et al., 2007).

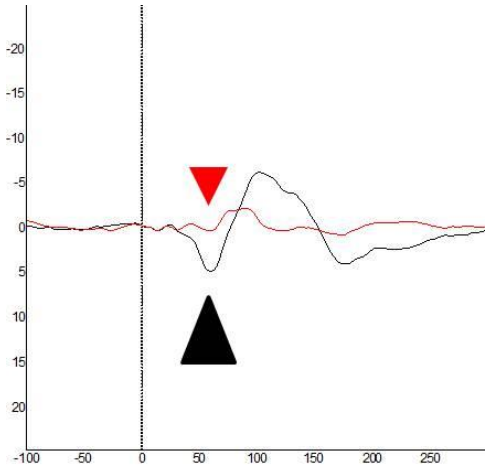

Figure 5: Sensory gating mechanism. The black triangle represents the P50 response to S1, the red triangle represents the weaker P50 response to S2 representing successful suppression.

Regarding the proposed mechanism of P50 deficit in ADHD, the prime suspect is an altered catecholamine balance. Catecholamines play an important role for sensory gating, and Adler et al., (1988) were able to demonstrate that the administration of amphetamine – a drug that enhances dopaminergic neurotransmission primarily in striatum and reward-related areas - interfered with suppression of the second stimulus, and this could be countered with the DA antagonist and antipsychotic haloperidol. Furthermore, amphetamines effected a P50 response to the conditioning stimulus that was decreased in amplitude and latency, which again could be returned to normal with haloperidol (Adler et al., 1988). According to this line of evidence, high DA levels seem to actually be counterproductive with respect to the filtering of surplus information.

Genetic Modulation of Sensory Gating

COMT Dopaminergic signalling is essential for intact sensory gating. Prepulse inhibition of the startle reflex is enhanced in homozygous Met carriers and inhibitory power decreasing with increasing number of Val alleles (Roussos et al., 2008, Quednow et al., 2009). Studies on P50 sensory gating in schizophrenia patients found either an advantage for Val/Val genotypes (Lu et al., 2007) or no association of COMT and gating potential (Shaikh et al., 2011), while in healthy controls there was a consistent lack of association. Majic and colleagues (2011) replicated the independence of P50 gating from COMT genotype in a large sample

of healthy adults. Both P50 and P100 capture aspects of sensory gating, but P50 is less dependent on psychological variables and reflects comparatively pure pre-attentional processes. Interestingly, while P50 suppression was not modulated by the Val158Met polymorphism, gating ratios of the N100 were found to be stronger in Val/Val carriers (Majic et al., 2011). In light of the fact that stronger gating is usually indicative of better cognitive functioning, and subjects with at least one Met allele have an advantage in various cognitive operations, this result is surprising.

DAT To our best knowledge, Millar and colleagues (2011) were the first to investigate the modulation of sensory gating by DAT genotype in healthy volunteers (18-40 years). They found the carrying of at least one 9R allele - associated with lower gene expression - to be related to better filtering abilities. Only in this genotype group could gating be further enhanced with nicotine (Millar et al., 2011). Taken together with the fact that nicotinic acetylcholine (nACh) neurotransmission interacts with expression and function of the DAT (Li et al., 2004, Parish et al., 2005), and activation of presynaptic nACh receptors supports striatal DA release (Grady et al., 2002), the importance of a functional variant within the DAT gene for sensory gating needs to be further explored.

1.4.4 Response Time Variability

Response time variability (RTV) expresses the degree to which reactions vary in their speed within one person across tasks. It is common for healthy individuals to develop a characteristic and stable response speed as reflected by mean reaction time, with the standard deviation as an indicator of RTV becoming smaller. Support for this comes e.g. from Rommelse et al. (2008), who could show that response time variability decreases with age in healthy controls (Ø 11.6 ± 3.2 years 5-19), and reaction times more or less settle to an individual level with comparatively little variance (Rommelse et al., 2008d). However, this can of course be disrupted by factors like a transient change in the state of alertness or effects of various kinds of drugs.

Instead of a linear decline of attention and focus over time, ADHD is more characterized by patients' inability to adequately regulate their energetic state, which provokes frequent lapses in attention (Sergeant, 2005). One possible explanation is intrusions of the Default Mode Network (DMN) associated with rest and interfering with task-related activation (Sonuga-Barke and Castellanos, 2007). The term DMN describes a distributed set of functionally strongly connected brain structures comprising the ventral medial PFC, posterior cingulate cortex and precuneus, which is active at rest and attenuates its activity when the brain shifts into task mode (Raichle et al., 2001). The degree of deactivation increases with task difficulty (Singh and Fawcett, 2008) and is correlated with performance (Weissman et al., 2006, Li et al., 2007). Although results are still inconclusive with regard to the exact nature of the disturbance in ADHD, various studies found compromised functional connectivity in ADHD within the DMN, as well as between DMN and other regions (Castellanos et al., 2008, Tian et al., 2008). Peterson and colleagues demonstrated that the excess DMN activity at the expense of speed and accuracy observed in ADHD can be partly remedied with MPH (Peterson et al., 2009). One compelling explanation for ADHD-related deficits comes from the default mode interference hypothesis by Sonuga-Barke and Castellanos (2007), which postulates that the brain fails to adequately attenuate the task-negative DMN when faced with a cognitive task, and this rest-associated activity then interferes with performance by means of periodic lapses of attention (Sonuga-Barke and Castellanos, 2007). ADHD patients have consistently been shown to display slower reaction times along with a higher variability [e.g. during CPT (Borger et al., 1999, Heinzel et al., 2012); during basic motor task (Rommelse et al., 2008d). Additionally, a greater increase of variability along with a faster deterioration of performance (on-task behaviour, omission errors did not increase as the task went on, even though that type of error was more frequent in ADHD children) over time could be observed in the ADHD groups as compared to controls (Borger et al., 1999). This variability was shown to be related to most symptoms of ADHD (Epstein et al., 2003) and highly heritable (Kuntsi et al., 2006). Furthermore, non-affected siblings score between that of controls and their affected siblings (Uebel et al., 2010), speaking to the suitability of RTV as an endophenotype

for ADHD. RTV can be decreased by stimulant administration, suggesting the catecholaminergic regulation of intra-individual variability (Nandam et al., 2011). Interestingly, this effect is independent of stimulant effects on performance (SSRT).

Genetic Modulation of RTV

COMT In healthy individuals, RTV in a CPT proves to be largely unaffected by COMT or DAT genotype, either singly or in combination (Bender et al., 2012, Heinzel et al., 2012). Heinzel and colleagues (2012) also included an ADHD group, which despite having a higher mean RTV mirrored the genotype-independence of the variability of reaction times in controls. Contrasting these negative results, Stefanis et al. (2005) found the met allele to be favourable for the stability of RTs in a large of young male adults (Stefanis et al., 2005).

DAT Higher RTV has been found to be related to Dopaminergic system genes such as DRD4 (Kebir and Joober, 2011). Looking at comparisons between ADHD and healthy controls, high-risk (10/10) ADHD children had more variable RTs than controls (Bellgrove et al., 2005), whereas low risk ADHD patients with at least one compensatory 9R allele did not differ from controls. Within an ADHD sample, being homozygous for the10R corresponds to having even more variable RTs than those patients with at least one 9R allele (Loo et al., 2003). In contrast to these reports, in a sample of Korean boys with ADHD, the DAT VNTR did not influence reaction times or RTV (Oh et al., 2003). Finally, widening the scope to additional functional variants within the DAT gene, several SNPs in the DAT gene were implicated in RTV, however the two included VNTRs came up negative (Cummins et al., 2012).

1.4.5 Outlook: Developmental course of the candidate endophenotypes

A few lines of evidence led to our including an exploratory catamnestic part re-examining a small subset of participants after approximately three years to take a closer look at developmental effects on response inhibition, working memory and response time variability.

Since developmental lag rather than a fundamental deviation from normal developmental templates has emerged as the leading explanation for ADHD-related deficits (Kinsbourne, 1973), and normal cortical development is prominently altered in patients, it is vital to monitor changes in ADHD-associated behavioural and electrophysiological deficits related to maturational processes as patients grow up. Shaw et al. (2007) found ADHD specific abnormalities in the speed of cortical maturation, while the normal temporal sequence of regions reaching full maturity was preserved. The motor cortex reached peak cortical thickness earlier in ADHD, whereas in those children prefrontal areas necessary for regulating motor behaviour lagged approximately 5 years behind normal controls. Stimulant medication exerted a normalising effect on ADHD-related deviant cortical thickness (Shaw et al., 2009a). On average, cortical thickness was reduced in prefrontal and temporal areas in ADHD compared to controls, and worse clinical outcome was linked to thinner cortices in those two regions. Longitudinally, ADHD children with better clinical outcomes also showed a normalisation of cortical thickness in the parietal but not the motor cortex by late adolescence (Shaw et al., 2006). Typically developing children on average attained a higher mean prefrontal thickness before entering the thinning phase, and they furthermore reached that point of peak thickness faster than ADHD children (Shaw et al., 2007). The subsequent process of cortical thinning obliterating surplus connections was entered into earlier by healthy controls, this this group reached the fully mature state of the cortex at a younger age than their ADHD peers. Unmedicated ADHD patients showed an abnormally slow rate of cortical thinning (Shaw et al., 2011), and thinner prefrontal cortices in ADHD were furthermore associated with more severe clinical outcomes (Shaw et al., 2006). Support for the dimensional nature of ADHD comes from findings that this slowed cortical thinning can also be observed in normally developing children depending on their level of hyperactive traits (Shaw et al., 2011). Since most ADHD patients receive stimulant medication over long periods of time, Shaw and colleagues investigated the influence of those substances on the developing cortex, and reported excessive thinning in unmedicated ADHD children in comparison to controls of the same age, which was slowed to normal levels with medication (Shaw et al., 2009). This contradictory

finding might be due to the separate analysis of medicated and unmedicated ADHD groups, which were not distinguished in the previous study. The COMT gene has also been implicated in this process of cortical shaping during development. The number of Met alleles was positively related to cortical thickness in the right inferior frontal cortex and temporal areas, the former of which is prominently associated with response inhibition (Shaw et al., 2009b).

Behavioural parameters Attentional functions and response time variability are time-dependent to varying degrees, with differences between ADHD and controls fluctuating during the transition from childhood to adolescence (Drechsler et al., 2005). Biederman and Faraone (2009) postulated that cognitive and executive functioning (e.g. working memory, flexibility) was largely independent of the clinical outcome of ADHD symptoms, as both patients in remission and with a persistent ADHD performed worse than controls (Biederman et al., 2009). A meta-analytic review of studies pertaining to response inhibition and memory impairments in adult ADHD patients confirmed the persistent nature of executive dysfunction (Hervey et al., 2004). Although ADHD symptoms, particularly of the hyperactive domain, tend to decline with age (Faraone et al., 2006), inhibitory deficits associated with childhood ADHD are also present in adult patients (Boonstra et al., 2010). In normally developing individuals, errors tend to decrease and reaction times speed up with age, while ADHD deficits remained stable. In fact, performance of ADHD children was comparable to that of younger controls, supporting the developmental lag hypothesis (Doehnert et al., 2010). Reaction times stabilise at an individual level in adulthood, accordingly RTV is diminishes with age (Rommelse et al., 2008). While a recent meta-analyses comparing younger and older adults report an age-related increase in RTV (Dykiert et al., 2012), a study examining children and adolescents found a pronounced linear decrease in RTV with age (Tamnes et al., 2012).

Response inhibition Electrophysiologically, Doehnert et al., (2010) observed reduced cue P3a and P3b in the ADHD group; this along with a persistently reduced NoGo-P300 was a largely stable deficit over the 2.5 years covered. In sum, these

authors' findings are mixed, partially supporting the developmental lag model and partially being more compatible with a deviation from normal development. There remains the possibility of the aforementioned lag being too great to be caught up within the critical period, thus making it permanent. Ultimately, Doehnert et al. (2012) followed a group of 11 ADHD patients (Ø 10.9 years) diagnosed in childhood over the course of 11 years and assessed them at four time points (baseline, T2 = 1.1 years, T3 = 2.4 years and T4 = 11 years) with a CPT / Go-NoGo paradigm, looking both at preparatory and inhibition-related processes. The absence of group by time interactions suggest that none of the parameters deviated from the typical developmental trajectory, the direction of change over time was the same for ADHD and controls. Behavioural parameters (RT, RTV, errors of omission) and preparatory potentials (Contingent Negative Variation CNV, Cue P300) decreased over time, with ADHD patients having higher RTV and lower Hit rate and magnitudes of Cue-P300 and CNV at single measurement points. Interestingly, the CNV was the only marker to be consistently diminished, lending support to its suitability as a stable candidate endophenotype present even in patients no longer meeting full ADHD criteria. NoGo global field power amplitude decreased with age, but was higher in ADHD compared to controls at T3. Early studies looking into developmental changes in event-related potentials specifically to visual language stimuli noted a speeding up of N2 with a minimum in adolescence and P3 with shortest latencies in adulthood (Taylor and Williams, 1988). The adult group in the study by Taylor ranged only from 20 to 29 years, so later potential reversals of changes in timing and strength of the ERPs could not be ruled out. Indeed, for the P300 there seems to be a subsequent increase in latencies throughout adult life, and this latency lengthening with age seems to be a stable phenomenon [see meta-analysis by (Polich, 1996)]. P300 amplitudes are decreased in ADHD, and this attenuation with regard to healthy controls grows stronger with age (Szuromi et al., 2011). In a study employing a large adult age range (20-88 years), amplitude was negatively and latency was positively correlated with age for visual P3a and P3b to target and distractor stimuli (Fjell and Walhovd, 2004). Looking at P3b in more detail, the relationship appears more complex, with amplitudes decreasing from childhood into late adolescence and increasing again in

later life (Stige et al., 2007). Taylor on the other hand pinpointed the turning point at around 11 years of age (Taylor, 1988). In healthy people, better cognitive abilities have been linked to greater P300 amplitudes, indicating a performance augmenting effect of this additional recruitment of resources (Daffner et al., 2006). I the consequence, higher amplitudes in ADHD subjects might be a marker for a successful compensation of underlying deficits. Findings regarding N200 are mixed, depending on the subtype of the component. There is little to no influence of age on visual and auditory MMN, while visual oddball N2b latency is decreased in older subjects. In their review Patel & Assam (2005) concluded that N2b latency increases and amplitude decreases with age throughout adulthood (Patel and Azzam, 2005). Similar to P300, a U-shaped course over the whole lifespan meant that while in a younger sample [7-24 years (Van der Stelt et al., 1998)] latencies decreased with age, the opposite pattern was true for a samples covering the adult lifespan (Amenedo and Diaz, 1998, Falkenstein et al., 2002).

Topographically, while both centroids shift towards frontal areas with age, the NGA as the difference measure of the two remains unaffected (Fallgatter et al., 1999). In adulthood, NGA is a very stable marker with high test-retest-reliability (Fallgatter et al., 2002a). However so far no study has established the age at which NGA first emerges**.** So while we do not expect to find differences in NGA between measurements, the location of both centroids should shift towards more frontal areas in controls and this anteriorization should be weaker in the unmedicated ADHD group. However, depending on the peak age, ADHD children who show low initial NGA might very well improve as the PFC matures, and the distance to healthy individuals might become smaller. ADHD patients should display dampened ERPs owing to a general state of hypo-arousal due to unstable vigilance regulation, and this should be countered by psychostimulant action (Sander et al., 2010). Lower amplitudes particularly on late components are expected to persist across both measurements in the unmedicated ADHD group. Along those lines, N200 and P300 should decrease in amplitude and latency between measurements for healthy controls and remain lower respectively delayed in unmedicated ADHD.

Working memory Approaching the question of developmental effects on working memory on a behavioural level, Lamkbek & Shevlin (2011) conducted a study assessing response inhibition as well as verbal and spatial working memory with the objective to establish whether these were changing independently during normal development. Children and adolescents aged 7 to 16 showed a marked improvement i all three domains with age, which furthermore proved to be linked despite being clearly distinguishable factors (Lambek and Shevlin, 2011). This improvement seems to be attributable to the intensified recruitment of crucial frontal, striatal and parietal areas subserving working memory (Bunge and Wright, 2007). In later life working memory capacities deteriorate, and this process is particularly pronounced for spatial compared to verbal working memory (Myerson et al., 1999). Correspondingly, ERP studies on working memory described an increase in amplitude for early auditory and visual components like P100 (Pelosi and Blumhardt, 1999) and P200 (McEvoy et al., 2001). P300 responses in working memory tasks have been found to decrease in magnitude and slow down in older subjects (McEvoy et al., 2001). This could point to the recruitment of different areas in different stages of life (parietal in early life to frontal in later life). Indeed, young adolescents rely on both hippocampus and PFC, while late adolescence marks the start of a period where hippocampal regions loose importance until in adults they are only additionally employed for highly demanding tasks (Finn et al., 2010). Regarding ADHD specific development, Keage and colleagues (2008) compared children (Ø 10.4 years) and adolescents (Ø 14.9 years) of combined and inattentive subtype with matched controls, and those mean ages are mirrored in the two measurement points of the present study. Both age groups had lower P450 activation (see also Strandburg et al., 1996 for age-independence of P450 attenuation), however ADHD children had dampened and ADHD adolescents had delayed N300 responses. Early potentials arising from perceptual processes were normal in ADHD patients irrespective of age and subtype. N300 and P450 as largely endogenous potentials were altered, indicating difficulties with incorporating new information into working memory storage. So while we expect healthy control children to follow those developmental trajectories, ADHD patients should lag behind

in terms of speeded up and more efficient processing as indicated by shorter latencies and decreasing amplitudes and remain impaired at T2.

Candidate genes Decreasing basal DA levels with age and the PFC becoming more important in most cognitive operations are both already effective during adolescence, thus making this period likely to be marked by changing modulating influence of out candidate genes. Most executive functions are known to be in in the process of maturation well into early adulthood (De Luca et al., 2003). COMT metabolism gains significance with the progressive maturation of the PFC as its main site of action throughout adolescence and early adulthood. Dumontheil and colleagues (2011) reported on behavioural and functional implications of COMT genotype on working memory. The performance advantage associated with carrying a Met allele only set in after the age of 10, and corresponding lower frontal and parietal activation with age compared to homozygous Val carriers. If this is an incremental effect, met carriers should differ from the Val/Val to a greater degree at T2. Age has been found to exacerbate the moderating effects of COMT on cognitive functioning, with the Val allele corresponding to impaired cognitive flexibility and slower responses in a spatial working memory especially in older versus younger adults (Nagel et al., 2008). DAT genotype also gains relevance in adolescence, since DA levels are known to be inversely related to age (Barkley et al., 2006b) and should predominantly benefit striatally mediated functions since DAT is the main modulator of Dopaminergic transmission. This is supported by a study by Bäckmann et al. (2000) showing that cognitive functioning and decline in cognitive abilities with age is mediated by striatal DA metabolism (Backman et al., 2000).

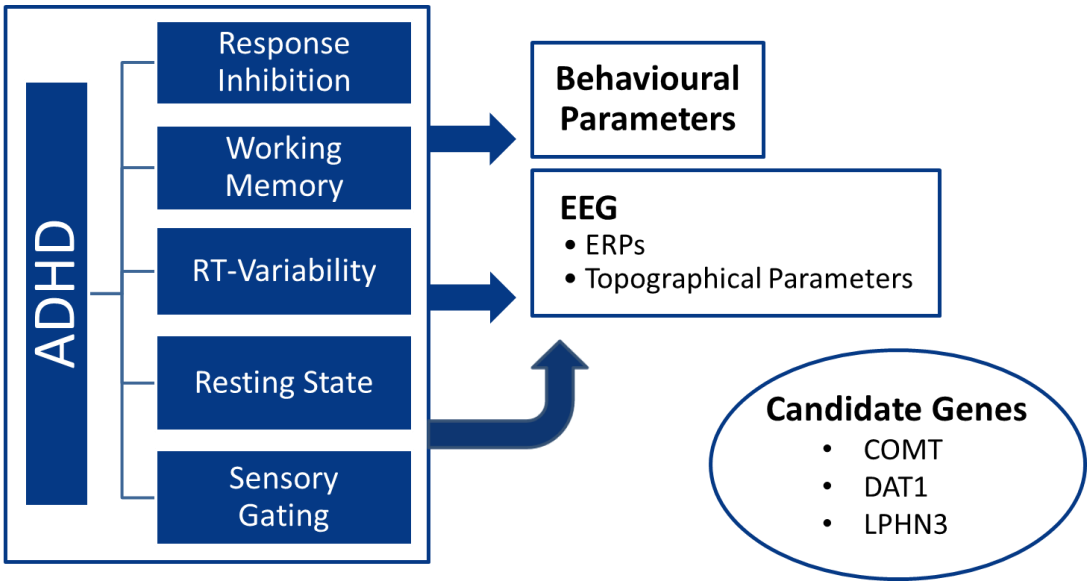

Figure 6: Study design

1.5 Research Objectives and Hypotheses

1) Does ADHD negatively influence behavioural performance on tasks assessing response inhibition and working memory?

   1.1 Influence of diagnostic status on behavioural parameters

   - produce more errors of omission and commission across tasks.
   - show prolonged and more variable reaction times across tasks.

   1.2 Modulation by candidate genes

   - For COMT, carriers of at least one Met allele should perform better since this variant is associated with better cognitive functioning
   - For DAT, homozygosity for the 10R allele should confer impaired cognitive performance.
   - For LPHN3, not having the risk variants leads to superior performance.

2) Do ADHD patients differ from healthy controls in behavioural and electrophysiological parameters pertaining to response inhibition?

   2.1 Influence of diagnostic status on response inhibition

   The unmedicated ADHD group is expected to

   - commit more false alarms across tasks.
   - show reduced NGA and more posterior centroids in the CPT.
   - have lower amplitude and longer latency for N200 and P300.

2.2 Modulation by candidate genes

- For COMT, the risk Met allele should confer stronger NGA and more posterior Go centroids in ADHD, while it should be of less importance in healthy controls.
- For DAT, the homozygous 10R group is expected to show lower NGA in ADHD, but not in controls.
- For LPHN3, ADHD patients with the risk haplotype have a lower NGA due to more anterior Go centroid.

3) Is working memory negatively affected by ADHD?

3.1 Influence of diagnostic status on working memory

Unmedicated ADHD patients are expected to show

- prolonged latencies for N100, P150 and N300; P100.
- dampened P450 activity reflecting weaker working memory updating.
- lower P100 and P300 amplitudes reflecting impaired vigilance and event categorization.

3.2 Modulation by candidate genes

- For COMT, the Met allele evokes P100 and P300 of lower amplitude and longer latency due to lower task related activation of the working memory network.
- For ***DAT,*** 10R/10R carriers have lower amplitudes and delayed latencies since individuals with this genotype display more focused working memory network activation

4) Is Sensory Gating impaired in ADHD patients?

4.1 Influence of diagnostic status on sensory gating

Without stimulant medication, ADHD patients should display

- weaker rates of suppression compared to healthy controls.
- delayed and enhanced testing P50.

4.2 Modulation by candidate genes

- For COMT, Met carriers should show compromised suppression rates.
- For DAT, the 9R allele produces better gating and higher suppression.

5) Response Time Variability

5.1 Influence of diagnostic status on RTV

- In unmedicated ADHD patients, we expect to find increased RTV in compared to controls due to disturbed state regulation

5.2 Modulation by candidate genes

- For COMT, the Met allele is associated with less variable responses.
- For DAT, homozygous 10R children display higher RTV.

6) Does ADHD affect maturational effects on behaviour, response inhibition and working memory as evidenced in the exploratory longitudinal examination of a subsample or patients and controls?

From the first measurement point (T1) to the second examination (T2)

- NGA should improve and reflect maturation of the PFC
- amplitudes and latencies should decrease. Target P300 decreases in controls with age, whereas ADHD patients show the opposite pattern.
- RTV should decrease especially in controls, since reaction times become more stable with age, and differences to ADHD should be magnified at T2.
- differences between COMT genotypes should get bigger, since beneficial effects of the Met allele begin to show around age 10.
- differences in relation to DAT genotype should be diminished as the ADHD risk allele for DAT switches with age.

7) Administration of psychostimulants is expected to remedy deviations owing to ADHD.

2 Methods

2.1 Sample characteristics and procedure

Patients diagnosed with cADHD from the in-patient and out-patient facility of the Department for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Würzburg as well as children and adolescent from the department's control subjects pool were approached and briefly informed about the purpose of the study. If they expressed an interest in participating, they were thoroughly briefed about the aims and the exact study procedure. Providing informed consent, they answered a selection of questionnaires and came in for an appointment of approximately 2 hours duration for

electrophysiological testing, at the end of which a compensation of 30 Euros was provided. For participants under the age of 18, additional informed consent was obtained from the parents. Psychopathology was extensively assessed by means of a semi-structured clinical interview [KIDDIE-SADS-PL, (Kaufman et al., 1997); German version by Deutsche K-SADS-Arbeitsgruppe, 2001]. Current ADHD was confirmed by a clinically trained observer using both patient and parents as information sources (parental version of the KIDDIE-SADS-PL without medication and DSM-IV criteria for < 18; DSM-IV criteria only for > 18). Additionally, the presence of other psychiatric and behavioural problems was assessed with the Child Behaviour Checklist [CBCL; (Achenbach and Edelbrock, 1983); German adaptation by Döpfner and colleagues 1998)], which can further distinguish between externalizing and internalizing symptoms. Exclusion criteria were IQ below 70 or presence of conditions that would prevent the recording of a sufficiently clean electroencephalogram (e.g. Tourette Syndrome). The main criterion for control subjects was absence of psychiatric disorders. Comorbidities observed in the ADHD sample included conduct disorder (N=5), oppositional defiant disorder (N=22), depression (N=8) and anxiety disorders (specific phobia N=4, separation anxiety N=1), enuresis (N=12) and encopresis (N=1), tics (N=6) and obsessive compulsive disorder (N=1). Patients receiving medication for their ADHD were either asked to discontinue pharmacological treatment for at least 48 hours prior to testing (unmedicated ADHD) or to follow their normal routine (medicated ADHD). The predominantly male sample (male-to-female ratio of 1.8 at T1 and 1.4 at T2) thus comprised two ADHD groups (unmedicated ADHD or $ADHD_{unmed}$ and medicated ADHD or $ADHD_{med}$) and matched healthy controls, since we were interested in both performance under presumably optimal conditions and in a natural state in ADHD as well as normally developing children. The unmedicated ADHD group also included medication naive subjects. Mean age of the total sample was 10.55 ± 0.26 (SE) years at T1 and 13.52 ± 0.40 (SE) years at T2. For a details on the sample, please refer to Table 1.

		$ADHD_{unmed}$	$ADHD_{med}$	Controls	*p*
Age	mean (SE)	10.14 (0.39)	10.81 (0.43)	10.73 (0.51)	.509
Gender	(male /female)	26/16	29/7	22/19	.043
Subtype	Inattentive Combined	6 37	4 32	-	.748
CBCL	Sum Internalizing Externalizing	12 (1.20) 18.32 (1.81) 47.37 (3.3)	13.27 (1.6) 20.52 (2.09) 55.94 (4.87)	4.05 (0.59) 2.03 (0.44) 5.34 (1.04)	Controls < $ADHD_{med}$ < $ADHD_{unmed}$
DSM	Inattentive Hyperact-imp	7.29 (0.36) 7.08 (0.35)	7.67 (0.29) 7.84 (0.24)	-	.425 .089
Medication type	MPH Atx AMPH MPH + Atx	-	30 1 4 1	-	
		42	**36**	**41**	

Table 1: Sample description at measurement point T1

All experiments were conducted in a quiet and darkened room with a constant temperature in the Department of Psychiatry, Psychosomatics and Psychotherapy Würzburg. Participants were seated in front of a computer screen at a distance of approximately 1.2 meters and instructed to move as little as possible during the recording. For the sensory gating paradigm, a fixation cross attached to the screen served as a visual orientation aid. The neuropsychological test battery probed response inhibition with the CPT (Rosvold et al., 1956), working memory with the n-back task in two load conditions (1-back and 2-back) and sensory gating with an auditory double-click-tone paradigm (Adler et al., 1982). All procedures involved were approved by the university's ethics committee and in accordance with the latest version of the declaration of Helsinki.

		T1	**T2**
CPT		105	38
n-Back	targets	95	45
	non-targets	111	44
P50		46	-
Out of total		119	50

Table2: Participants with > 15 valid EEG epochs

2.2 Electrophysiological recording

Twenty-one EEG channels were recorded using a 32-channel DC amplifier (Brain-Star System, Erlangen) and the software VisionRecorder (Brain Products GmbH, Hamburg, Germany) with a sampling rate of 1000 Hz, a bandpass between 0.1 to 100 Hz and a 50Hz notch filter to compensate for external electrical influences. The ground electrode was located between Fz and Fpz, the recording reference between Fz and Cz. The 21 data electrodes were placed in accordance with the international 10-20 system (Jasper, 1958) at frontal (Fp1 Fpz, Fp2, F3, F4, Fz, F7, F8), central (C3, Cz, C4), temporal (T3, T4, T5, T6) and posterior (P3, Pz, P4, O1, Oz, O2) sites as well as right and left mastoids. Additional electrodes were located at the outer canthi of both eyes for horizontal and under the right eye (recorded against Fp2) for vertical eye movements. Offline data analysis was performed with the Brain Vision Recorder software (Brain Products, Munich, Germany).

After application of task-appropriate filter settings, the data was re-referenced and segmented into epochs of 850 ms length including a 150 ms pre-stimulus baseline. For detection of blink artifacts, the algorithm developed by Gratton & Coles (1989) was employed. Segments containing signals exceeding ± 100 µV were automatically rejected. Additionally, all kept segments were visually inspected. If less than 15 artifact free epochs remained for any test subject, individual channels were excluded if they were not relevant for the components of interest and constituted the sole source of interference. Peak detection was performed in a semi-automatic manner and the investigator confirmed each identified peak.

2.3 Neuropsychological Test Battery

2.3.1 Response Inhibition

2.3.1.1 Continuous Performance Test

A cued CPT was employed to study response inhibition capabilities. Stimuli for this task consisted of eleven letters: nine distractors (A through G, J and L), a primer (O) and the go-signal X. Participants were instructed to press the space bar as quickly as possible whenever the letter O was followed directly by the letter X (Go-trials), but to not react to any other combination of stimuli. In the case of the go-signal X

appearing after any other letter than the primer, it was also treated as a facultative distractor (DisX). NoGo trials were those specifically designed to assess the capacity for inhibition of a prepared motor response and consisted of the primer stimulus O being followed by one of the distractors. Seeing the primer puts participants in a state of vigilance and has them involuntarily preparing for a button press, so refraining from executing it requires inhibitory control from the PFC and deficits should be reflected in the number of false alarms in the behavioural output (errors of commission). Failing to respond to the go-stimulus constitutes an error of omission and is thought to reflect inattention. All stimuli were present for 200 ms, with an inter stimulus interval (ITI) of 1650 ms.

2.3.1.2 EEG specifications

Offline, the signal was bandpass-filtered between 0.1-50 Hz and re-referenced to an average reference. Data was segmented into Go- and No-Go epochs (850 ms with a 150 ms baseline) and those segments were averaged. A semi-automatic peak detection algorithm was applied in order to identify N200 (250-350 ms) and P300. For further analyses, the mean N200 amplitudes and latencies of all electrodes where this peak was scored (Fz and Cz) were used. P300 was scored at Pz for Go-trials (265-420 ms) and at Cz for NoGo-trials (325-475 ms). For calculation of the NGA, the P300 peaks of the Global Field Power (GFP) are identified in identical time windows, and the centre of the positive electrical field of the brain at this peak time is then mapped onto a spatial coordinate system ranging from 1 (anterior) to 5 (posterior). The NGA as the difference between the centroid location in Go- versus NoGo-trials represents the condition-specific anteriorization of the brain's activation focus. Additionally, peaks at individual electrode sites (Cz and Pz) were subjected to the same procedure.

2.3.2 Working Memory

2.3.2.1 n-Back task

Working Memory was assessed with an n-back task in two load conditions. For each condition, a total of 216 letters (J, B, C, D, E, F, G. H, L) including 54 target stimuli

were presented for 200 ms each, with an ITI of 1650 ms. Subjects were required to press a button whenever the letter on screen was identical to the last (1-back) or second-to last (2-back) letter. The two conditions were presented in separate blocks.

2.3.2.2 EEG specifications

Signals between 0.1 – 25 Hz were re-referenced to linked mastoids and segmented into target and non-target trials. Two kinds of trials were used for analysis of corresponding brain activation, namely trials when subjects made a correct response to a target stimulus (target trial) or when no response occurred after a distractor (non-target trial). Non-target ERPs included a minimum of 20 epochs. For non-target ERPs, we looked at four components reflecting the different stages of working memory operations: the N100 at frontal sites (F3, Fz, F4) reflecting early discrimination was defined as the most negative peak between 50 and 150 ms. P150 (implicated in the selection of material) and N300 (associated with memory retrieval) were analyzed at frontal and central sites (F3, Fz, F4, C3, Cz, C4) within a timeframe of 120 – 300 ms and 200 – 400 ms, respectively. P450wm (involved in working memory updating) was defined as the mean activity at central and parietal sites (C3, Cz, C4, P3, Pz, P4) between 440-460 ms post-stimulus. For target trials, fronto-polar electrodes were excluded prior to artefact rejection to increase the number of trials going into the averaged ERP. The most negative peak at occipital electrodes (O1, Oz, O2) within 70-150 ms post-stimulus represented the P100 (early visual processing). P300 (event categorisation and evaluation) was defined as the most positive parietal peak (P3, Pz, P4) within the classical timeframe between 250 and 400 ms.

2.3.3 Sensory Gating

2.3.3.1 Dual-Click paradigm

To elicit the P50 response and induce sensory gating in the form of suppression of a temporally close interfering stimulus, pairs of auditory click tones with an inter-stimulus interval of 500 ms and an inter trial interval of 1750 ms were used, with a

volume calibrated for the tones to be clearly audible but not of startle-inducing magnitude. Two blocks of forty click-pairs were presented via headphones, with a break of 30 seconds between blocks. The ratio of P50 amplitude to the second (testing) to the first (conditioning) stimulus was multiplied by 100 and the result subtracted from 1 to calculate the individual percentage of suppression: $[1 - \left(\frac{S1}{S2}\right) * 100]$ (e.g. Durukan et al., 2011).

2.3.3.2 EEG specifications

The tip of the nose served as recording reference. Offline, after applying a bandpass filter (10-45 Hz) and correction of blink artefacts, the data were segmented into conditioning and testing epochs of 400 ms including a 100 ms baseline. After excluding epochs containing activity exceeding 50 µV, a minimum of 20 segments were averaged. Peaks in the P50 window (40-70 ms) were detected semi-automatically at Cz, since the component has a well-known fronto-central distribution, and exported after visual inspection.

2.4 Genotyping

2.4.1 Catechol-O-Methyl-Transferase

DNA was extracted from whole blood. Standard PCR protocols were used for the genotyping of the COMT Val158Met variant using the forward primer 5' GGG GCC TAC TGT GGC TAC TC and the reverse primer 5' TTT TTC CAG GTC TGA CAA CG. A reaction volume of 25µl containing 2.5 µl buffer solution, 25 nM $MgCl_2$, 2.5 nM of each nucleotide, 10 pmol of each primer, 0.5 µl Taq DNA polymerase and 50-100 ng of genomic template DNA was used at an annealing temperature of 58°C (35 cycles). Products were digested for 3 hours at 37°C with NLA III and separated on a 5% agarose gel. The G allele corresponds to the high-activity aminoacid Val and has a fragment size of 114 bp; the A allele has a fragment size of 96 + 18 bp and leads to the integration of the low-activity aminoacid Met.

2.4.2 Dopamine Transporter 1

For genotyping of the 40 bp DAT/SLC6A3 3' UTR VNTR, the primers were 5´- TGT GGT GTA GGG AAC GGC CTG AG (forward) and 5´- CTT CCT GGA GGT CAC GGC TCA AGG (reverse). The reaction volume of 25µl contained 2.5 µl of buffer solution, 15 nM $MgCl_2$, 2.5 nM of each nucleotide, 10 pmol of each primer, 0.5 µl Taq DNA polymerase and 50-100 ng of genomic DNA. Annealing temperature was 67.5°C (38 cycles). Products were visualised on a 3% agarose gel. Depending on the number of repeats, fragment lengths were 316 bp (6R), 396 bp (8R), 436 bp (9R), 476 bp (10R) or 516 bp (11R).

2.4.3 Latrophilin-3

A reaction volume of 25µl containing 2.5 µl buffer solution, 15 mM $MgCl_2$, 2.5 mM of each nucleotide, 10 pmol of each primer, 0.5 µl Taq DNA polymerase and 50-100 ng of genomic template DNA was used.

- For rs2345039 primers used were 5'-CTTGGCTTTTCTCCACTCCCTTCTC (forward) and 5'-AAAACTATACTGGCAGCAGGGGGA (reverse). Annealing temperature was 60°C (40 cycles). Products were digested over night at 37°C with BseRI and separated on a 3% agarose gel. G/G has a fragment size of 184 + 283 + 733 bp, G/C leads to fragments of the sizes 36 + 148 + 184 + 283 + 733 bp, and C/C has 36 + 148 + 283 + 733 bp.
- For rs6551665, primers used were 5'-CAGCATGCAGTAGCCCTCTCAC (forward) and 5'-TGACTTTTCTAGGGCAGACAGGCT (reverse). Annealing temperature was 65°C (35 cycles). Products were digested for 3 hours at 37°C with HphI and separated on a 3% agarose gel. G/G has a fragment size of 64+ 97 + 735 bp, G/A leads to fragments of the sizes 64+ 97 + 735 + 799 bp, and A/A has 97 + 799 bp.
- rs1947274 was analysed by sequencing from the reverse primer (5'-GCATGTGACACAGAAGAGGGGTCA). Variants were either C or A.

2.4.4 Hardy-Weinberg-Equilibrium and Group Differences

For seven participants, no genotyping data were available. Due to the relatively low sample size, we stratified genotypes in order to get comparable group sizes, so for COMT we compared the group with at least one risk allele (Val/Met and Met/Met; N = 72) with homozygous Val/Val carriers (N = 39). COMT genotypes were in Hardy-Weinberg-Equilibrium (HWE) in (χ^2 = .34, p = .56). There were no differences in binary genotype frequencies (at least one Met allele vs. no Met allele) between groups (χ^2 = .96, p = .672). Regarding DAT, we looked at homozygous risk allele carriers (10/10; N=55) versus carriers of less than two risk alleles (9/9 and 9/10; N = 58). Genotype distribution was in Hardy-Weinberg-Equilibrium (χ^2 = .036, p = .85). No differences in binary genotype frequencies (10/10 vs. other) between diagnostic groups were observed (χ^2 = .492, p = .782). For LPHN3, genotypes for the three investigated markers rs6551665 (χ^2 = 1.349, p = .245), rs2345039 (χ^2 = 1.999, p = .157) and rs1947274 (χ^2 = .866, p = .352) were in HWE. Comparing carriers of all risk SNPs vs. other genotypes, no differences between diagnostic groups were observed (χ^2 = .794, p = .672).

2.5 Statistical analysis

All statistical analyses were carried out with the software SPSS 18. For non-normally distributed behavioural parameters (errors of commission and omission, reaction times and response time variability), we used Kruskal-Wallis tests for general group comparisons and Mann-Whitney U-tests for post-hoc pair-wise comparisons. Due to the relative robustness of Analyses of Variance (ANOVA) to non-normal data distribution, we applied this test procedure to all electrophysiological data. For all electrophysiological data, parallel analyses were conducted for all three candidate genes, since the sample size was too small to study gene-by-gene interactions. Owing to low cell counts in the homozygous minor-allele carriers, we treated genotypes as binary variables. For COMT, we compared individuals carrying at least one Met allele with homozygous Val/Val carriers. For DAT, the group of homozygous 10R/10R carriers was tested against those with at least one 9R allele. With respect to LPHN3, subjects

were categorized into carriers of the risk variants at all SNP sites (risk haplotype carriers) versus individuals with any other constellation of variants (no risk haplotype).

NGA and P50 suppression ratios were entered as dependent variables in univariate ANOVAs, with the between factors 'diagnostic group' (3) and 'genotype' (2). For post-hoc comparisons, univariate ANOVAs and t-tests for paired and independent samples were used. Centroids in the CPT and all peaks in the n-back paradigm were subjected to repeated measures ANOVAs with the within factor 'condition' (2; Go vs. NoGo for the CPT and 1-back vs. 2-back for the n-back task) and the between factors 'diagnostic group' (3) and 'genotype' (2). For post-hoc comparisons, univariate ANOVAs and t-tests for paired and independent samples were used. Only effects with a nominal p>.05 and trends of interest will be reported in the body of the text. For all other discovered trends, please see the appendix.

3 Results

3.1 Behavioural Parameters

We expected unmedicated ADHD patients to perform worse than medicated patients and controls, manifesting in more errors of omission and commission, longer reaction times and greater response time variability across all tasks. Furthermore, carriers of the risk genotypes (COMT, DAT) or haplotype (LPHN3) were expected to commit more errors. For this reason, only targeted group comparisons were performed with Mann-Whitney U-tests for all behavioural parameters and the reported *p*-values reflect one-sided significances.

Diagnostic Group Non-parametric Mann-Whitney-U tests showed a greater number of omission errors in unmedicated compared to medicated patients (CPT: p = .018; 1-back: p < .001; 2-back: p = .008) and controls (CPT: p = .009; 1-back: p = .008; 2-back: p = .007) across tasks. Furthermore, they had more variable reaction times compared to medicated patients (CPT: p = .040) or controls (1-back: p = .032).

Genotype effects In the CPT, carriers of at least one COMT Met allele had higher RTV (p = .016) and more False Alarms (.013) than those without Met allele. Individuals

with the LPHN3 risk haplotype committed more False Alarms than the non-risk group, (p = .022). In the 1-back condition, homozygous carriers of the 10R variant in the DAT gene had a greater RTV than the other genotypes (*p* = .029), whereas for 2-back they showed longer reaction times (*p* = .045).

3.2 Response Inhibition

Regarding the direction of the main effects for COMT, carriers of at least one Met allele always showed more posteriorly located centroids. Main effect for condition always indicated that the NoGo centroid was located more anteriorly than the Go centroid (for details, see Table x).

3.2.1 NoGo-Anteriorization

The NGA is a stable phenomenon, risk genotypes bring about worse NGA (DAT) and more posterior centroids (COMT) in all diagnostic groups or only in unmedicated ADHD patients (LPHN3).

a) COMT

Genotype affects location of both centroids (risk = more posterior). Looking at diagnostic groups individually shows negative impact of genotype in unmedicated ADHD patients.

NGA and COMT The ANOVA with the factors COMT genotype and group found a trend level interaction effect for diagnostic 'group x genotype' ($F_{2, 94}$ = 2.965, *p* = .056). Follow-up tests did not find any further effects for group or COMT, all *p*s > .113.

Centroids and COMT The repeated measures ANOVA confirmed a stable main effect of condition, with NoGo centroids (3.81 ± .07) being located more anteriorly than Go centroids (4.08 ± 05), $F_{1, 94}$ = 17,840, *p* < .001. Furthermore, we found a trend level main effect for COMT genotype ($F_{1, 94}$ = 3.270, *p* = .074), with carriers of one or more Met alleles having more posterior centroids in both

conditions (Go = 3.95 and NoGo = 3.69 for no Met, Go = 4.15 and NoGo = 3.87 for Met).

Additionally, we observed a trend level interaction 'condition x group x COMT genotype' ($F_{2, 94} = 2.965$, $p = .056$). Following up this interaction by condition, in Go trials carrying at least one Met allele led to more posterior centroids (4.15 vs. 3.95) compared to Val/Val, $p = .029$. No genotype effects were observed in the NoGo condition, all *p*s > .126. Stratifying subjects by genotype, both genotype groups showed a main effect of condition ($p = .012$ for no Met; $p = .001$ for Met). Lastly, separate analyses for each diagnostic group returned main effects of condition and COMT genotype for the unmedicated sample, with $p = .011$ and $p = .033$. In the control group, only a main effect of condition was observed, $p < .001$. For medicated patients, neither COMT genotype nor condition significantly affected centroid locations.

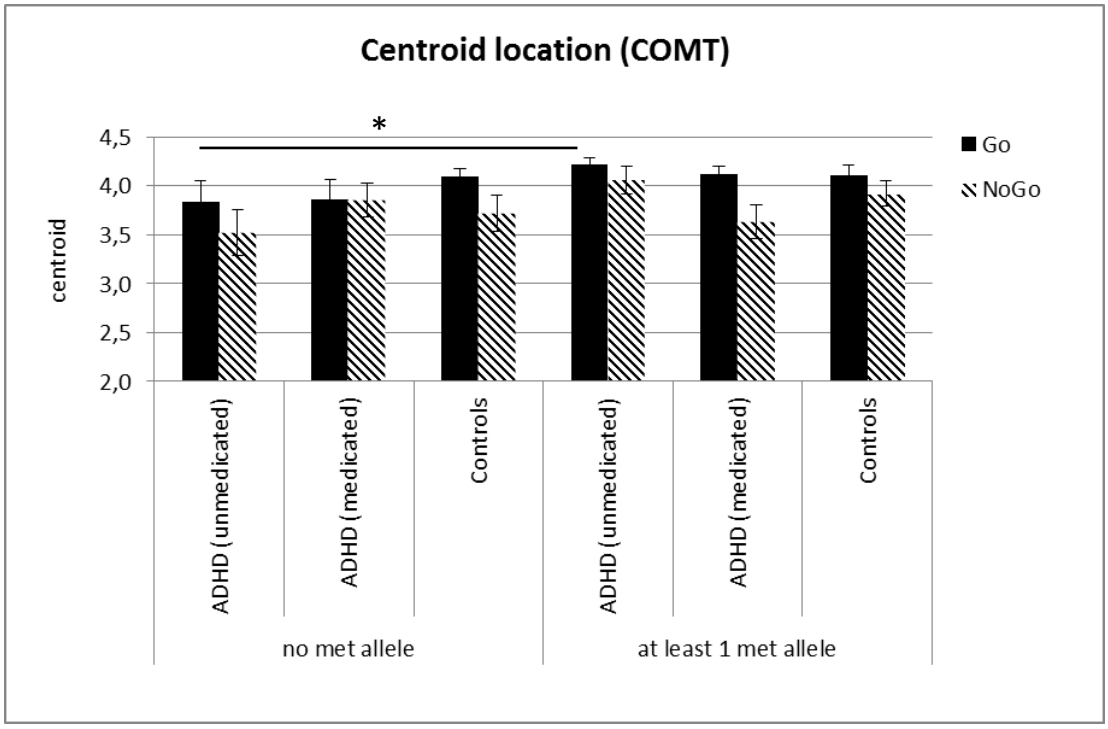

Figure 7: Modulation of centroid location from anterior to posterior by COMT genotype and diagnostic status

b) DAT

Without risk genotype, medicated patients have more anterior centroids than unmedicated ADHD patients

NGA and DAT The genotype by group ANOVA returned a main effect of DAT genotype ($F_{1, 95} = 5.854$, $p = .017$), indicating a better anteriorization in non-homozygous as compared to homozygous carriers of the 10R allele in the sample.

Centroids and DAT Comparing centroid locations with a repeated Measures ANOVA, we found a main effect 'condition' ($F_{1,95} = 20.581$, $p < .001$) indicating more posterior Go centroids.

The interaction 'condition x genotype' ($F_{2, 95} = 5.854$, $p = .017$) was further explored with t-tests comparing Go and NoGo centroids within each DAT genotype group and confirmed a more anterior NoGo centroid compared to the Go location in both genotype groups. However, this effect was more pronounced in the non-homozygous 10R group, $p < .001$ and $p = .043$, respectively.

Following up the interaction 'group x genotype' ($F_{2, 95} = 3.637$, $p = .030$), for 10/10 carriers no differences between diagnostic groups emerged. Only among non-homozygous 10R carriers, medicated patients had more anteriorly located centroids compared to unmedicated patients (p = .024) and controls (p = .072).

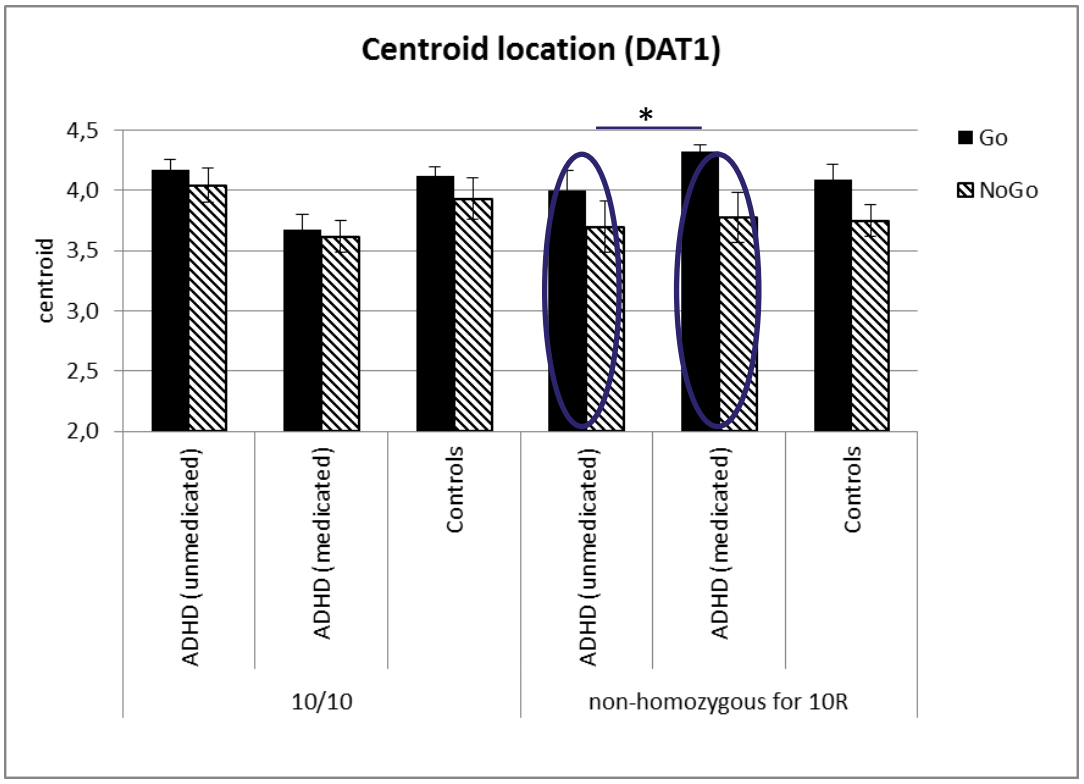

Figure 8: Modulation of centroid location from anterior to posterior by DAT genotype and diagnostic status

c) LPHN3

While Go centroids were negatively influenced by genotype, during NoGo only having the risk haplotype brought out more posterior centroid locations in unmedicated ADHD

NGA and LPHN3 For NGA, an interaction 'Group*LPHN3' ($F_{2, 91} = 3.401$, $p = .038$) was further explored. Among risk variant carriers, a trend level group effect ($F_{2, 48} = 2.596$, $p = .085$) indicated tendentially lower NGA values in members of the unmedicated ADHD group compared to medicated patients ($p = .072$), whereas no group effect emerged in subjects without the risk SNPs. Comparing the genotypes within each diagnostic groups reveals LPHN3 to only moderate NGA in both unmedicated ($p = .055$) and medicated ($p = .050$) ADHD patients, where the risk haplotype conferred higher NGA.

Centroids and LPHN3 Regarding centroid location, the interaction of LPHN3 genotype, group and condition ($F_{2, 91} = 3.401$, $p = .038$) meant that for Go trials risk carriers had more posterior centroids ($F_{1, 91} = 4.686$, $p = .033$), while only during the NoGo condition unmedicated patients with the risk genotype had also more posterior centroids compared to the medicated group ($p = .014$).

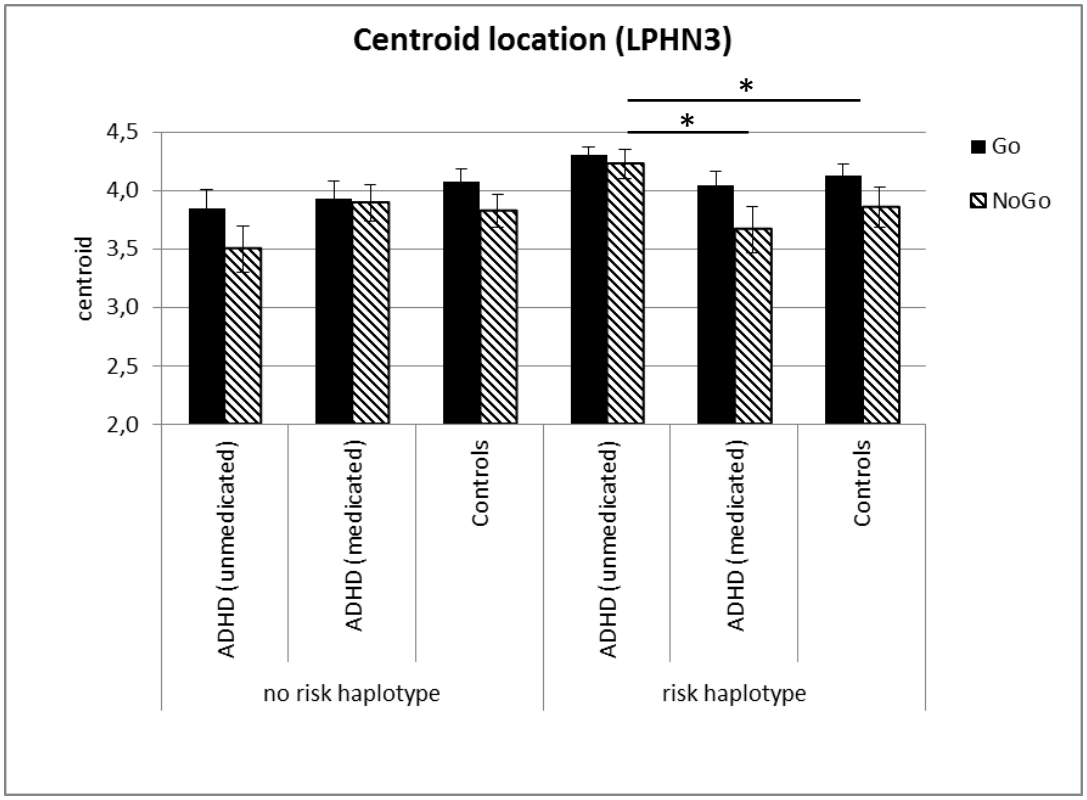

Figure 9: Modulation of centroid location from anterior to posterior by LPHN3 genotype and diagnostic status

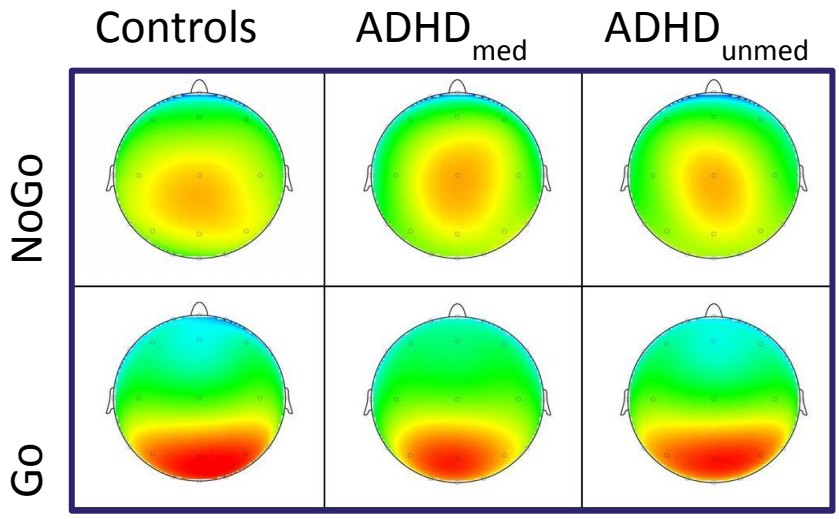

Figure 10: Topographical maps of mean Go and NoGo ERPs at P300 peak time in individuals carrying the LPHN3 risk haplotype

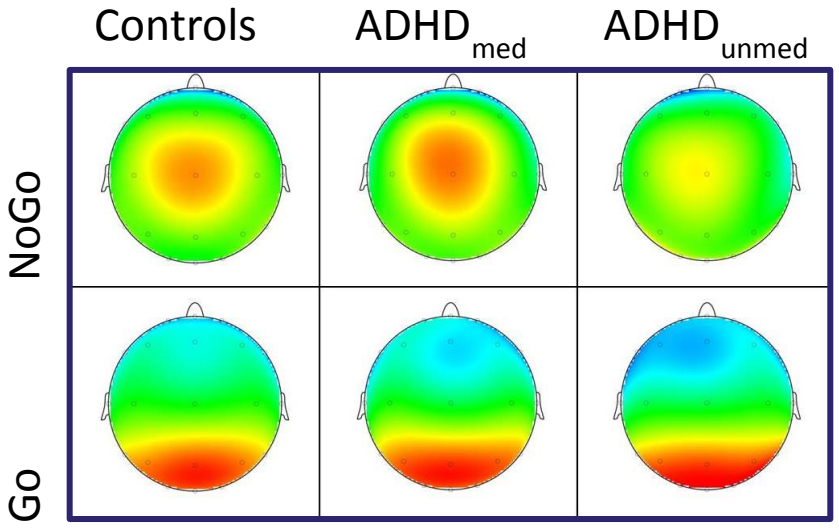

Figure 11: Topographical maps of mean Go and NoGo ERPs at P300 peak time in individuals without the LPHN3 risk haplotype

3.2.3 N200

NoGo elicits higher amplitudes regardless of genotype; Go longer latencies than NoGo (COMT), unmedicated ADHD patients delayed in both conditions (DAT), risk haplotype delayed NoGo N200 (LPHN3)

a) Amplitudes

The most significant finding regarding N200 amplitudes in the CPT was a main effect of condition regardless of included candidate gene, all ps < .001 ($F_{1, 93}$ = 60.390 for COMT; $F_{1, 94}$ = 63.049 for DAT; $F_{1, 91}$ = 62.130 for LPHN3). As expected, the elicited response was always greater for NoGo compared to Go trials.

b) Latency

COMT Including COMT genotype into the analysis, we only observed trend level effects for N200 latency, again for condition (Go > NoGo with $F_{1,93}$ = 3.284 , *p* = .073) and an interaction of condition and group that was not further explored ($F_{2, 93}$ = 2.404, *p* = .096).

DAT With DAT genotypes, a trend level main effect for group ($F_{1, 94}$ = 2.826, *p* = .064) meant that unmedicated patients had more delayed N200 compared to the medicated ADHD group (*p* = .047). This effect was qualified by the interaction 'condition' x 'group' ($F_{2,94}$ = 2.932, *p* = .058). Following Go stimuli, unmedicated had longer latencies than medicated ADHD patients (*p* = .047), while in the, whereas in the NoGo condition, unmedicated patients were delayed in comparison to controls (*p* = .083).

LPHN3 The interaction of 'LPHN3 x condition' ($F_{1, 91}$ = 4.865, *p* = .030) signified that the risk group had higher mean NoGo N200 latencies than that without the risk haplotype (*p* = .029), whereas LPHN3 genotype did not play a role for Go latencies (p =.945). Marginal group differences with regard to N200 latencies ($F_{2, 91}$ = 2.704, *p* = .072) suggest longer latencies in unmedicated compared to medicated

ADHD patients (p = .078), and longer latencies in NoGo compared to Go on a trend level ($F_{1, 91}$ = 3.822, p = .054).

3.2.4 P300

a) P300 and COMT

NoGo amplitudes (Cz) smaller for unmedicated ADHD patients compared to controls, while for Go only unmedicated patients without risk had lower amplitudes (Pz) than both other groups. Only without risk genotype could medication decrease latencies for both conditions (at electrodes) below level of controls.

GFP The main effect of condition for P300 amplitude and latency, with p = .009 and p < .001, respectively signified that in the Go condition, higher P300 amplitudes and shorter latencies compared to NoGo were observed.

Electrodes A main effect of condition indicted - that similar to the GFP results - Go stimuli generated higher amplitudes with shorter latencies compared to NoGo stimuli (both ps < .001).

To further elucidate the trend-level interaction of 'condition' x 'group' x 'COMT genotype' ($F_{2, 94}$ = 3.064; p = .051) for P300 amplitudes, separate ANOVAs for Go and NoGo were performed. The main effect 'group' in the NoGo condition ($F_{2, 94}$ = 3.223, p = .044), indicated that unmedicated ADHD patients had marginally lower amplitudes than controls (p = .075). In the Go condition, an interaction of 'group' x 'COMT genotype' ($F_{2, 94}$ = 2.649; p = .073) was observed. Among subjects without met allele, unmedicated ADHD patients had lower P300 amplitudes compared to both medicated patients (p = .096) and healthy controls (p = .020). For Met carriers, diagnostic group status had no effect on P300 amplitudes.

Regarding P300 latency at individual electrodes, there was an interaction of 'group' x 'COMT' ($F_{2, 94}$ = 3.595, p= .031). Subjects without Met allele showed no group differences, whereas among carriers of at least one Met allele medicated ADHD patients had shorter P300 latencies than both unmedicated patients (p = .010) and controls (p = .018).

b) P300 and DAT

Risk genotype (10/10) longer Go and shorter NoGo latencies in Global Field Power

Main effects of condition indicated shorter latencies and higher amplitudes for Go compared to NoGo for Global Field Power peaks and the peaks at the respective electrode sites, with $p = .006$ for GFP amplitude, all other p-values < .001.

GFP For GFP latency, the significant interaction 'condition' x 'DAT genotype' ($F_{1, 95} = 9.868$, $p = .002$) meant that for Go stimuli, homozygous 10R carriers had the longest latencies ($p = .040$) compared to other genotypes, whereas this effect was reversed for NoGo ($p = .073$).

Electrodes Looking at the latencies at electrode sites, we observed a trend-level group effect ($p = .091$), which was due to longer latencies in unmedicated patients compared to controls (p = .090).

c) P300 and LPHN3

NoGo peaks have smaller amplitude and longer latencies compared to Go peaks

For P300 peaks both scored according to global field power and individual electrode sites, main effects of condition signified that NoGo P300 peaks were of smaller amplitude (GFP: $F_{2, 91} = 7.215$, $p = .009$; electrodes: $F_{2, 91} = 34.802$, $p < .001$) and longer latency than Go amplitudes (GFP: $F_{2, 91} = 64.749$, $p < .001$; electrodes: $F_{2, 91} = 176.649$, $p < .001$).

Electrodes A trend-level three-way interaction 'Condition*Group*LPHN3' ($F_{2, 91} = 2.411$, $p = .095$) for P300 latency at Cz and Pz was not further explored, and a marginal group main effect ($F_{2, 91} = 2.499$, $p = .088$) did not return significant group differences in post-hoc tests.

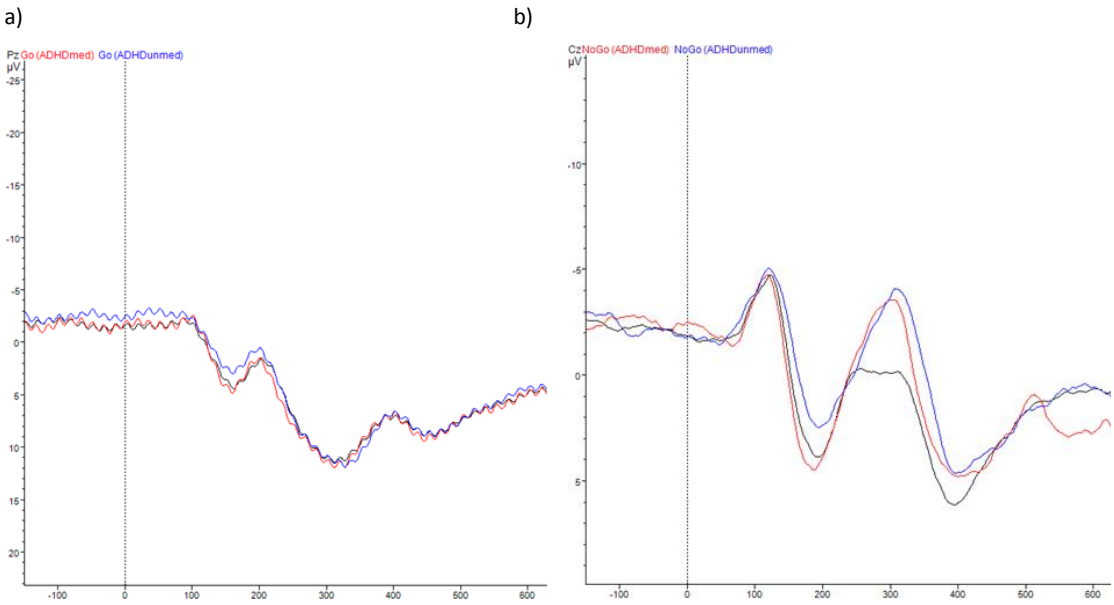

Figure 12: Grand Average ERPs during CPT for a) Go (at Pz) and b) NoGo (at Cz) trials, black curves are from healthy control subjects

3.3 Working Memory

3.3.1 COMT

Non-targets **Met allele carriers had delayed N100; P150 later in unmedicated compared to medicated ADHD; controls with Met allele elicit higher P450 than those without Met**

COMT modulated N100 timing, as Met allele carriers had delayed N100 peaks compared to non-Met carriers ($F_{1, 99} = 5.265$, $p = .044$).

P150 latencies were longer in unmedicated compared to medicated patients ($p = .023$), as a main effect for group ($F_{2, 99} = 3.263$, $p = .042$) confirmed.

Analysis of P450 mean activity returned a significant group x COMT interaction ($F_{2, 99} = 3.705$, $p = .028$). Further exploration of this interaction with respect to COMT and group effects only returned a trend level genotype influence in controls (p = .079), with Met allele carriers having higher mean amplitudes than those without Met allele, all other *p*s > .219.

Main effects of condition could be observed for P150 ($F_{1, 99}$ = 6.570, p = .012; 1b > 2b) and N300 latencies ($F_{1, 99}$ = 22.109, p < .001; 2b > 1b) as well as for P450 ($F_{1, 99}$ = 16.182, p < .001; 1b > 2b) and P300 amplitude ($F_{1, 84}$ = 6.064, p = .016; 2b > 1b).

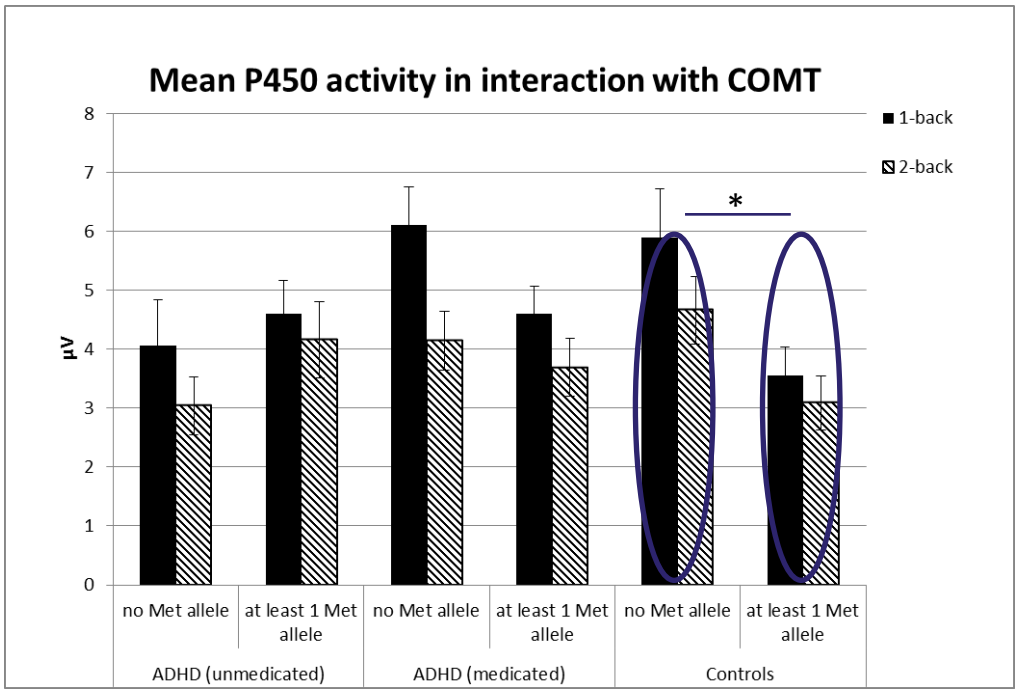

Figure 13: Mean P450 activity in interaction with COMT genotype, diagnostic status and condition

3.3.2 DAT

Non-targets **For P150 under high load, unmedicated patients had the longest latencies. For low load additional genotype influence: only in risk genotype group had medicated ADHD the fastest response. Genotype differences only in controls (risk > no risk).**

Targets **Genotype had only an effect in unmedicated patients, where risk carriers had higher P100 and P300 amplitudes. Group differences emerged in the low risk genotype, where unmedicated patients had lower amplitudes for both components (P100 < medicated ADHD patients and controls; P300 < medicated ADHD patients). In the high-risk group, unmedicated ADHD had greater P300 than controls.**

Non-targets P150 latencies differed between conditions ($F_{1, 100}$ = 8.863, p = .004; 1b >2b) and diagnostic groups ($F_{2, 100}$ = 4.289, p = .016; unmedicated ADHD > medicated ADHD with p = .013). A three-way interaction of condition, group and DAT genotype ($F_{2, 100}$ = 4.110, p = .019) was observed. Looking separately at the two load levels, main effects of group were evident in both conditions: During 1-back trials, medicated patients had faster responses than the unmedicated group (p = .025). For 2-back, unmedicated patients had slower responses than both medicated patients (p = .0) and healthy controls (p = .048). In the low load condition, the main effect was qualified by an interaction of group and DAT ($F_{2, 100}$ = 3.253, p = .043). Group differences only existed among the homozygous 10R carriers, where ADHD patients receiving stimulant medication had faster P150 responses than unmedicated patients (p = .062) and controls (p = .015). Conversely, genotypes only affected latencies in healthy controls, where the 10/10 genotype went along with delayed peaks (p = .015).

For non-targets, additional effects of condition on N300 latency ($F_{1, 100}$ =24.097, p < .001; 1-back < 2-back) and P450 amplitude ($F_{1, 100}$ = 13.720, p < .001; 1-back > 2-back) were observed.

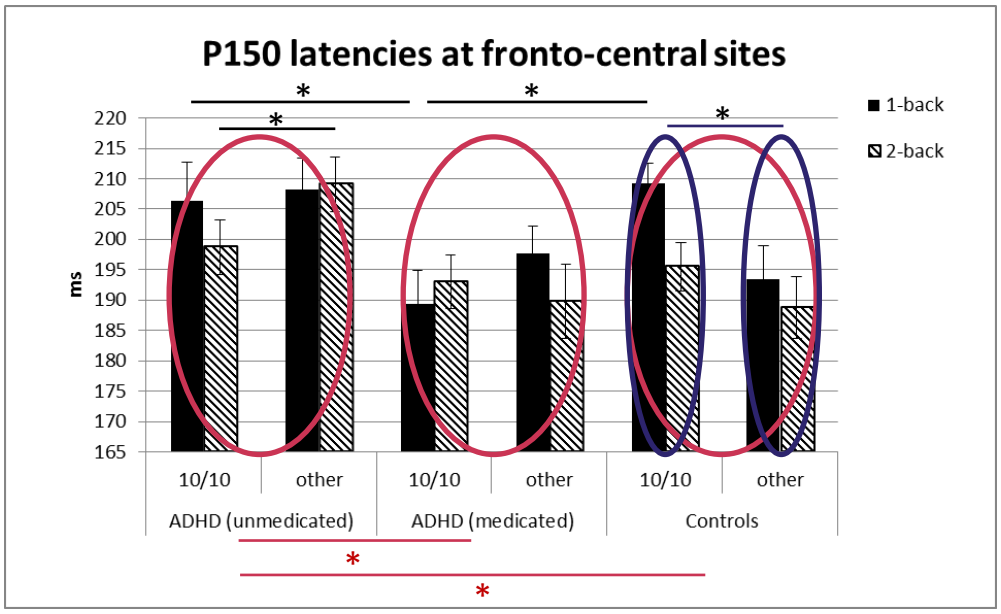

Figure 14: P150 activity in interaction with DAT genotype, diagnostic status and condition

Targets Group and DAT genotype shaped P100 amplitudes in an interactive way ($F_{2, 85}$ =3.833, p = .025). While diagnostic groups did not differ if homozygous for the 10R allele, without risk genotype unmedicated patients had lower amplitudes than medicated patients (p = .010) and a trend in the same direction compared to controls (p = .092). If splitting the sample by diagnostic group, genotype effects were only evident in unmedicated ADHD patients, where 10R/10R carriers had greater responses (p = .003).

Similar to findings regarding P100, the homozygous 10/10 group also had greater P300 amplitudes ($F_{1, 85}$ = 4.101, p = .046). This relationship was further qualified by the interaction of DAT genotype and group ($F_{2, 85}$ = 5.191, p = .007). Again, differences were only present in non-homozygous 10R probands, where unmedicated patients had lower P300 amplitudes than the medicated group (p = .014). On a trend-level, unmedicated patients with the risk genotype however had higher P300 amplitudes compared to controls (p = .051). Genotype effects were limited to the unmedicated ADHD group, with 10/10 carriers having greater amplitudes (p = .003).

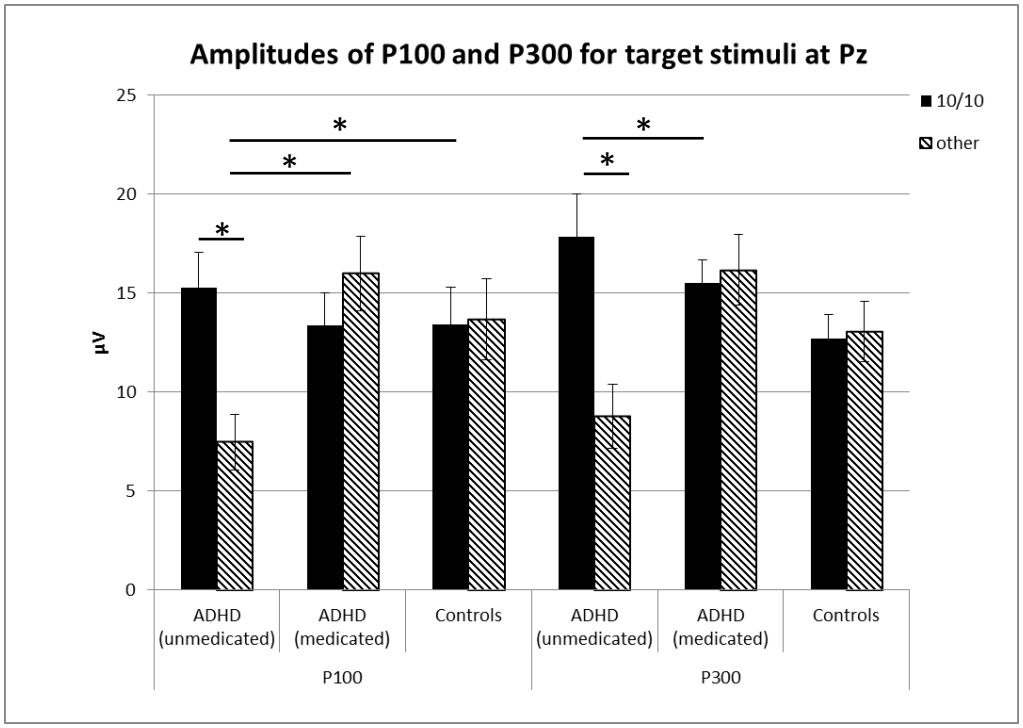

Figure 15: P100 and P300 responses to target stimuli (1-back and 2-back) in interaction with DAT genotype and diagnostic status

3.3.3 Latrophilin-3

Non-targets P150 delayed for unmedicated compared to medicated ADHD patients, N300 stronger for risk haplotype

Non-targets N300 amplitudes were greater for carriers of the LPHN3 risk haplotype ($F_{1, 96}$ = 4.969, p = .028), whereas P300 amplitudes were only dependent on condition ($F_{1, 81}$ = 4.578, p = .035), with responses being greater for 2-back. For P150 latency, main effects of condition ($F_{1, 96}$ = 7.356, p = .008) and group ($F_{2, 96}$ = 3.854, p = .025) signified delayed responses for 1-back compared to 2-back and unmedicated compared to medicated ADHD patients (p = .020). The reverse effect of condition could be found for N300 latencies, where 1-back elicited a faster reaction ($F_{1, 96}$ =21.490, p < .001).

3.4 Sensory Gating

Separate ANOVAs with factors 'group' and 'genotype' were performed for each candidate gene. Subsequent correlational analyses between P50 suppression rate and behavioural output from CPT and n-back task should be regarded as strictly exploratory, as the cell counts were very low.

a) Sensory Gating Ratio

LPHN3 risk haplotype beneficial for gating in controls and medicated ADHD patients, opposite pattern for unmedicated ADHD patients

Analyses of the influence of the LPHN3 risk haplotype on sensory gating returned an interaction 'Group by LPHN3' ($F_{2, 53}$ = 5.849, p = .005). Subjects with the risk haplotype showed a main effect for group ($F_{2, 26}$ = 6.312, p = .006), indicating a more effective P50 suppression in medicated compared to unmedicated patients (p = .004). No such difference was observed in participants without risk haplotype (p = .352). Among unmedicated patients, those without risk haplotype had more efficient

sensory gating than risk carriers (p = .014), whereas the exact opposite was observed in controls (p = .023) and medicated ADHD (p = .042), where those with the risk haplotype showed better suppression.

For medicated patients without LPHN3 risk haplotype, exploratory correlational analyses showed better P50 suppression comes with more errors of omission in the n-back task (r = .990, p = .010), while risk carriers without medication have a negative relationship between suppression rate and errors of omission (r =- .770, p = .043).

For COMT and DAT, no significant effects on P50 suppression were observed, all ps > .254.

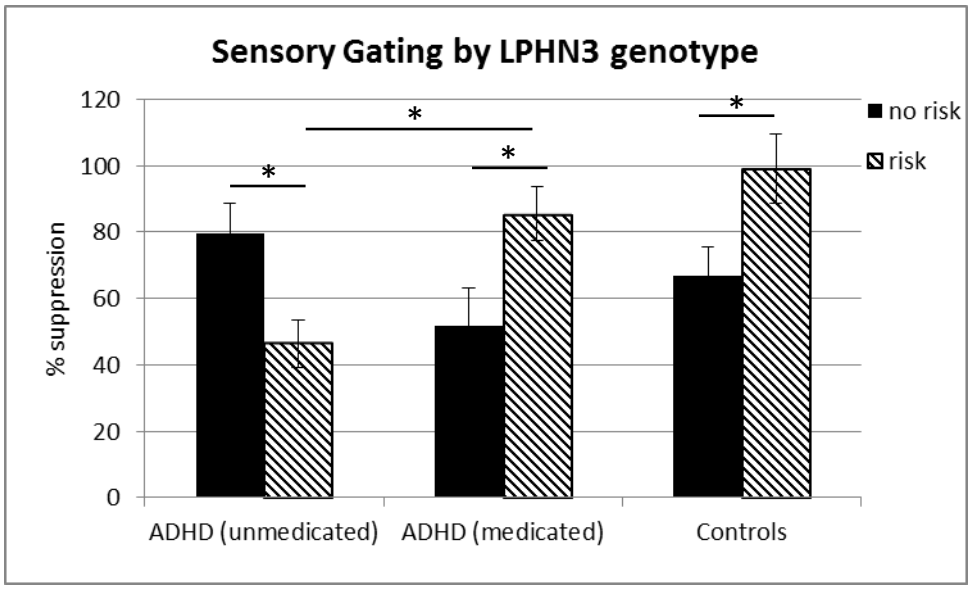

Figure 16: Mean P50 suppression rate in interactio with LPHN3 genotype and diagnostic status

b) P50 Amplitudes and latencies

Having at least one Met allele means lower conditioning amplitudes

Individual comparisons for conditioning and testing amplitudes and latencies with the factors 'group' and 'genotype' (COMT, DAT and LPHN3) returned a main effect for COMT genotype on conditioning amplitudes across all diagnostic groups ($F_{1, 53}$ = 3.995, p = .051). Met allele carriers had smaller amplitudes in response to the first stimulus than probands without Met allele. Exploratory inclusion of sex instead of

genotype as a factor returned only a trend-level interaction effects of 'group by sex' for conditioning amplitudes ($F_{1, 61}$ = 5.107, p = .072) and testing latencies ($F_{1, 61}$ = 3.160, p = .080), which were not further explored.

3.5 Exploratory catamnestic analysis

Seeing that only 50 subjects returned for the catamnestic part of the study, we reduced the number of factors used for analysis in order to avoid low cell counts. So we conducted Repeated Measures ANOVAs with the within factor 'condition' and one between factor at a time. The included between factors were 'group', 'COMT genotype', 'DAT genotype' or 'LPHN3 genotype'.

		$ADHD_{unmed}$	**$ADHD_{med}$**	**Controls**	***p***
Age	mean (SE)	13.86 (0.73)	14.94 (0.62)	12.16 (0.64)	.012
Gender	(male /female)	6/8	13/4	10/9	.141
Subtype	inattentive combined	1 13	3 14	-	.607
		14	17	19	

Table 3: Sample description at measurement point T2

Reaction times decreased over time in all tasks, while this was only true for RTV and omission errors in CPT and 2-back. False alarms only showed a time-dependent decline in the CPT. For details, see Table x.

	Variable	***p***	
CPT	RT	.026	T1 > T2
	SD	< .001	
	miss	.019	
	False Alarms	< .001	
1-back	RT	< .001	
2-back	RT	.013	
	SD	.036	
	Miss	.002	

Table 4: Changes in behavioural parameters from T1 to T2

3.5.1 Changes in Response Inhibition from T1 to T2

N200 amplitudes were higher for T1 and NoGo trials. Latencies were always longer at T1, however the delay for Go responses was only observed at T2. P300 responses quickened and decreased in strength from T1 to T1. Go stimuli elicited faster responses than NoGo commands.

N200 When including the factor time into the repeated measurement ANOVAs, for both amplitudes and latencies we only found main effects of time and condition as well as interactions of the two factors. Amplitudes were higher at T1 and for Go trials. Responses at T1 were both of larger magnitude and more delayed compared to T2, and Go stimuli evoked reactions of smaller amplitude with longer latencies. Since genotype and diagnostic group did not play a role for the development of N200 amplitudes or latencies and the main effects all pointed in the same direction, we followed up the interactions of condition by time in a separate analyses without the factor genotype. N200 amplitudes were bigger for Go compared to NoGo at both time points, and higher at T1 for both conditions. Latencies were only greater for Go at T1, however faster responses were observed at T2 in both response inhibition and execution trials. For details, see table supplementary table S6-M.

A main effect of DAT genotype ($F_{1, 28}$ = 9.488, p = .005) indicating dampened N200 amplitudes for homozygous 10R carriers was qualified by the interaction of condition and DAT ($F_{1, 28}$ = 4.614, p = .041). Follow-up t-tests confirmed that this was only true for the Go condition (p = .006). However both genotype groups showed increased amplitudes for NoGo compared to Go. N200 latencies were modulated by an interaction of time and DAT genotype ($F_{1, 28}$ = 5.730, p = .024). Only at the second measurement probands homozygous for the 10R allele had slower N200 latencies (p = .013). But again both genotype groups showed the overall quickening of responses from T1 to T2 (all ps < .003)

NGA and P300 For NGA, no developmental effects were found. Exploratory analyses with both genotype and diagnostic group as factors despite small cell counts and shift in NGA as dependent variable did not return any significant results.

Centroids showed the familiar more anterior location for the Go condition regardless of diagnostic group or genotype (with $p = .045$ for DAT, $p = .044$ for LPHN3, $p = .083$ for group and $p = .062$ for COMT). A main effect for COMT was indicative of more posteriorly located centroids in probands carrying at least one Met allele ($F_{1, 29} = 6.316$, $p = .018$).

P300 amplitudes both in terms of Global Field power and at individual electrode sites were larger at T1, all *p*s < .019. Additionally, at Cz and Pz main effects of condition indicated larger P300 amplitudes for NoGo, all *p*s <.001. NoGo responses were always later than Go responses for Global Field power and at individual electrode sites, all *p*s < .001. The peaks at Cz and Pz were delayed at T1 compared to T2, all *p*s < .001.

	GFP	**Electrodes**	
P300 Amplitude	m.e. time	m.e. time	m.e. condition
Group	$F_{1, 28} = 7.272$, $p = .012$	$F_{1, 28} = 10.161$, $p = .004$	$F_{1, 28} = 17.368$, $p < .001$
COMT	$F_{1, 27} = 6.205$, $p = .019$	$F_{1, 27} = 9.891$, $p = .004$	$F_{1, 27} = 16.879$, $p < .001$
DAT	$F_{1, 27} = 7.313$, $p = .011$	$F_{1, 29} = 10.822$, $p = .003$	$F_{1, 29} = 22.093$, $p < .001$
LPHN3	$F_{1, 27} = 9.478$, $p = .005$	$F_{1, 29} = 11.489$, $p = .002$	$F_{1, 29} = 16.879$, $p < .001$
P300 Latency	m.e. condition	m.e. time	m.e. condition
Group	$F_{1, 28} = 27.253$, $p < .001$	$F_{1, 28} = 22.381$, $p < .001$	$F_{1, 28} = 102.549$, $p < .001$
COMT	$F_{1, 27} = 27.630$, $p < .001$	$F_{1, 27} = 21.143$, $p < .001$	$F_{1, 27} = 89.538$, $p < .001$
DAT	$F_{1, 29} = 28.713$, $p < .001$	$F_{1, 29} = 23.269$, $p < .001$	$F_{1, 29} = 100.29$, $p < .001$
LPHN3	$F_{1, 29} = 28.077$, $p < .001$	$F_{1, 29} = 27.511$, $p < .001$	$F_{1, 29} = 89.538$, $p < .001$

Table5: Developmental Effects on Response Inhibition Related Components - P300

3.5.2 Changes in Working Memory from T1 to T2

3.5.2.1 Development of working memory in interaction with COMT

Non-targets **Genotype effect on P150 amplitude at T1 (risk > no risk); unmedicated ADHD delayed N300 only under high load (T1 and T2)**

Targets **Decrease in P100 and P300 amplitude (unmedicated and medicated ADHD) and P100 latency over time only in patients; controls show weaker P300 responses than either patient group at T2**

Strong effect of time on all amplitudes and latencies were the most prominent findings, with T1 responses being both larger and later than at T2 (see Table x). Additionally, main effect of condition for N100 amplitude ($F_{1, 34}$ = 4.387, p = .044), N300 latency (($F_{1, 34}$ = 8.998, p = .005 and P450 amplitude ($F_{1, 34}$ = 21.256, p < .001) emerged.

Non-targets

N100 An interaction of condition and time ($F_{1, 34}$ = 5.8824, p = .021) indicated that only at T1 were N100 amplitudes higher for 2-back compared to 1-back (p = .017). However, amplitudes decreased from T1 to T2 in both conditions (all ps < .001).

The timing of this component was also altered by an interaction of time, group and COMT ($F_{1, 25}$ = 5.824, p = .021. Further probing of this interaction only returned effects for time (T1 > T2) within both COMT genotype groups (p = .039 and p = .019 for “no Met” and “Met”, respectively) as well as unmedicated ADHD patients and controls.

P150 For P150 latency, we found a Time by COMT interaction ($F_{1, 34}$ = 4.135, p = .050). Post-hoc tests showed a marginal effect for COMT at T1 (p = .082; no Met > Met), whereas this effect was absent at T2 (p = .517). Again the factor time significantly influenced both genotype groups (p ≤ .001).

N300 The Condition by Group interaction for N300 latency ($F_{2, 34}$ = 3.671, *p* = .036) illustrated that only for 2-back did unmedicated patients show longer latencies than controls (*p* = .002). Looking individually at the diagnostic groups, medicated patients (*p* = .045) and controls (*p* = .011) have longer latencies for 2-back compared to 1-back.

Targets

P100 Exploring a Time*Group interaction for P100 amplitudes ($F_{2,25}$ = 4.145, *p* = .028), a group effect at T2 ($F_{2, 32}$ = 7.444, *p* = .002) indicated that controls responses were less strong than those of unmedicated (*p* = .003) or even medicated ADHD patients (*p* = .011). Both patient groups had higher P100 amplitudes at T1 compared to T2, all *p*s ≤ .001.

For P100 latencies on the other hand, the interaction Time*Group ($F_{2\ 26}$ = 5.663, *p* = .009) showed that in unmedicated patients, latencies at T1 were longer than at T2 (*p* = .016), all other follow-up *p*s > .077. A further Time*COMT interaction ($F_{1, 26}$ = 4.565, *p* = .042) additionally confirmed slower responses at T1 compared to T2 for both COMT genotype groups (*p* = .047 for "no Met" and *p* = .031 for "Met").

P300 Analysing P300 amplitudes, we observed a three-way interaction of Condition*Time*Group ($F_{1, 25}$ = 4.602, *p* = .020). In addition to main effects for time in both conditions (*p* = .004 for 1-back and *p* > .001 for 2-back), a Time*Group interaction in 2-back ($F_{1, 28}$ = 4.122, *p* = .027) indicated greater P300 responses at T2 in controls compared to unmedicated patients (*p* = .031) and a tendency for the same effect in the medicated ADHD group (*p* = .079). Both ADHD patients on (*p* =.041) and off medication (*p* =.010) show a decrease in P300 amplitudes from T1 to T2. The exploration of a Condition*Time*COMT interaction ($F_{1, 25}$ = 5.198, *p* = .031) only confirmed the time effect in 1-back and 2-back (T1> T2), but did not show any further effects with *p* < .05.

3.5.2.2 Development of working memory in interaction with DAT

Non-targets **At T1 the risk group displayed faster N100 in high load compared to low load. Only controls have higher P150 amplitudes to low compared to high load. P150 latency was dependent on load in controls and Medicated ADHD patients.**

Targets **Patient groups displayed shortening of P100 latency between measurements; medicated (T1) and unmedicated (T2) ADHD had higher 1-back than 2-back P300; under high load controls highest P300 amplitudes**

Non-targets

N100 The main effect of condition on N100 amplitudes ($F_{1, 34}$ = 4.925, p = .033; a-back > 2-back) was qualified by the interaction of condition and time ($F_{1, 34}$ = 5.865, p = .021), whereby both conditions showed stronger reactions at T1, but only at T1 could 2-back elicit higher responses than 1-back.

N100 latency was modulated by a Condition x Time x DAT interaction ($F_{1, 34}$ =5.233, p = .029). Follow up tests found a main effect of time for 1-back (p = .001; T1 > T2). Only at T1 there was a further interaction of condition and DAT genotype ($F_{1, 39}$ = 5.006, p = .031), which signified that only risk variant carriers (10/10R) differentiated between load in terms of N100 timing (p = .028; 1-back > 2-back).

P150 The interaction of group and condition ($F_{2, 34}$ = 3.669, p = .036) meant that only control subjects had higher P150 amplitudes for 1-back compared to 2-back (p = .046).

N300 The main effect of condition on N300 latency ($F_{1, 34}$ = 11.099, p = .002) was further explained by an interaction of condition and group ($F_{1, 34}$ = 3.346, p = .031). In the high load condition, unmedicated ADHD patients had faster responses

than controls (p = .002). However, only medicated patients (p = .045) and controls (p = .011) had faster responses in 1-back compared to 2-back trials.

P450 The low load condition evoked greater mean activity in the P450 window than the high load condition ($F_{1, 34}$ = 21.147, p = .0)

Targets

P100 Amplitudes were modified by an interaction of the factors group and DAT genotype ($F_{2, 25}$ = 3.832, p = .035). Follow-up tests failed to return any significant effects in either genotype or diagnostic group.

Analysis of P100 latency returned an interaction effect of condition by time by diagnostic group ($F_{2, 26}$ = 4.384, p = .023). Follow- up tests by condition found an effect of time for 1-back ($F_{1, 30}$ = 8.599, p = .006; T1 > T2), by time a marginal group effect at T1 (p = .079). Looking individually at the diagnostic groups, both patient groups had speeded up P100 responses at T2 compared to T1 (p = .016 for unmedicated ADHD and p = .080 for medicated ADHD), while latencies in controls were not dependent on time.

P300 Amplitudes were moderated by an interaction of condition, diagnostic group and time ($F_{2, 33}$ = 4.337, p = .024). Both T1 and T2 showed interaction effects of condition and group (T1 p = .017; T2 p = .019). Follow-up t-tests showed for T1 higher 1-back amplitudes compared to 2-back in medicated ADHD patients (p = .023), while at the second measurement only the unmedicated ADHD group showed this effect (p = .019). Furthermore in the high load condition controls had higher amplitudes compared to both ADHD groups (unmedicated ADHD p = .031; medicated ADHD p = .079) at T2.

3.5.2.3 Development of working memory in interaction with LPHN3

Non-targets Higher amplitudes and longer latencies for all components at T1; P150 delayed in unmedicated ADHD risk carriers and N300 greater for risk haplotype and compared to medicated ADHD patients

All amplitudes and latencies were subject to development, as ubiquitous main effects of time indicated (for details, see Table x). Main effects of condition ($F_{1, 32}$ = 5.896, p = .021, 2b > 1b) and time on N100 amplitudes were qualified by the interaction of condition and time ($F_{1, 32}$ = 7.968, p = .008). While at T1 there was a higher amplitude for 2b compared to 1b (p = .017), this effect was absent at T2. For P150 latency, exploration of an interaction group*LPHN3 ($F_{2, 32}$ = 3.525, p = .041) showed that only among carriers of the risk haplotype did unmedicated patients show increased latencies compared to controls (p = .033). N300 amplitudes showed main effects of time, group ($F_{2, 32}$ = 3.452, p = .044) and LPHN3 ($F_{1, 32}$ = 4.386, p = .044) indicated that the N300 was of greater magnitude at T1 compared to T2 and in risk haplotype compared to non-risk haplotype carriers, and there was a trend for greater N300 in unmedicated compared to medicated ADHD patients (p = .052). Besides main effects of time and condition ($F_{1, 32}$ = 13.039, p < .001) on N300 latency, the interaction of the two factors ($F_{1, 32}$ = 4.497, p = .042) illustrated longer latencies for 2b condition compared to 1b at both measurement points (T1: p = .031; T2: p =.004) and a decrease in latencies from T1 to T2 (1b: p < .001; 2b: p = .018). Lastly, the main effect of condition ($F_{1, 32}$ = 17.505, p < .001) on P450 activity indicated greater P450 responses for 1-back compared to 2-back.

Peak	Amp (V) / Lat (L)	F	*p*	Direction of effect
N100	V	$F_{1,34}$ = 30.897	< .001	T1 > T2
	L	$F_{1,34}$ = 13.678	= .001	
P150	V	$F_{1,34}$ = 36.753	< .001	
	L	$F_{1,34}$ = 62.012	< .001	
N300	V	$F_{1,34}$ = 25.606	< .001	
	L	$F_{1,34}$ = 15.764	< .001	
P450	V	$F_{1,34}$ = 10.013	.003	
P100	V	$F_{1,25}$ = 37.094	< .001	
	L	$F_{1,25}$ = 17.381	< .001	
P300	V	$F_{1,25}$ = 14.595	= .001	

Table 6: Effects of time on n-Back components (COMT)

Peak	Amp (V) / Lat (L)	F	*p*	Direction of effect
N100	V	$F_{1,34} = 37.331$	< .001	T1 > T2
	L	$F_{1,34} = 8.321$	.007	
P150	V	$F_{1,34} = 29.048$	< .001	
	L	$F_{1,34} = 56.158$	< .001	
N300	V	$F_{1,34} = 29.751$	< .001	
	L	$F_{1,34} = 16.132$	< .001	
P450	V	$F_{1,34} = 11.356$	.002	
P100	V	$F_{1,34} = 27.241$	< .001	
	L	$F_{1,34} = 10.655$	.003	
P300	V	$F_{1,34} = 12.209$	.002	

Table7: Effects of time on n-Back components (DAT)

Peak	Amp (V) / Lat (L)	F	*p*	Direction of effect
N100	V	$F_{1, 32} = 27.271$	$p < .001$	T1 > T2
	L	$F_{1, 32} = 7.198$	$p = .011$	
P150	V	$F_{1, 32} = 30.275$	$p < .001$	
	L	$F_{1, 32} = 52.645$	$p < .001$	
N300	V	$F_{1, 32} = 25.761$	$p < .001$	
	L	$F_{1, 32} = 16.136$	$p < .001$	
P450	V	$F_{1, 32} = 9.381$	$p = .004$	

Table 8: Effects of time on n-Back components (LPHN3)

Time	Gene	Peak	Amp (V) / Lat (L)	Effect	F	*p*
T1	COMT	N100	V	condition*group	$F_{2, 99} = 2.626$	.077
	COMT		V	group*COMT	$F_{2, 99} = 2.751$	.069
	COMT	P300	V	group*COMT	$F_{2, 84} = 2.963$	.057
T2	COMT	P150	V	COMT	$F_{1, 36} = 2.969$	.093
	COMT	N300	V	condition	$F_{1, 36} = 2.900$	.097
	COMT	P100	V	COMT	$F_{1, 33} = 3.341$	.077
	COMT		L	cond*group	$F_{2, 34} = 2.874$	.070
	COMT	P300	V	group	$F_{2, 33} = 3.011$	.063
T1 → T2	COMT	P150	V	COMT	$F_{1, 34} = 4.087$	.051
	COMT		V	cond*group	$F_{2, 34} = 3.185$	.054
	COMT		L	condition	$F_{1, 34} = 3.392$	.074
	COMT	N300	V	condition*COMT	$F_{1, 34} = 3.542$	.068
	COMT		L	cond*time	$F_{1, 34} = 3.559$	.068
	COMT	P450	V	COMT	$F_{1, 34} = 3.554$	.068
	COMT		V	cond*time	$F_{1, 34} = 3.393$	.074
	COMT	P300	L	time	$F_{1,26} = 3.971$	.057

Table 9: Trend level effects for working memory tasks (COMT)

Time	Gene	Peak	Amp (V) / Lat (L)	Effect	F	*p*
T1	DAT	N100	V	condition*group	$F_{2, 100} = 2.954$	.057
	DAT			condition*DAT	$F_{1, 100} = 3.350$	.070
	DAT		L	condition*group*DAT	$F_{2, 100} = 2.393$	.097
	DAT	N300	L	DAT	$F_{1, 100} = 2.798$	.098
	DAT	P100	L	DAT	$F_{1, 85} = 3.833$	.079
	DAT	P300	L	condition*group	$F_{2, 85} = 2.398$	.097
T2	DAT	P150	L	group*DAT	$F_{2, 36} = 3.150$	.055
	DAT	N300	L	group*DAT	$F_{2, 36} = 2.980$	.063
	DAT	P450	V	condition*group*DAT	$F_{2, 36} = 3.071$	.059
	DAT	P300	V	group	$F_{2, 33} = 2.898$	.069
	DAT			condition*group*DAT	$F_{2, 33} = 2.824$	.074
T1 → T2	DAT	P150	V	condition	$F_{1, 34} = 3.668$	.064
	DAT		L	condition	$F_{1, 34} = 3.319$	.077
	DAT	N300	L	condition *time	$F_{1, 34} = 3.386$	.074
	DAT	P450	V	condition *time	$F_{1, 34} = 3.967$	.054
	DAT	P100	V	condition	$F_{1, 25} = 4.133$	.053
	DAT		L	condition *time	$F_{1, 26} = 3.142$	.088
	DAT	P300	V	condition *group	$F_{2, 25} = 3.393$	.050
	DAT			condition *time	$F_{1, 25} = 3.599$	.069
	DAT			condition *group*DAT	$F_{2, 25} = 3.080$	.064
	DAT			condition *time*DAT	$F_{1, 25} = 3.428$	.076

Table 10: Trend level effects for working memory tasks (DAT)

Time	Gene	Peak	Amp (V) / Lat (L)	Effect	F	*p*
T1	LPHN3	N100	V	condition*group	$F_{2, 96} = 2.944$	.057
	LPHN3	P100	L	condition*group*LPHN3	$F_{2, 81} = 3.085$	.051
	LPHN3	P300	V	group*LPHN3	$F_{2, 81} = 2.685$	.074
T2	LPHN3	P150	L	Group*LPHN3	$F_{2, 35} = 2.606$	.088
	LPHN3	N300	V	cond	$F_{1, 34} = 3.231$	.081
	LPHN3	N300	V	cond*LPHN3	$F_{1, 34} = 2.911$	.097
	LPHN3	P100	V	cond	$F_{1, 31} = 3.400$	.075
	LPHN3	P100	L	cond*group	$F_{2, 32} = 2.976$	.065
T1 → T2	LPHN3	P150	V	cond*group	$F_{2, 32} = 2.784$	.077
	LPHN3	P150	L	condition	$F_{1, 32} = 3.108$	.087
	LPHN3	P150	L	time*group	$F_{2, 32} = 2.495$	.098
	LPHN3	N300	L	group*LPHN3	$F_{2, 32} = 2.664$	.085
	LPHN3	N300	L	cond*group	$F_{2, 32} = 3.254$	.052
	LPHN3	P450	V	cond*time	$F_{1, 32} = 3.634$	.066
	LPHN3	P100	V	cond	$F_{1, 23} = 3.627$	.069
	LPHN3	P100	V	time*group	$F_{2, 23} = 2.877$	.076
	LPHN3	P300	V	time*group	$F_{2, 23} = 2.764$	.084
	LPHN3	P300	V	group*LPHN3	$F_{2, 23} = 3.192$	.060

Table 11: Trend level effects for working memory tasks (LPHN3)

4 Discussion

We partly confirmed the predicted behavioural deviations associated with ADHD across neuropsychological tasks manifesting in prolonged and more variable reaction times as well as a greater tendency towards errors of omission and commission. We replicated the ubiquitous finding of more omission errors of unmedicated ADHD patients in Go-NoGo tasks (Fallgatter et al., 2004; Fallgatter et al., 2009; Fisher et al., 2011) and n-back (Keage et al., 2008; Sunohara et al., 1999) both compared to healthy controls and medicated patients, pointing towards problems with both inattention and working memory. Psychostimulants such as MPH are known to improve inhibition (SSRT) and variability of response times in healthy individuals (Nandam et al., 2011), the mechanism most likely being increased stimulus salience via enhanced striatal DA (Volkow et al., 2004, Volkow et al., 2005). Interestingly, Atomoxetine as an effective alternative drug for the treatment of ADHD left those parameters unchanged in the same group despite a significant reduction in behavioural ADHD symptoms (see meta-analysis by Faraone, 2009). The lack of group differences regarding false alarms has been observed before with this particular paradigm by Fallgatter et al. (2004) in a sample of ADHD boys, however we did not find prolonged reaction times for ADHD patients in any of our tests and this goes against most of the previously published research on ADHD (Fisher et al., 2011; Fallgatter et al, 2004; Uebel et al., 2010). Risk genotype carriers of COMT (Met) and LPHN3 (risk haplotype) committed more false alarms in the CPT, indicating difficulties with inhibiting responses, while DAT (homozygous 10R) corresponded to longer reaction times in the more taxing working memory task. The increased rate of commission errors in the LPHN3 risk haplotype could be linked to decreased striatal neuronal activity in the risk group (Arcos-Burgos et al., 2010)

4.1 Response Inhibition

NGA NGA could not distinguish between ADHD patients and healthy control children. However, all examined ADHD candidate genes modulated NGA in some way, and we could identify differences between diagnostic groups when taking into account the individual's genotype on our ADHD risk genes. While for DAT the 10-repeat allele

had a negative influence on inhibitory functioning as reflected in lower NGA, Latrophilin-3 only influenced NGA in combination with diagnostic status. Surprisingly, one-sided t-tests revealed a positive influence of the LPHN3 risk haplotype on this particular index of response control in ADHD patients irrespective of medication, as risk carriers of in both patient groups had trend-level higher NGA values.

When discussing NGA results, it is important to note that looking at raw NGA values in the present study, the observed mean NGAs (T1: 0.27 ± 0.53) seem small in comparison to those reported for adults (e.g. Fallgatter et al., 2009 with mean NGA = 0.6 ± 0.5 for adult ADHD and 0.7 ± 0.4 for adult controls). The big age range might have obscured the fact that a majority of participants were still quite young even at the second assessment and hadn't reached mature degrees of anteriorization; therefore in total the mean NGA also appeared unchanged in the longitudinal assessment. However, dividing the sample by presence or absence of NGA showed adult level NGA values (T1: Ø 0.56 ± 0.47) in the group with at least minimal anteriorization for response inhibition. In our case absolute NGA values were not related to participants' age and absence or presence of NGA was independent of diagnostic status. So independent of ADHD, a big proportion of participants had not yet mastered that crucial step. A considerable number of participants did not show an NGA at T1 (40 %) or T2 (43 %); their Go centroids were more frontally located than the NoGo centroids. Initial reports on NGA as a marker of prefrontal functioning stressed finding the effect in all included subjects; this might have been partly due the selection of adult participants (Fallgatter & Strik, 1997; Fallgatter et al., 1999). Absence of NGA in a percentage of participants is not an uncommon finding among psychiatric populations (e.g. 25% of adult personality disorder with childhood ADHD symptoms and 0% of healthy controls in Fallgatter et al., 2005) Among healthy individuals, this has also been reported for a sample of children and adolescents despite general independence of NGA and age already in this young sample (Renner, 2007). Approximately half of our control children had not yet developed an NGA; hence it is likely that their NGA will improve over time as they enter adulthood, whereas this might not be the case in the

ADHD groups. This would ultimately manifest in the aforementioned decreased NGA findings for adult ADHD patients.

Centroids and COMT While NGA was independent of COMT genotype, having at least one Met allele moved both centroids more towards posterior areas on a trend level, thus putatively facilitating or influencing response execution rather than inhibition. Behavioural observations support this idea, since Met carriers had more errors of commission as well as more variable responses. So while they did not miss cues and thus did not differ in the rate of omission errors, they had trouble inhibiting responses. This also fits with the preliminary results from Fallgatter et al. (2009), although here more posterior Go centroids with Met were only observed in the ADHD group. They furthermore found a genotype main effect on NGA in adult ADHD patients indicating homozygous Val carriers had smaller NGA values, but COMT did not modulate this parameter in healthy controls. Nevertheless, NGA did not differentiate between ADHD and controls either, in accordance with our own results. After adding more patients, the only stable findings of Fallgatter et al.'s study were the presence of an NGA in all groups, and generally more anterior centroids in ADHD individuals, while all effects involving COMT genotype vanished. This suggests more difficulties with response execution rather than inhibition since Go centroids are more anterior, and indeed the ADHD group predominantly showed elevated rates of omission errors, although false alarms were more frequent in patients on a trend level as well. In contrast to our own negative reports for COMT and NGA, Ehlis et al. (2007) identified a beneficial effect of Met on NGA in a schizophrenic sample. In contrast to our ADHD sample, in the schizophrenic population it was the NoGo centroid, which was affected by COMT and carried the effect. So in disorders involving dopaminergic neurotransmission, the Met allele is in some cases beneficial for prefrontal functioning as captured by NGA. Taken together however, the relationship of both the COMT Val158Met polymorphism to ADHD and COMT activity to prefrontal functioning, as indicated by NGA is not a stable phenomenon in our sample, hence findings remain inconclusive.

Centroids and DAT Not being homozygous for the childhood risk allele 10R meant better NGA. These **r**esults regarding implications of DAT for NGA fit with indications of poorer neuropsychological functioning of homozygous 10R carriers among childhood ADHD populations (Loo et al., 2003), whereas this pattern seems to be reversed in adult ADHD where the 9R allele confers the risk of a diminished NGA (Dresler et al., 2010). Interestingly, even though t-tests examining genotype effects within each diagnostic group did not turn out significant, the differences between genotypes was most pronounced in the medicated ADHD group in the expected direction (9R < 10R) and virtually absent in controls, which fits with previous research (Dresler et al., 2010). Having at least one 9R allele allowed for psychostimulant medication to lead to an anteriorization of the brain electric field both during executed and inhibited reactions. The lack of group difference in the 10/10 genotype group has to be interpreted in the light of the small degrees of anteriorization in this high-risk genotype, which might make genotype effects hard to detect with this small sample size.

Centroids and LPHN3 During successful response execution, the LPHN3 risk haplotype was associated with more posterior centroids irrespective of diagnostic group or medication. So while more posterior Go centroids might be beneficial for swift motor responses this also might facilitate unwanted behaviour resulting in false alarms. Indeed risk carriers regardless of diagnosis did commit more errors of this kind, i.e. failed inhibition. During inhibition trials, unmedicated patients with the Latrophilin-3 risk variants had more posterior centroids than those receiving medication. This is in line with the fact that the NGA was also lower – albeit on trend level – in unmedicated ADHD compared to medicated patients with the risk variants. In the case of LPHN3, the combination of carrying a genetic risk and being without the support of medication ultimately could be seen in a lower NGA as an electrophysiological indicator of response control, and this was caused by a shift in the surface recorded potential reflecting response inhibition. Supporting this, the combination of SNPs defined as risk haplotype in the present study has been found to confer a decrease in activity in striatum, cerebellum and thalamus (Arcos-Burgos et al., 2010) – putatively in the

inhibitory loop. Even though the component responsible for the NGA phenomenon originates in the ACC, cross-talk between regions and top-down inhibitory commands to motor areas in the striatum contribute in a vital way to a successful inhibition of on-going or prepared responses.

P300 amplitudes and latencies DAT modulated P300 GFP latencies in interaction with condition. For inhibition trials, homozygous 10R carriers had significantly faster responses; this effect was reversed in the response execution condition where having two copies of the 10R meant longer latencies. When including COMT genotypes into the analyses, we found a trend suggesting that when inhibition of a response was required (NoGo), control subjects had higher P300 amplitudes than unmedicated patients, while during Go trials this held only true for probands without Met allele. In this genotype group, stimulant medication also led to higher amplitudes compared to unmedicated ADHD. On the whole, methylphenidate is known to have a normalizing effect on P300 amplitudes (Zillessen et al., 2001, Seifert et al., 2003, Groom et al., 2010). Furthermore, among Met carriers, latencies were faster for unmedicated patients with respect to both other groups. So COMT genotype predominantly modulated the strength of the Go P300. Go amplitudes were only diminished in unmedicated ADHD if they had no Met allele. This fits with previous findings that - following the inverted U-shape description of prefrontal functioning - only ADHD patients with the Val/Val genotype lie clearly outside of the normal range. Having a Met brought unmedicated patients up to normal levels, whereas without Met support of stimulant medication was required to achieve normal responses. Regarding the proposed mechanism behind normalising psychostimulant effects on inhibition-related ERP components, stimulants like methylphenidate primarily support target detection by making the relevant stimuli more salient. In the case of the CPT this would be the NoGo signal, commanding the interruption of the prepared response. Crucial to this beneficial action is their supporting striatal DA availability, which might make up for the prefrontal disadvantage of having a Val allele.

4.2 Working Memory

Early and mid-latency working memory components Our study echoes previous work in that it largely could not identify sensory deficits in ADHD (Lopez et al., 2006; Sergeant and van der Meere, 1990). Early visual stimulus discrimination as indicated by the N100 peak was comparable between ADHD children irrespective of medication status and healthy controls. This is supported by the absence of a pre-attentive auditory processing deficit in the P50 paradigm. Responses to the first auditory stimulus (conditioning P50) necessitate no sensory gating, thus strength and timing of this mid-latency auditory component can be interpreted as an indicator of the functioning of the primary auditory cortex regardless of gating success. Since there were no group differences between ADHD and controls regarding conditioning P50 amplitudes or timing, it is in line with the finding of normal early visual processing. Karayanidis et al. (2000) did report increased N100 latencies in ADHD boys; however their sample had a much narrower age range (6-10 years) where development is still on-going to a greater degree, and they had all been medication naïve before testing. It is conceivable that previous treatment with psychostimulants or after-effects of discontinued medication for the experiment may have normalised stimulus discrimination. COMT genotype was the only factor modulating early sensory potentials in non-target trials the form of timing of the N100. Met carriers had longer latencies, hinting at a delay for visual information to be routed on to higher processing centres and processed. This is surprising considering the Met allele is associated with impulsivity and would thus be more readily able to explain latency decreases. In the working memory task, where this was observed, there were however no overt behavioural consequences of this delay. So the functional Val 158Met polymorphism starts to exert its influence resulting in performance differences or overt behaviour very early on, at the stage of stimulus discrimination.

Looking at ERPs to target stimuli, we could however see impairments in unmedicated ADHD in the occipital P100 as a correlate of comparatively early visual processing. Exploring the interaction of group and DAT genotype, separate analyses by diagnostic group found that being homozygous for the 10R allele was only associated

with larger P100 responses in unmedicated ADHD, whereas it was of no consequence for early visual processing of target stimuli in medicated ADHD or control subjects. Without the risk genotype however, unmedicated patients had the smallest P100 responses. In conclusion, having the ADHD associated DAT risk genotype 10R/10R brought out enhanced P100 responses in unmedicated ADHD patients, who otherwise had dampened P100 amplitudes. Target stimuli are more resource and attention demanding than non-target stimuli, since they constitute a signal that the initiation of a more or less complex behavioural response is required. Conversely, in this area ADHD patients show the most consistent deficits. Errors of omission (i.e. non-responsiveness to target stimuli) were elevated in unmedicated patients across tasks, whereas false alarms (i.e. erroneous reactions to non-target stimuli) were independent of diagnostic group.

ADHD patients differed in their P150 response reflecting fronto-central networks preparing for impending change. A main effect for diagnostic group consistently showed longer P150 latencies in unmedicated compared to medicated ADHD patients. This is in line with findings by Karayanidis et al. (2000) and extends ERP differences identified by Keage et al. (2008) in their investigation of non-target components in ADHD. The latter authors did not find ADHD patients on or off medication to differ from controls in P150 responses. Karayanidis (2000) did not require subjects to update working memory, and instead had them perform a motor response to every stimulus. Keage (2008) on the other hand used only a simple load condition (1-back) while at the same time requiring a more complicated motor response to targets; also they differentiated between ADHD subtypes and children vs. adolescents for their analyses while for our study we merged those four categories.

DAT genotype interacted with diagnostic group and load level in shaping P150 timing. When cognitive load was low, medication only normalised P150 latencies and thus presumably material selection in the presence of a genetic risk conferred by the 10/10 genotype. Without risk genotype, ADHD subjects showed normal responses. No differences in performance emerged. This does not fit with reports of particular

importance of DAT genotype under high load conditions, also in absence of compromised performance (Stollstorff et al., 2010). It was surprising to find that DAT genotype did not play a role for 2-back as opposed to Stollstorff et al. (2010), since in our study unmedicated patients had prolonged P150 latencies irrespective of DAT genotype. In adults the 10R/10R genotype was shown to be associated with more focused activation during working memory operations (Bertolino et al., 2009), faster reactions and more errors of commission (Caldu et al., 2007). Seeing that in children the DAT risk genotype is reversed, the prolonged P150 latencies for homozygous 10R carriers would go with longer and more variable reaction times and might be indicative of less focused activity in the working memory network. Stimulant medication speeded up electrophysiological responses corresponding to the selection of material or preparation for impending change and supports those processes in ADHD children.

For N300, no ADHD specific impairment in memory retrieval was found, similar to Keage et al., 2008, but contrasting findings of decreased N300 amplitudes in ADHD patients (Sartory et al., 2002). The LPHN3 risk haplotype came with stronger N300 responses indicative of better memory retrieval. Indeed, N300 amplitudes were correlated negatively with almost all behavioural parameters, indicating faster and less variable reactions and fewer errors of both types in subjects with greater N300 amplitudes. This finding is surprising in light of the fact that the haplotype is more common in ADHD, but may be explained by more resources being invested in the retrieval process to achieve normal levels of functioning. Also this effect only being present in controls, the changes associated with LPHN3 genotype might interact with altered cortical architecture in ADHD and be detrimental only in combination with those alterations.

Late working memory components More endogenous components indicative of higher-order cognitive control were used to assess the categorisation of targets (P300) and non-targets (P450). ***P300 and DAT.*** A similar pattern as for P100 was seen for the target P300 peaks, where diagnostic group modulated the response in interaction with DAT genotype. Again, under the low load condition patients without

medication and without risk genotype were less responsive and had lower P300 amplitudes than the medicated group. Carrying the risk genotype meant tendentially higher amplitudes in unmedicated patients, whereas without genetic risk, they had the lowest P300 amplitudes. Indeed, DAT genotype effects only manifested in this unmedicated group in the shape of higher amplitudes in 10R/10R individuals. However, high P300 amplitudes have been linked to better working memory span (Nittono et al., 1999) and there are reports of better cognitive functioning for homozygous risk allele carriers in ADHD (Barkley et al., 2006b; Karama et al., 2007), although the opposite pattern has also been found. So it is feasible that the 10R allele with higher DAT activity could have a compensatory effect through better phasic DA release at the cost of more variable responses, whereas the normally beneficial 9R is a disadvantage in terms of certain forms of cognitive performance for ADHD. This effect might be absent in medicated ADHD since their Dopaminergic transmission has probably not yet returned to pre-treatment levels. P300 latency has been reported to be associated with performance on working memory tasks (Polich et al., 1996), but in our study we could not confirm latency differences in any of the target components despite higher error rates in for ADHD children and adolescents.

P450 and COMT Additionally, COMT also interacted with ADHD status on the late P450 component indicative of working memory updating. Upon closer inspection, only the control group had higher activation associated with the Met allele, whereas genotype was not relevant with respect to P450 in individuals with ADHD. This contradicts findings in healthy controls that Val/Val individuals display heightened and faster P300 responses (Yue et al., 2009). Since stronger P450 signifies a more capacities for the accommodation of new information (Clark et al., 1998), this is in line with reports of better cognitive functioning healthy Met carriers. The presence of a Met allele is associated with dampened activity and connectivity in some parts of the working memory network (DLPFC in Sambataro et al., 2009) and higher activation in others (VLPFC in Sambataro et al., 2009; right inferior frontal gyrus and intra-parietal sulcus in Dumontheil et al. 2011), so resources might be used in a more focused and efficient manner. Concerning the lack of COMT effects in ADHD patients, COMT is

mainly relevant for prefrontally mediated functions. Since maturational processes in the PFC go on well into early adulthood, and the majority of our sample was still quite young, COMT genotype might gain importance at a later point during development. Controls already show first indications of COMT effects, but since ADHD children are known to lag behind in normal development, this gene's influence has likely not yet taken hold.

4.3 Sensory Gating

COMT Regarding COMT, diagnostic groups without Met allele did not differ, whereas having a Met allele brought about worse sensory gating in unmedicated compared to medicated ADHD patients. Without Met allele, even patients without medication perform equal to controls, medication brings no additional benefit. The absence of an overall genotype (main) effect rules out that this is due to a floor or ceiling effect in either genotype group. This is in line with the study by Majic et al. (2011), who also did not find a main effect for COMT genotype on P50 gating ratios in a large sample of healthy subjects. However, the weaker suppression in unmedicated patients with Met allele compared to Val/Val homozygotes is mirrored by findings by Majic et al. (2011), who confirmed stronger N100 gating in their Val/Val group of healthy individuals, although the P50 peak captures a different aspect of sensory gating. In animal models receiving stimulant doses comparable to those administered to humans with ADHD, lead to an increase in prefrontal NE as well as DA (Berridge and Stalnaker, 2002). NE levels are associated with executive functioning and impulsiveness (Kieling et al., 2008, Hess et al., 2009) and more DA in the PFC enhances signal-to-noise ratio via eliminating background noise through stimulation of D1 receptors and making the cell less responsive to irrelevant stimulation (Vijayraghavan et al., 2007), but balance is crucial: both too much NE (Birnbaum et al., 2004) and too much DA (Vijayraghavan et al., 2007) disrupt PFC and cause the cells to cease firing altogether. The Met allele of the COMT gene slows down the degradation of catecholamines (DA and NE) in PFC and stimulants increase extracellular levels of DA and NE via transporter inhibition (also in the PFC), so the combination should bring the best results in terms of phasic prefrontal activity, whereas both too low levels (in

unmedicated ADHD) and too high levels (in controls) can interfere with targeted activity necessary for sensory gating. Stimulant medication put them just at the right end of the inverted U-shaped curve of optimal prefrontal catecholamine levels.

In both patient groups with at least one Met allele, greater degrees of suppression were associated with more false alarms in neuropsychological tests (e.g. CPT). This might be counter-intuitive seeing that the Met allele has frequently been found to be favourable for cognitive performance (e.g. Mattay et al., 2003), and intact sensory gating is a prerequisite for higher cognitive processing (Wan et al., 2008, Lijffijt et al., 2009a, Yadon et al., 2009). However, this apparent contradiction of the often observed better cognitive functioning in Met/Met carriers and worse suppression of potentially interfering sensory information might be explained in terms of a generally higher capacity for the processing of sensory information in the PFC. It is feasible that the PFC areas involved in sensory gating might purposefully reduce the suppression rate to take advantage of those resources. Alternatively, the nature of the tasks involved might mediate the relationship between sensory gating, genotype and performance. As the direction of the relationship between sensory gating and cognitive performance appears heterogeneous, task complexity might to be an important moderator. While it could be beneficial to have low filter settings for sensory information during some cognitive operations (e.g. interference in Stroop task, Yadon et al. 2009), it might be disadvantageous during others (e.g. Attention Network Test, Wan et al., 2008; inhibition in a Go/NoGo task, Yadon et al. 2009). Another possible explanation are the low cell counts in this tentative correlational analysis, especially since the relationship between False Alarm rate and P50 suppression was inverted in the n-back task in the medicated ADHD group ($r = -.914$, $p = .030$). It is also possible that despite a higher mean P50 suppression, patients could overall display more variable gating behaviour, as ADHD has been associated with increased variability in state regulation (Sergeant, 2005), and this would result in stretches of poor gating bringing about false alarm responses. Furthermore, studies uncovering sex as a mediating variable (Barnett et al., 2007: in healthy sample only COM effect in boys) or not finding any interactions between genotype and performance in executive

function tasks (Mills et al., 2004) illustrate the complex nature of the relationship between genotype and phenotype.

DAT Our finding that carriers of the DAT 9R allele in all diagnostic groups showed better gating is in line with the study by Millar et al. (2011), where these individuals were not only superior to homozygous 10R carriers but also were the only group where gating could be enhanced with nicotine, which downstream feeds into the same mechanisms as stimulant drugs. Findings that tobacco consumption led to an improvement of deficient sensory gating in schizophrenic patients (Millar et al., 2011) combined with the knowledge that one of the effects of nicotine is the release of DA (Grady et al., 2002) provided hints towards the involvement of the Dopaminergic system in sensory gating. Indeed, the authors observed a main effect of genotype on the P50 gating measure (9R > 10R) along with an effect for drug (nicotine > placebo). Lower expression of DAT in the 9R carriers signifies greater availability of DA in the striatum (Fuke et al., 2001) and thus better dopaminergic tone. Striatal DA levels are also crucial for prefrontal functioning as the striato-thalamo-cortical loop regulates cognitive and motor behaviour and impulsivity, and the DAT 3' VNTR modulates prefrontal activation in healthy individuals (Bertolino et al., 2006, Caldu et al., 2007, Yacubian et al., 2007). Potentially the lower suppression rate in homozygous 10R carriers masked any improvements medication might have had, even though better responses to methylphenidate have been reported for the 10R (Kirley et al., 2003, Stein et al., 2005). On the other hand having at least one 9R allele brought out differences between medicated and unmedicated patients, possibly due to a higher baseline suppression capacity. Kooij (2008) found that carriers of one 10R - the risk allele for childhood ADHD (Franke et al., 2010) - responded better to stimulants than 10/10 (Kooij et al., 2008), which makes sense since for stimulants to be considered effective, at least 50% of striatal DAT needs to be blocked, and that's harder to accomplish when there is a higher expression of DAT. DAT density and its affinity for its substrates DA und NE determine striatal Dopaminergic functioning. Within the DAT gene, the 10R allele confers increased availability of DAT in the striatum compared to the 9R (Heinz et al., 2000). It follows that DA and NE are cleared from the synaptic cleft

at a much quicker pace and this might contribute to impaired sensory gating, as the neurotransmitters are being made available for the initiation of subsequent action potentials (e.g. P50 to the second stimulus in the paired click-tone paradigm). Adler et al. (1988) found an increase in the NE metabolite 3-methoxy 4-hydroxyphenylglycol (MHPG) indicative of greater amounts of degraded NE to go along with impaired P50 suppression in acute mania, and treatment normalising plasma MHPG levels corresponded to a normalisation in gating. Stimulants can normalise gating, as they block the reuptake and thus degradation of DA and NE, which leads to less neurotransmitter agents in the pre-synapse and smaller likelihood of a second action potential. So our finding that stimulant medication improves sensory gating only in the non-homozygous 10R group fits with previous research.

LPHN3 Notably, we found an interaction of LPHN3 genotype with diagnostic group. Unmedicated patients who had the risk haplotype were impaired in terms of sensory gating, while for controls this very same haplotype actually promoted better gating ratios. As exploratory correlational analyses showed, better sensory gating led to more errors of omission in medicated ADHD and this relationship was reversed in patients without medication, where better gating was accompanied by less errors of omission in the n-back task. When receiving stimulant medication, having the LPHN3 risk haplotype laid the ground for a negative relationship between gating capacity and false alarms (CPT), whereas having not having all risks SNPs meant better gating went along with more errors of omission (n-back). Among control children, those without the risk haplotype showed a positive relationship between P50 suppression and speed and variability of reaction times: The better the gating the slower and less consistent the responses, i.e. more variable. The thalamus as the brain's most important relay station, where decisions about what will be passed on to higher sensory association areas and what will be blocked are made, is one of the generators of the P50 response (Tregellas et al., 2009, Williams et al., 2011). LPHN3 is expressed in thalamic nuclei and the risk haplotype has been found to be associated with decreased neural activity in thalamus and striatum and an increase in the cerebellar vermis (Arcos-Burgos et al., 2010). So better suppression rates in carriers of the risk haplotype might be explained

by less activation of thalamic areas, which in turn exert less stimulating influence on higher auditory cortical areas.

4.4 Response Time Variability

ADHD children without medication had an increased variability of responses only in comparison to patients receiving psychostimulants, since those showed a slightly attenuated RTV even compared to controls. Medication seems to decrease RTV to below-normal levels, and this suggests stimulants drugs help with poor state regulation, even though the difference to controls did not reach statistical significance. This is in line with previous reports on improved RTV under psychostimulants in healthy individuals (Nandam et al., 2011) and ADHD samples (Uebel et al., 2010). Uebel et al. (2010) studied a range of behavioural parameters in a non-cued go/NoGo task with a comparable age range. ADHD children and adolescents had more variable but slower responses than controls, while unaffected siblings had intermediate scores in terms of RTV and both error types. In an exploratory manner, we additionally looked at changes in RTV over time. Arranging the tasks by their order in our investigation and adding diagnostic group as a factor, we did however only find a general increase in variability over the course of one session that was not more pronounced in ADHD. Response time variability was increased for homozygous 10R carriers (DAT) and carriers of at least one Met allele (COMT). This has been reported previously in ADHD children (Bellgrove et al., 2005; Loo et al., 2003). Two other studies did not find any implications of the DAT VNTR on variability of responses (Cummins et al., 2011; Oh et al., 2003), however Oh (2003) investigated a sample of Korean boys, and there are well-known differences in different ethnicities, which might explain the divergent findings. And Cummins (2011) compared SD of Go reaction times in the SSRT between in healthy young adults, and this age group might have been on the cusp of DAT risk genotypes switching.

4.5 Exploratory catamnestic analysis

The overarching finding when looking for the effect of time on electrophysiological parameters was a marked decrease in amplitude combined with a quickening of

responses, i.e. shorter latencies at the second measurement. We could prove that there was a No-Go-Anteriorization at the second measurement. Unfortunately the subsample returning for the second wave of testing was too small for a meaningful study of interactions between diagnostic group and genotype. However, one would expect DAT to become less important for the ADHD phenotype with age, as it is mainly expressed in the striatum and might thus be more relevant for the motor hyperactivity, decreases with age. This might be indicative of compensatory mechanisms taking effect, possibly due to better prefrontal control, as this structure only fully matures by late adolescence. At the second measurement point, only condition and group modulated centroid locations, with the centre of the positive brain electric field being more at frontal sites during inhibition compared to response execution trials, thus confirming the existence of NGA at T2. Receiving stimulant medication went along with more anterior inhibitory activity as well as faster and less variable reactions compared to unmedicated ADHD.

N200 amplitudes did show an attenuation over time, as the strength of the response was smaller at the second measurement point. In addition to being smaller in magnitude, latencies also decreased, potentially paving the way for faster signalling of response conflicts. These effects were independent of condition and diagnostic group, both Go and NoGo amplitudes decreased to a similar extent in patients and controls. NoGo signals led to an earlier N200. This could however not be found at T2 and potentially hints towards higher processing demands of response execution commands in younger children. Of our candidate genes, only DAT exerted an influence on the development of the N200. Homozygous 10/10 carriers had lower Go amplitudes compared to people with at least one 9R allele at both T1 and T2. Latencies were delayed for homozygous 10R carriers at T2. The overall acceleration of N200 over time and the greater NoGo amplitude could be found for all DAT genotypes.

We could confirm the existence of an NGA at both measurement points in terms of centroid location, however there was no difference between T21 and T2, nor did the diagnostic groups develop along different paths. It is possible that the catamnestic

time frame was either too short or didn't capture a critical developmental period. Relatively low NGA values compared to previous publications speak to that (e.g. 0.36 for ADHD and 0.50 for controls in Dresler et al., 2010; 0.59 for ADHD and 0.67. for controls in Fallgatter et al., 2009). For P300, we looked both at Global Field Power and values at the respective peak sites – Cz for NoGo and Pz for Go. Both kinds of P300 amplitudes showed a decrease between measurement points. When comparing peaks at individual electrode sites, it also emerged that Go stimuli evoked faster reactions than NoGo signals, and those were also greater in magnitude.

Response Inhibition During response inhibition, this held true for N200 and P300 peaks both in terms of Global Field Power and at individual electrode sites during the response inhibition task. Amplitude decrease with age fits with previous research findings for target P300 (Fjell & Walhovd, 2004), whereas the negative relationship of age and P300 latency is in stark contrast with these authors' findings. It does however fit with the study by Stige et al., (2007), who also observed a quickening of P300b responses in addition to extending the known development of P300 amplitudes by identifying an increase in later life following the initial attenuation of the evoked response. The same U-shaped course has previously been described for P300 latencies as well, with latencies starting to increase again in early to late twenties [(e.g. (Mullis et al., 1985). Faster and more efficient responses from childhood to adolescence could be indicative of the fact that the demands of a given task subjectively decrease with brain maturation, until after a switch point in adult life age again necessitates the recruitment of to achieve comparable results. Neither the Go nor the NoGo centroid locations showed developmental effects in comparisons between measurement points as a two; consequentially the NGA also remained unaffected by time. This corresponds well to reports on the relative independence of age on NGA (Fallgatter et al., 1999), however we were hoping to gain insight into the age at which NGA first emerges as a stable phenomenon. To this end, we conducted additional nonparametric correlational analyses between the two parameters. We did not find significant correlations between age and NGA, neither in the total sample nor in the individual diagnostic groups. We could however replicate the negative relationship between age and

locations of both Go and NoGo centroids at T1. Differences in P300 amplitudes were no longer identifiable at T2 in our study, which is in contrast with Doehnert et al., (2010) postulating the temporal stability or rather progressive nature of a reduced NoGo- P300 in ADHD. This was not the case in our sample, where NoGo amplitude was unrelated to age in control and ADHD patients, regardless of whether medicated and unmedicated cases were examined independently or grouped together. However, differences in age composition of the samples and catamnestic period (3.5 years in the present study vs. 2.5 years in Doehnert et al., 2010) might have contributed to the divergent results.

Working memory For the working memory task, only interactions of time and diagnostic groups will be discussed, since we were primarily interested in diverging developmental paths between ADHD children and healthy controls, and potential modifying effects of stimulant medication. In longitudinal analyses involving COMT genotype as a factor, timing of N100 was moderated by an interaction of time, diagnostic group and COMT genotype: While both genotype groups showed the expected latency decrease, individual analysis within each diagnostic group revealed that only unmedicated ADHD patients and healthy controls speeded up their N100 responses over time. Psychostimulants seem to interfere with early responses involved in stimulus discrimination getting more automated and thus faster with age. To conclusively determine the underlying mechanism, future research need to address this question with a within-subject comparison on and off medication. In a previous study on early auditory and visual potentials in working memory tasks (Pelosi & Blumhardt, 1999), no age effects on latency were observed in healthy adults (aged 19-71), which suggest that medication might delay this adaptive process that reaches a plateau at the end of adolescence. At the second measurement point controls had lower amplitudes P100 than either ADHD group, while the latency decrease from T1 to T2 was only present in unmedicated patients. Regarding P300 amplitudes, differences between diagnostic groups were limited to T2, where controls responded more strongly than ADHD patients.

4.6 Limitations

There were several limitations to the present study. As is common practise in examinations of ADHD populations, the sample comprised considerably more males than females, and patients were only of the combined subtype. For better generalizability and to compare the distinct phenotypical manifestations of ADHD on an electrophysiological level, it is necessary to invest in the recruitment of a more diverse sample of sufficient size. Correspondingly, for analyses of genetic contributions to electrophysiological endophenotypes, a bigger sample is better suited to elucidate interactions between diagnostic status, sex and genotype, which was not possible within the framework of this study. It would have been interesting to check for sex differences both in the developmental trajectories and moderating effects of this variable on genotype. In particular, we would have been interested in looking into gene-by-gene interactions as well, as previous studies have shown genes e.g. of the Dopaminergic system to act in concert to modulate phenotypes and underlying neuronal processes. Bertolino et al. (2006) demonstrated additive effects of COMT and DAT on working memory related brain activity with functional brain imaging methods functional magnetic resonance imaging and near-infrared-spectroscopy, hinting at more focused and thus efficient activation of the respective areas. It would be interesting to see how this affects Event-Related Potentials. The main issues regarding longitudinal questions were the small sample size at T2 and inhomogeneous intervals between measurement points. This neither allowed for the sub-division of the sample according to sex nor was it sensitive for genotype effects.

Supplementary

Appendix A: Instructions and Questionnaires

A1: Information for Participants and Confirmation of Consent

DFG - Klinische Forschergruppe

Aufmerksamkeitsdefizit-/Hyperaktivitätssyndrom - Molekulare Pathogenese und Endophänotypen im Therapieverlauf

Teilprojekt 1

Charakterisierung von Patient/innen mit Aufmerksamkeitsdefizit-/Hyperaktivitätssyndrom (ADHS) unter Einschluss familiengenetischer Untersuchungsstrategien und Längsschnittbeobachtung

Sehr geehrte Frau, sehr geehrter Herr.....

Wir haben uns die Aufgabe gestellt, im Rahmen eines von der deutschen Forschungsgemeinschaft (DFG) geförderten Projektes, die Symptome und den Verlauf des Aufmerksamkeitsdefizit-/Hyperaktivitätssyndrom (ADHS) bzw. des hyperkinetischen Syndroms zu untersuchen. Wir möchten Sie herzlich bitten, uns in dieser wichtigen Aufgabe zu unterstützen. Sie würden damit einen sehr wertvollen Beitrag zur Erforschung des hyperkinetischen Syndroms leisten und mithelfen, die Behandlungsmöglichkeiten in Zukunft weiter zu verbessern. Dieses Informationsblatt fasst die wesentlichen Aspekte des oben genannten Forschungsprojektes zusammen. Sie wurden bereits ausführlich hierzu von einer/m Ärztin/Arzt, die/der an dem Projekt mitarbeitet, über das Vorgehen und den Zweck der Untersuchung informiert. Falls Sie weitere Fragen haben, wenden Sie sich bitte an Herrn Dr. Romanos mit dem Stichwort „Katamnese“ (Tel.: 0931/201- 78600) oder an die Ihnen bekannten Kontaktpersonen.

Die klinischen Untersuchungen werden koordiniert von

Frau PD. C. Mehler-Wex und Herrn Prof. Dr. A. med. Warnke,
Klinik für Kinder und Jugendpsychiatrie und Psychotherapie der Universität Würzburg

Bisherige wissenschaftliche Erkenntnisse zur Erblichkeit des Aufmerksamkeitsdefizit-/Hyperaktivitätssyndroms

Bei dem Aufmerksamkeitsdefizit-/Hyperaktivitätssyndrom handelt es sich um eine Störung, die ca. vier Prozent aller Knaben und ein Prozent aller Mädchen betrifft. An der Entstehung dieser Störung wirken sowohl Umwelt- als auch genetische Faktoren mit. Man geht davon aus, dass bei gegebener erblicher Veranlagung Umwelteinflüsse die Symptomatik verhindern oder aber verstärken können. Die Bedeutung von erblichen

Faktoren lässt sich aufgrund von Zwillings-, Adoptions- und Familienstudien nachweisen. So sind beispielsweise häufig bei einem eineiigen Zwillingspaar beide Zwillinge, bei einem zweieiigen Zwillingspaar hingegen nur ein Zwilling von der Störung betroffen. Allgemein ist des Weiteren bekannt, dass Eltern, besonders Väter von Kindern mit einem hyperkinetischen Syndrom selbst eine entsprechende Symptomatik in ihrer Kindheit hatten bzw. aktuell noch aufweisen. So wissen wir, dass die typischen Symptome des Aufmerksamkeitsdefizit-/Hyperaktivitätssyndroms– motorische Hyperaktivität, Aufmerk-samkeitsstörung und Impulsivität – in der Regel nicht über das gesamte Leben durchgängig vorhanden sind. Vielmehr treten diese Symptome ganz besonders stark im Kindesalter auf. Während die Impulsivität und die Aufmerksamkeitsstörung häufig auch noch im Erwachsenenalter anhalten, lässt die motorische Hyperaktivität bei vielen Betroffenen im Jugendalter deutlich nach. Aufgrund dieser Zusammenhänge ist es wichtig, dass bei einer Untersuchung zur Erblichkeit des Aufmerksamkeitsdefizit-/Hyperaktivitätssyndroms (ADHS) nicht nur nach gegenwärtig vorhandenen Symptomen sondern auch nach solchen in der Vergangenheit und besonders im Kindesalter gefragt wird.

Ziele der Untersuchung

Unser Forschungsprojekt dient dem genauen Erkennen und Beschreiben (Charakterisierung) der Symptome der Patienten mit ADHS und bei Ihren Eltern. Eine Blutentnahme von 20 ml Blut erfolgt zur Erkennung von Erbanlagen, die an der Entstehung des Aufmerksamkeitsdefizit-/Hyperaktivitätssyndroms ADHS beteiligt sind. Um dies zu ermöglichen, wird die Erbsubstanz (DNA) von den betroffenen Kindern und deren Angehörigen untersucht. Sehr vereinfacht ausgedrückt geht es darum, spezifische Genvarianten zu identifizieren, die bei von einem hyperkinetischen Syndrom Betroffenen häufiger als bei Nichtbetroffenen vorkommen. Darüber hinaus gibt es aber auch beispielsweise Familienuntersuchungen, bei denen ermittelt wird, ob bestimmte Genvarianten häufiger als erwartet von den Eltern an die Kinder weitervererbt werden. Wenn zwei oder mehr Geschwister erkrankt sind, wird untersucht, ob diese überzufällig häufig den gleichen DNA-Abschnitt von ihren Eltern ererbt haben. Für solche Untersuchungen benötigt man auch eine umfassende statistische Auswertung, da nur hierdurch gewährleistet ist, dass tatsächlich die relevanten Varianten identifiziert werden können. Weiterhin möchten wir Erkenntnisse über den Verlauf der ADHS erhalten, da die Symptome im Erwachsenenalter teilweise abnehmen, zum Teil jedoch bestehen bleiben und sich verändern können. Wir werden Sie daher im Abstand von mehreren Jahren erneut in unsere Ambulanz einladen, um an den Verlaufsuntersuchungen teilzunehmen. Auch die Teilnahme an diesen Untersuchungen ist selbstverständlich jederzeit freiwillig.

Untersuchungen in der Klinik und Poliklinik für Kinder- und Jugendpsychiatrie der Universität Würzburg

Ausführliche Untersuchung und Diagnostik Ihres Kindes

Um eine genaue Einschätzung von den Problemen Ihres Kindes zu bekommen, benötigen wir eine Reihe von Informationen von Ihnen und Ihrem Kind. Wir möchten Sie deshalb bitten, einige Fragebögen über das Verhalten Ihres Kindes auszufüllen und möchten auch eine kurze Einschätzung der Symptomatik durch den Lehrer einholen. Ferner werden wir Ihnen Fragen

darüber stellen, ob neben dem hyperkinetischen Syndrom noch weitere Auffälligkeiten bei Ihrem Kind bestehen. Mit Ihrem Kind werden wir einige Aufgaben, zum Teil am Computer durchführen, um eine objektive Einschätzung seiner kognitiven Fähigkeiten und seiner Konzentrationsprobleme zu bekommen. Ferner soll Ihr Kind zwei kurze Fragebögen zu seiner Stimmung und zu möglichen Ängsten ausfüllen. Da wir in dieser Studie insbesondere an der Erblichkeit des hyperkinetischen Syndroms interessiert sind, möchten wir Sie ferner darüber befragen, inwieweit Sie in der Kindheit auch unter bestimmten typischen Symptomen gelitten haben bzw. ob diese gegenwärtig noch vorhanden sind. Die Untersuchungsdauer Ihres Kindes wird ca. 120 Minuten betragen. Für das Ausfüllen der Fragebögen und die Durchführung der Interviews (bei zwei betroffenen Kindern) werden wir ca. 2 Stunden Ihrer Zeit beanspruchen. Wir werden versuchen, möglichst zeitlich flexibel und parallel Ihre Befragung und die Untersuchung Ihres Kindes durchzuführen.

Verlaufsuntersuchung

Die Familien, welche an der Studie teilnehmen, werden im Abstand von mehreren Jahren erneut eingeladen, um an einer Verlaufsuntersuchung teilzunehmen. Die Symptome der ADHS können im Laufe der Zeit Veränderungen unterliegen. Bislang ist ungeklärt, warum in manchen Fällen einzelne oder alle Symptome bestehen bleiben oder abnehmen. Auch können die langfristigen psychosozialen Folgen sehr unterschiedlich sein. Für das Verständnis der ADHS und um zukünftig eine optimale Therapie gewährleisten zu können, ist es notwendig, die Ursachen für die unterschiedliche Entwicklung der Störung zu erkennen. Zu diesem Zweck laden wir die teilnehmenden Familien im Abstand von 3 Jahren erneut ein, um erneut eine genaue klinische Untersuchung mit den gleichen Untersuchungsmethoden wie bei der Erstuntersuchung durchzuführen. Dadurch kann ein eventueller Wandel der Symptomatik erfasst werden. Wenn Ihr Kind bereits die Volljährigkeit erreicht haben, werden die Verlaufsuntersuchungen durch Teilprojekt 2 (Erwachsenenpsychiatrie) durchgeführt werden. Für diesen Fall wird eine gesonderte Einladung und separate Aufklärung erfolgen.

Untersuchungen zur funktionellen Molekulargenetik

Um molekulargenetische Untersuchungen durchführen zu können, benötigt man die Erbsubstanz. Diese wird aus den weißen Blutkörperchen gewonnen. Insofern ist es erforderlich, dass sowohl bei dem Betroffenen als auch dessen Eltern und ggf. betroffenen Geschwistern eine Blutentnahme zur Gewinnung der DNA erfolgt. Hierbei werden 20 ml Blut benötigt. Auch für ein Kind ist die Entnahme einer solchen Blutmenge unbedenklich. (Ein separates Informations- und Aufklärungsblatt liegen bei).

Untersuchungen zur Neurophysiologie

Das Elektroenzephalogramm (EEG) erfasst an der Kopfoberfläche die schwachen elektrischen Ströme, mit denen das Gehirn arbeitet. Hierfür werden Ihrem Kind zunächst mittels einer Paste schmerzfrei Meßelektroden auf die Kopfhaut geklebt. Ihr Kind soll dann den „Continous performance Test“ durchführen, bei dem es z.B. auf bestimmte an einem Bildschirm dargebotene Buchstaben mit Knopfdruck reagieren oder nicht reagieren soll. Die Dauer beträgt 90 min. Nebenwirkungen sind nicht

bekannt. (Ein separates Informationsblatt und eine separate Einwilligungserklärung erhalten Sie von der neurophysiologischen Abteilung vor der Untersuchung.)

Untersuchung am Institut für Psychologie der Universität Würzburg
Psychobiologie

Das ADHS ist häufig verbunden mit der Tendenz auf positive Ereignisse geringere Reaktionen zu zeigen. In dem ersten Versuch wird Ihr Kind z.B. kleine Belohnungen erhalten für Reaktionen auf nicht relevante Reize, die einem (harmlosen) Schreck auslösenden Reiz vorangehen. In einem zweiten Versuch sollen Reaktionen erfasst werden auf positiv und negativ besetzte Bilder, die Ihnen, wenn Sie es wünschen, gerne vorher gezeigt wurden. Die Dauer beträgt 120 min. Nebenwirkungen sind nicht bekannt. (Ein separates Informationsblatt und eine separate Einwilligungserklärung erhalten Sie von der biologischen und klinischen Psychologie vor der Untersuchung).

Untersuchungen in der Abteilung für Neuroradiologie des Instituts für Röntgendiagnostik der Universität Würzburg

Funktionelle Magnetresonanztomographie

Einige wenige Patienten und Probanden sollen mit einem modernen radiologischen Verfahren untersucht werden, das nicht nur die Struktur, sondern auch die Funktion umschriebener Regionen des Gehirns darstellt. Die Magnetresonanztomographie benötigt für diese Darstellung im Gegensatz zu anderen Verfahren keine radioaktiv markierten Substanzen. Ich Kind sieht eine Serie von Buchstaben auf einer Leinwand und soll auf eine bestimmte selten vorkommende Buchstabenkombination reagieren. Die Dauer der Untersuchung beträgt 40 min. Die Strahlenbelastung überschreitet nicht das Maß der radiologischen Routineverfahren. (Ein separates Informationsblatt und eine separate Einwilligungserklärung erhalten Sie von der Neuroradiologie vor der Untersuchung).

Laboruntersuchung bei medikamentöser Behandlung

Falls bei Ihrem Kind eine Aufmerksamkeitsdefizit/Hyperaktivitätsstörung vorliegt und Ihr Kind mit einem Medikament behandelt werden sollte, sind immer vor Beginn der Behandlung die Blutwerte zu untersuchen, nach Beginn der Behandlung werden die Blutwerte in größeren Abständen kontrolliert, um Nebenwirkungen ausschließen zu können. Im Rahmen dieser Blutuntersuchungen, würden wir gerne bei den ersten 3 Kontrolluntersuchungen einen kleinen Teil der Blutabnahmen (jeweils 5 ml) abtrennen, um weitere mögliche Nebenwirkungen untersuchen bzw. ausschließen zu können. Zusätzliche Blutentnahmen sind dafür nicht notwendig.

Ablauf

Die Untersuchungen erfolgen während der stationären oder ambulanten Behandlung Ihres Kindes, ohne dass Verzögerungen der Behandlung oder des Entlasszeitpunktes resultieren. Die geplanten Untersuchungen werden in einem Zeitraum von 2-3 Wochen durchgeführt, so dass die Untersuchungen nicht zu einer Belastung führen. Sie werden vor den entsprechenden Untersuchungen jeweils mit den entsprechenden Einverständniserklärungen in persönlichen Gesprächen noch einmal aufgeklärt.

Welche Vor- und Nachteile gibt es für Sie und Ihr Kind?

Durch Ihre Bereitschaft an der Untersuchung teilzunehmen, leisten Sie einen wichtigen Beitrag zur Erforschung der möglichen Ursachen des Aufmerksamkeitsdefizit-

/Hyperaktivitätssyndroms (ADHS). Die gewonnenen Erkenntnisse könnten möglicherweise zur Entwicklung neuer und besserer Medikamente beitragen. Ein unmittelbarer Nutzen besteht gegenwärtig jedoch weder für Sie noch Ihre Familienangehörigen. Wie bei jeder herkömmlichen Blutentnahme können an der Einstichstelle vorübergehende Reizungen auftreten.

Freiwilligkeit. Können Sie oder Ihr Kind aus der Untersuchung wieder ausscheiden?
Selbstverständlich ist Ihre Teilnahme an dieser Untersuchung und den unterschiedlichen Teiluntersuchungen freiwillig. Sie können die Untersuchung oder Teiluntersuchungen jederzeit und ohne Angabe von Gründen abbrechen, ohne dass sich dadurch Nachteile für Ihre weitere ärztliche Versorgung ergeben. Wenn Sie es wünschen, vernichten wir Ihre Blutprobe bzw. die aus den weißen Blutkörperchen gewonnene Erbsubstanz (DNA).

Wie vertraulich werden die ermittelten Daten behandelt?
Die im Rahmen dieses Forschungsprojektes erhobenen Daten aus den Interviews, der verschiedenen Untersuchung, einschließlich auch der Untersuchungen der Erbsubstanz werden in Computersystemen der beteiligten Kliniken und Forschungseinrichtungen in anonymisierter Form auf unbestimmte Zeit gespeichert.
Die Schlüsselliste, die allein eine Zuordnung der Daten zu den untersuchten Personen gestattet, verbleibt unter Verschluss in unserer Klinik. Sobald der Forschungszweck erreicht ist – ein Zeitpunkt lässt sich derzeit nicht angeben – wird die jeweilige Schlüsselliste gelöscht. Bis zu diesem Zeitpunkt wird die Schlüsselliste in einem verschlossenen Raum der jeweiligen Klinik aufbewahrt und die Datenspeicherung- und Bearbeitung erfolgt in anonymisierter Form.
Im Rahmen von Projekten mit anderen Forschungseinrichtungen werden häufig wissenschaftliche Daten ausgetauscht. Hierbei können Daten zu Ihrem Kind oder Ihrer Person in anonymisierter Form an derartige Forschungseinrichtungen möglicherweise in Zukunft weitergegeben werden. In keinem Fall werden die Namen von Personen bzw. Familien weitergegeben, die an der Untersuchung teilgenommen haben.

Name der Kontaktpersonen
Bei Rückfragen wenden Sie sich bitte zunächst an die verantwortlichen Studienleiter der jeweiligen Klinik oder an:

Dr. med. M. Romanos, Fr. Dr. med. Wirth, Stichwort „Katamnese“
Klinik und Poliklinik für Kinder- und Jugendpsychiatrie und Psychotherapie der Universität Würzburg;
Füchsleinsstraße; 97080 Würzburg
Tel.: 0931/ 201-78600 od. 77590
Fax: 0931/ 201-78620

Wir möchten uns bei Ihnen für Ihre Mitarbeit ausdrücklich bedanken!

Würzburg, den 1.9.2003, geändert am 01.05.2005, 06.11.2006, 29.11.2006 und 08.07.2008.

Prof. Dr. A. Warnke und PD Dr. C. Mehler-Wex

DFG - Klinische Forschergruppe
Aufmerksamkeitsdefizit-/Hyperaktivitätssyndrom - Molekulare Pathogenese und Endophänotypen im Therapieverlauf

Teilprojekt 1
Charakterisierung von Patient/innen mit Aufmerksamkeitsdefizit-/Hyperaktivitätssyndrom (ADHS) unter Einschluss familiengenetischer Untersuchungsstrategien und Längsschnittbeobachtung

Einwilligungserklärung

Die Teilnahme an der Studie ist freiwillig, das Einverständnis kann jederzeit (auch für einzelne Teile der Studie widerrufen werden) ohne Angabe von Gründen und ohne Nachteile für Sie widerrufen werden.
Ihre Angaben und die Ihres Kindes werden selbstverständlich streng vertraulich behandelt. Sie werden niemandem außerhalb der an der Untersuchung beteiligten Ärzte zugänglich gemacht. Schriftliche Aufzeichnungen werden in der Klinik sicher verwahrt. Die Auswertung der Daten, einschließlich deren wissenschaftlichen Veröffentlichung erfolgt ohne Namensnennung, so dass keinerlei Rückschlüsse auf Ihre Person möglich sind. Die Datenschutzbestimmungen werden eingehalten.

Ich erkläre, dass ich dieses Informationsblatt gelesen und verstanden habe und meine Fragen durch Dr. med. …….. zufrieden stellend beantwortet wurden. Ich bin mit der Teilnahme an der obigen Untersuchung und der Speicherung meiner Dateien unter Beachtung aller relevanten datenschutzrechtlichen Aspekte einverstanden und habe keine weiteren Fragen. Ich kann jederzeit das Einverständnis zur Teilnahme an dem gesamten oder einzelnen Vorhaben widerrufen, ohne dass mir dadurch Nachteile entstehen.

....., den .....

_____ _____

_____

Unterschrift des aufklärenden Arztes

Unterschriften der Erziehungsberechtigten

A2: DSM-IV Criteria

Diagnostische Kriterien für Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung
aktuell

A. Entweder Punkt (1) oder Punkt (2) müssen zutreffen:

(1) sechs (oder mehr) der folgenden Symptome von Unaufmerksamkeit sind während der letzten 6 Monate beständig in einem mit dem Entwicklungsstand des Kindes nicht zu vereinbarenden und unangemessenen Ausmaß vorhanden gewesen:

Unaufmerksamkeit

(a) beachtet häufig Einzelheiten nicht oder macht Flüchtigkeitsfehler bei den Schularbeiten, bei der Arbeit oder bei anderen Tätigkeiten
(b) hat oft Schwierigkeiten, längere Zeit die Aufmerksamkeit bei Aufgaben oder beim Spielen aufrechtzuerhalten
(c) scheint häufig nicht zuzuhören, wenn andere ihn/sie ansprechen
(d) führt häufig Anweisungen anderer nicht vollständig durch und kann Schularbeiten, andere Arbeiten oder Pflichten am Arbeitsplatz nicht zu Ende bringen (nicht aufgrund oppositionellen Verhaltens oder Verständnisschwierigkeiten)
(e) hat häufig Schwierigkeiten, Aufgaben und Aktivitäten zu organisieren
(f) vermeidet häufig, hat eine Abneigung gegen oder beschäftigt sich häufig nur widerwillig mit Aufgaben, die länger andauernde geistige Anstrengungen erfordern (wie Mitarbeit im Unterricht oder Hausaufgaben)
(g) verliert häufig Gegenstände, die er/sie für Aufgaben oder Aktivitäten benötigt (z.B. Spielsachen, Hausaufgabenhefte, Stifte, Bücher oder Werkzeug)
(h) lässt sich öfter durch äußere Reize leicht ablenken
(i) ist bei Alltagstätigkeiten häufig vergesslich

(2) sechs (oder mehr) der folgenden Symptome der Hyperaktivität und Impulsivität sind während der letzten 6 Monate beständig in einem mit dem Entwicklungsstand des Kindes nicht zu vereinbarenden und unangemessenen Ausmaß vorhanden gewesen:

Hyperaktivität

(a) zappelt häufig mit Händen oder Füßen oder rutscht auf dem Stuhl herum
(b) steht in der Klasse oder in anderen Situationen, in denen Sitzenbleiben erwartet wird, häufig auf
(c) läuft häufig herum oder klettert exzessiv in Situationen, in denen dies unpassend ist (bei Jugendlichen oder Erwachsenen kann dies auf ein subjektives Unruhegefühl beschränkt bleiben)
(d) hat häufig Schwierigkeiten, ruhig zu spielen oder sich mit Freizeitaktivitäten ruhig zu beschäftigen
(e) ist häufig „auf Achse“ oder handelt oftmals, als wäre er/sie „getrieben“
(f) redet häufig übermäßig viel

Impulsivität

(g) platzt häufig mit den Antworten heraus, bevor die Frage zu Ende gestellt ist
(h) kann nur schwer warten, bis er/sie an der Reihe ist

(i) unterbricht und stört andere häufig (platzt z.B. in Gespräche oder in Spiele anderer hinein)

B. Einige Symptome der Hyperaktivität-Impulsivität oder Unaufmerksamkeit, die Beeinträchtigungen verursachen, treten bereits vor dem Alter von sieben Jahren auf.
C. Beeinträchtigungen durch diese Symptome zeigen sich in zwei oder mehr Bereichen (z.B. in der Schule bzw. am Arbeitsplatz und zu Hause).
D. Es müssen deutliche Hinweise auf klinisch bedeutsame Beeinträchtigungen der sozialen, schulischen oder beruflichen Funktionsfähigkeit vorhanden sein.
E. Die Symptome treten nicht ausschließlich im Verlauf einer tiefgreifenden Entwicklungsstörung, Schizophrenie oder einer anderen Psychotischen Störung auf und können auch nicht durch eine andere psychische Störung besser erklärt werden (z.B. Affektive Störung, Angststörung, Dissoziative Störung oder eine Persönlichkeitsstörung)

Codiere je nach Subtypus:
314.01 (F90.0) Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung, Mischtypus: liegt vor, wenn die Kriterien A1 und A2 während der letzten 6 Monate erfüllt waren
314.00 (F98.8) Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung, Vorwiegend Unaufmerksamer Typus: liegt vor, wenn Kriterium A1, nicht aber Kriterium A2 während der letzten 6 Monate erfüllt war
314.01 (F90.1) Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung, Vorwiegend Hyperaktiv-Impulsiver Typus: liegt vor, wenn Kriterium A2, nicht aber Kriterium A1 während der letzten 6 Monate erfüllt war

Codierhinweise: Bei Personen (besonders Jugendlichen und Erwachsenen), die zum gegenwärtigen Zeitpunkt Symptome zeigen, aber nicht mehr alle Kriterien erfüllen, wird Teilremittiert spezifiziert.

A3: Child Behaviour Check List (CBCL)

Sie finden im folgenden eine Reihe von Aussagen über bestimmte Verhaltensweisen, die auf Kinder und Jugendliche zutreffen können. Prüfen Sie bitte bei jeder Aussage, ob sie auf Ihren Sohn/Ihre Tochter **jetzt** oder innerhalb der **letzten 6 Monate** zutrifft.
Wenn das Verhalten Ihren Sohn/Ihre Tochter ziemlich genau kennzeichnet oder häufig auftritt, kreuzen Sie bitte die 2 an. Wenn die Aussage etwas oder manchmal zutrifft, kreuzen Sie bitte die 1 an. Wenn Ihr Sohn/Ihre Tochter das Verhalten nicht zeigt (nicht zutreffend), so kreuzen Sie bitte die 0 an.

0 = nicht zufreffend ***1 = etwas/manchmal*** ***2 = genau/häufig***

1. Verhält sich zu jung für sein/ihr Alter	0	1	2
2. Leidet unter einer Allergie	0	1	2
Bitte beschreiben: _____			
3. Streitet sich, widerspricht	0	1	2
4. Leidet unter Asthma	0	1	2
5. Bei Jungen: verhält sich wie ein Mädchen	0	1	2
Bei Mädchen: verhält sich wie ein Junge	0	1	2
6. Kotet ein	0	1	2
7. Gibt an, schneidet auf (prahlt)	0	1	2
8. Kann sich nicht konzentrieren, begrenzte Aufmerksamkeit	0	1	2
9. Kommt von bestimmten Gedanken nicht los	0	1	2
Bitte beschreiben: _____			
10. Kann nicht still sitzen, ist zappelig, zu aktiv	0	1	2
11. Ist für sein/ihr Alter zu abhängig von Erwachsenen	0	1	2
12. Beklagt sich über Alleinsein, fühlt sich einsam	0	1	2
13. Ist verwirrt oder zerstreut	0	1	2
14. Weint viel	0	1	2
15. Ist grausam zu Tieren	0	1	2
16. Ist gemein, rücksichtslos, schüchtert andere ein	0	1	2
17. Hat Tagträume, ist gedankenverloren	0	1	2
18. Hat sich absichtlich verletzt oder Selbstmord versucht	0	1	2
19. Fordert viel Aufmerksamkeit und Beachtung	0	1	2
20. Macht seine/ihre Sachen kaputt	0	1	2
21. Macht Sachen kaputt, die anderen gehören	0	1	2
22. Ist zu Hause/den Eltern gegenüber ungehorsam	0	1	2
23. Ist in der Schule ungehorsam	0	1	2
24. Ißt schlecht	0	1	2
25. Kommt mit anderen im gleichen Alter nicht aus	0	1	2
26. Fühlt sich nicht schuldig, wenn er/sie etwas Unerlaubtes getan hat	0	1	2
27. Wird leicht eifersüchtig	0	1	2
28. Ißt oder trinkt Dinge, die ungenießbar sind	0	1	2
Bitte beschreiben: _____			
29. Fürchtet sich vor bestimmten Tieren, Situationen oder Plätzen (Schule ausgenommen)	0	1	2
Bitte beschreiben: _____			
30. Hat Angst zur Schule zu gehen	0	1	2
31. Befürchtet, er/sie könnte etwas Schlimmes denken oer tun	0	1	2
32. Glaubt, perfekt sein zu müssen	0	1	2
33. Fühlt oder sagt, daß niemand ihn/sie mag	0	1	2
34. Glaubt, andere wollten ihm/ihr etwas antun	0	1	2
35. Fühlt sich wertlos oder unterlegen	0	1	2
36. Zieht sich ungewollt Verletzungen zu, neigt zu Unfällen	0	1	2
37. Gerät leicht in Raufereien, Schlägereien	0	1	2
38. Wird gehänselt	0	1	2
39. Hat Umgang mit Jungen/Mädchen, die Probleme oder Scherereien bereiten	0	1	2
40. Hört etwas, das nicht da ist	0	1	2
Bitte beschreiben: _____			
41. Handelt ohne zu überlegen, ist impulsiv	0	1	2
42. Möchte lieber allein sein als mit anderen zusammen	0	1	2
43. Lügt, schwindelt oder betrügt	0	1	2
44. Kaut an den Fingernägeln	0	1	2
45. Ist nervös, reizbar oder gespannt	0	1	2
46. Leidet unter Zuckungen (Tics) oder nervösen Bewegungen	0	1	2
Bitte beschreiben: _____			
47. Hat Alpträume	0	1	2
48. Ist bei anderen (Kindern/Jugendlichen) nicht beliebt	0	1	2
49. Leidet an Verstopfung, hat keinen Stuhlgang	0	1	2
50. Ist zu furchtsam oder ängstlich	0	1	2
51. Klagt über Schwindel	0	1	2
52. Hat starke Schuldgefühle	0	1	2
53. Ißt zuviel	0	1	2
54. Ist übermüdet	0	1	2
55. Hat Übergewicht	0	1	2
56. Körperliche Beschwerden ohne bekannte medizinische Ursache (der Arzt hat nichts gefunden):			
a) Schmerzen	0	1	2
b) Kopfweh	0	1	2
c) Übelkeit, Unwohlsein	0	1	2
d) Augenbeschwerden. Bitte beschreiben:____	0	1	2
e) Hautausschläge oder andere Hautprobleme	0	1	2
f) Magenschmerzen oder Bauchkrämpfe	0	1	2
g) Erbrechen, Würgen	0	1	2
h) andere Beschwerden. Bitte beschreiben: ___	0	1	2
57. Greift andere körperlich an	0	1	2
58. Bohrt in der Nase, zupft an der Haut oder anderen Körperstellen	0	1	2
Bitte beschreiben: _____			
59. Spielt in der Öffentlichkeit an den Geschlechtsteilen	0	1	2
60. Spielt zuviel an seinen/ihren Geschlechtsteilen	0	1	2
61. Ist schlecht in der Schule	0	1	2
62. Ist körperlich unbeholfen oder schwerfällig	0	1	2
63. Ist lieber mit Älteren als mit Gleichaltrigen zusammen	0	1	2
64. Ist lieber mit Jüngeren als mit Gleichaltrigen zusammen	0	1	2
65. Will nicht reden	0	1	2
66. Wiederholt bestimmte Handlungen immer wieder (wie unter Zwang)	0	1	2
67. Ist von zuhause weggelaufen	0	1	2

68. Schreit laut, kreischt 0 1 2
69. Ist verschlossen, behält Dinge für sich 0 1 2
70. Sieht Dinge, die nicht da sind 0 1 2
Bitte beschreiben: _____
_____
71. Ist befangen oder wird leicht verlegen 0 1 2
72. Zündelt gern bzw. hat schon etwas angesteckt . 0 1 2
73. Hat sexuelle Probleme 0 1 2
Bitte beschreiben: _____
_____
74. Produziert sich gern, kaspert herum, macht Faxen 0 1 2
75. Ist schüchtern oder zaghaft/ängstlich 0 1 2
76. Schläft weniger als die meisten Gleichaltrigen .. 0 1 2
77. Schläft tagsüber und/oder nachts mehr als die meisten Gleichaltrigen. Bitte genauer 0 1 2
beschreiben: _____
_____
78. Schmiert oder spielt mit Kot 0 1 2
79. Hat Probleme mit dem Sprechen 0 1 2
Bitte beschreiben: _____
_____
80. Starrt ins Leere oder vor sich hin 0 1 2
81. Hat zu Hause gestohlen 0 1 2
82. Hat anderswo (nicht zu Hause) gestohlen 0 1 2
83. Hortet Dinge, die er/sie nicht braucht 0 1 2
Bitte beschreiben: _____
_____
84. Verhält sich eigenartig 0 1 2
Bitte beschreiben: _____
_____
85. Hat seltsame Gedanken/Ideen 0 1 2
Bitte beschreiben: _____
_____
86. Ist eigensinnig, mürrisch oder dickköpfig 0 1 2
87. Zeigt plötzliche Stimmungs- oder Gefühlswechsel 0 1 2
88. Schmollt, ist leicht eingeschnappt/beleidigt 0 1 2
89. Ist mißtrauisch 0 1 2
90. Flucht oder gebraucht schmutzige Ausdrücke .. 0 1 2
91. Hat schon davon gesprochen sich umzubringen 0 1 2
92. Redet oder wandelt im Schlaf 0 1 2
Bitte beschreiben: _____
_____
93. Redet zuviel 0 1 2
94. Hänselt andere gern 0 1 2
95. Hat Wutausbrüche, wird leicht jähzornig/ reizbar 0 1 2
96. Denkt zuviel an Sex 0 1 2
97. Bedroht andere/will sie verletzen 0 1 2
98. Lutscht am Daumen 0 1 2
99. Ist zu sehr auf Ordentlichkeit oder Sauberkeit bedacht 0 1 2
100. Hat Schlafstörungen 0 1 2
Bitte beschreiben: _____
_____
101. Schwänzt die Schule (auch einzelne Unterrichtsstunden) 0 1 2
102. Hat nicht genug Energie, ist zu langsam oder träge 0 1 2
103. Ist unglücklich, traurig oder niedergeschlagen 0 1 2
104. Ist ungewöhnlich laut 0 1 2
105. Trinkt Alkohol, nimmt Drogen oder mißbraucht Medikamente 0 1 2
106. Richtet mutwillig Zerstörungen an 0 1 2
107. Näßt tagsüber ein 0 1 2
108. Näßt im Bett ein 0 1 2
109. Jammert und quengelt 0 1 2
110. Möchte gern vom anderen Geschlecht sein 0 1 2
111. Zieht sich zurück, nimmt keinen Kontakt zu anderen auf 0 1 2
112. Macht sich Sorgen 0 1 2
113. Bitte beschreiben Sie hier die Probleme Ihres Sohnes/Ihrer Tochter, die bisher noch nicht erwähnt wurden:
_____ 0 1 2
_____
_____
_____
_____
_____
_____ 0 1 2
_____
_____
_____
_____ 0 1 2
_____
_____
_____
_____

Bitte überprüfen Sie nochmal, ob sie alle Fragen beantwortet haben.

A4: Task instructions presented on a computer screen before

a) Continuous Performance Task

Sie werden gleich eine Reihe von Buchstaben sehen,
die nacheinander auf dem Bildschirm erscheinen.

Sie sollen dabei immer dann auf die Leertaste drücken,
wenn zuerst ein O und direkt danach ein X erscheint.

Erscheint nach einem O ein anderer Buchstabe als X,
drücken Sie bitte nicht.

Zum starten: Leertaste drücken

b) 1-back task

Sie werden gleich einige Minuten lang Buchstaben auf dem
Bildschirm präsentiert bekommen.

Drücken Sie bitte immer dann auf die Leertaste,
wenn ein Buchstabe mit dem vorherigen Buchstaben übereinstimmt.

zum Starten: Leertaste drücken

c) 2-back task

Sie werden gleich einige Minuten lang Buchstaben auf dem
Bildschirm präsentiert bekommen.

Drücken Sie bitte immer dann auf die Leertaste,
wenn ein Buchstabe mit dem vorletzten Buchstaben übereinstimmt.

zum Starten: Leertaste drücken

Appendix B: Tables and Figures

Tables and figure in text

Supplementary Tables

B 1 Genotype and Allele frequencies (T1)

		$ADHD_{unmed}$	$ADHD_{med}$	Controls			Chi^2	*p*
COMT	**No Met**	12	11	16	39	112	.796	.672
	Met	24	24	24	72			
DAT	**10/10**	18	16	21	55	113	.492	.782
	other	19	20	19	58			
LPHN3	**Risk**	18	19	20	57	108	.794	.672
	No risk	18	13	20	51			

Table S1 Comparison of binary genotype frequencies between diagnostic groups

							Group Differences (Genotypes)		Hardy-Weinberg	
			$ADHD_{unmed}$	$ADHD_{med}$	Controls		Total N	Chi^2	*p*	Chi^2	*p*
COMT		**CC**	12	11	16	39	112	1.151	.886	0.036	0.85
		CG	19	18	18	55					
		GG	5	7	6	18					
DAT1		**9/9**	4	3	4	11	113	2.752	.839	0.249	0.618
		9/10	15	15	14	44					
		10/10	18	16	21	55					
		10/11	0	2	1	3					
LPHN3	**rs6551665**	**AA**	13	13	14	40	108	1.560	.816	1.349	0.245
		AG	18	15	23	56					
		GG	4	5	3	12					
	rs2345039	**CC**	4	5	7		108	6.724	.151	1.999	0.157
		CG	20	23	17						
		GG	11	5	16						
	rs1947274	**AA**	14	13	14	41	110	2.368	.668	0.866	0.352
		AC	18	15	23	56					
		CC	4	6	3	13					

Table S2 Comparison of genotype frequencies between diagnostic groups and calculation of Hardy-Weinberg-Equilibrium

B 2 Behavioural Parameters (T1)

COMT (T1)	CPT					1-back					2-back				
	no Met		Met		*p*	no Met		Met		*p*	no Met		Met		*p*
	m	SE	m	SE		m	SE	m	SE		m	SE	m	SE	
Miss	2,92	,52	4,46	,79	,709	6,69	1,27	7,39	1,10	,624	21,64	1,74	21,59	1,09	,680
False Alarm	1,31	,365	2,35	,350	,025	2,28	,375	3,33	,60	,391	5,64	,99	5,95	,68	,452
Reaction times	490,67	20,92	510,78	15,53	,446	475,63	24,78	489,32	19,18	,539	518,49	29,23	578,76	22,04	,090
SD (RT)	135,61	8,01	165,8	8,63	,031	246,42	10,26	245,41	12,04	,781	343,17	13,86	366,99	11,65	,331

all *p*s 2-tailed

Table S3 Influence of COMT-Genotype on Error Rates, Response Times and RTV (T1)

DAT1 (T1)	CPT					1-back					2-back				
	10/10		other		*p*	10/10		other		*p*	10/10		other		*p*
	m	SE	m	SE		m	SE	m	SE		m	SE	m	SE	
Miss	3,47	,69	4,29	,81	,175	7,06	1,34	7,40	1,03	,248	21,02	1,24	22,46	1,42	,231
False Alarm	1,94	,323	2,03	,403	,765	2,15	,30	3,75	,72	,133	5,74	,72	5,93	,87	,660
Reaction times	500,42	15,68	507,21	18,88	,873	469,47	20,75	497,97	21,51	,404	565,77	24,62	543,71	25,32	,930
SD (RT)	155,87	8,62	154,25	9,26	,852	231,06	12,34	260,59	11,58	,057	371,9	12,28	343,29	12,63	,172

all *p*s 2-tailed

Table S4 Influence of DAT1-Genotype on Error Rates, Response Times and RTV (T1)

LPHN3 (T1)	CPT					1-back					2-back				
	Risk		No Risk		*p*	Risk		No Risk		*p*	Risk		No Risk		*p*
	m	SE	m	SE		m	SE	m	SE		m	SE	m	SE	
Miss	5,21	,98	2,66	,40	,337	7,95	1,401	6,50	,91	,439	22,23	1,38	21,52	1,38	,657
False Alarm	2,50	,397	1,48	,35	,044	3,23	,69	2,77	,44	,799	6,32	,94	5,50	,68	,803
Reaction times	513,28	15,39	489,66	18,95	,166	500,53	18,80	460,72	24,86	,168	560,94	26,34	547,32	25,42	,914
SD (RT)	162,71	8,28	147,08	10,35	,121	263,54	12,57	228,11	11,91	,158	351,98	13,74	364,76	12,49	,337

all *p*s 2-tailed

Table S5 Influence of LPHN3-Genotype on Error Rates, Response Times and RTV (T1)

Group (T1)	CPT						
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		*p*
	m	SE	m	SE	m	SE	
Miss	5,71	1,09	3,36	,89	5,32	1,89	$ADHD_{unmed}$ vs. $ADHD_{med}$: p = .036, $ADHD_{unmed}$ vs. $ADHD_{med}$: p = .017
False Alarm	2,48	,55	2,14	,50	1,71	,41	-
Reaction times	517,30	21,83	493,43	21,05	497,00	25,75	-
SD (RT)	172,58	11,51	140,96	7,33	142,07	11,97	$ADHD_{unmed}$ vs. $ADHD_{med}$: p = .080

	1-back						
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		*p*
	m	SE	m	SE	m	SE	
Miss	10,74	1,57	4,53	,88	5,74	,90	$ADHD_{unmed}$ vs. $ADHD_{med}$: p < .001, $ADHD_{unmed}$ vs. $ADHD_{med}$: p = .011
False Alarm	3,54	,58	3,17	1,01	2,26	,35	-
Reaction times	524,21	25,14	472,25	24,40	463,74	27,37	$ADHD_{unmed}$ vs. $ADHD_{med}$: p = .098,
SD (RT)	263,81	15,51	250,52	13,33	226,61	13,33	$ADHD_{unmed}$ vs. $ADHD_{med}$: p = .064

	2-back						
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		*p*
	m	SE	m	SE	m	SE	
Miss	27,54	1,98	19,94	1,24	20,11	1,35	$ADHD_{unmed}$ vs. $ADHD_{med}$: p = .015, $ADHD_{unmed}$ vs. $ADHD_{med}$: p = .014
False Alarm	8,30	1,47	5,06	,72	4,97	,63	-
Reaction times	596,88	33,38	532,65	30,72	549,25	28,18	-
SD (RT)	385,52	13,79	353,99	13,60	352,77	16,17	-

all *ps* 2-tailed

Table S6 Influence of Diagnostic Group on Error Rates, Response Times and RTV (T1)

B 3 Response Inhibition: Amplitudes and Latencies (T1)

COMT (T1)	no Met allele						at least one Met allele					
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
	m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
Go N200 (V)	-2,46	1,08	-3,55	1,11	-2,08	1,11	-5,22	1,00	-3,41	0,61	-4,19	0,83
NoGo N200 (V)	-5,24	1,53	-5,13	1,50	-5,05	1,11	-6,55	0,99	-6,00	0,72	-6,30	0,93
Go N200 (L)	294,92	6,13	300,70	10,57	295,61	8,21	313,80	4,01	286,26	5,56	306,93	4,42
NoGo N200 (L)	298,82	10,79	289,75	8,83	280,82	10,08	309,35	4,55	293,90	5,65	294,93	7,39
Go P300 (V) GFP	5,35	1,14	6,48	1,25	6,49	0,71	6,21	0,90	5,82	0,65	6,24	0,62
NoGo P300 (V) GFP	5,08	1,06	4,85	0,70	6,85	0,81	4,80	0,56	5,30	0,51	5,68	0,57
Go P300 (L) GFP	324,00	13,24	350,90	15,94	319,14	8,48	338,40	9,18	320,71	7,57	317,50	6,51
NoGo P300 (L) GFP	363,83	17,66	389,90	15,93	374,57	13,22	377,30	12,53	377,29	10,82	353,77	8,46
Go P300 (V) Pz	12,11	1,66	16,85	2,21	16,71	0,95	16,13	1,46	14,77	1,24	14,56	1,50
NoGo P300 (V) Cz	9,67	1,96	9,91	1,60	15,49	1,41	9,31	1,53	11,70	1,05	10,88	1,35
Go P300 (L) Pz	334,75	16,41	344,50	15,59	324,00	11,83	336,95	11,48	308,19	6,23	333,91	6,92
NoGo P300 (L) Cz	416,00	9,34	413,40	14,04	387,50	12,88	415,85	7,91	392,81	8,17	403,59	7,99
NGA	0,32	0,16	0,01	0,18	0,37	0,12	0,16	0,10	0,34	0,11	0,19	0,10
Centroid (Go)	3,84	0,21	3,86	0,21	4,09	0,08	4,22	0,06	4,10	0,08	4,12	0,10
Centroid (NoGo)	3,52	0,24	3,86	0,17	3,72	0,19	4,06	0,14	3,76	0,13	3,92	0,13

Table S7 Influence of COMT-Genotype on Go- and NoGo-Components in Diagnostic Groups during Continuous Performance Task (T1)

DAT1 (T1)	other						10/10					
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
	m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
Go N200 (V)	-3,56	1,14	-4,69	0,83	-3,57	1,11	-5,11	1,03	-1,95	0,34	-3,17	0,81
NoGo N200 (V)	-5,44	1,28	-6,26	1,08	-6,14	1,17	-6,78	1,02	-5,08	0,74	-5,48	0,84
Go N200 (L)	309,47	4,86	289,91	6,88	299,78	5,30	305,15	5,49	292,14	7,96	305,28	6,65
NoGo N200 (L)	303,43	7,78	287,68	7,38	286,81	8,71	308,38	5,68	298,50	5,17	292,08	8,47
Go P300 (V) GFP	5,34	1,05	6,57	0,73	6,62	0,61	6,57	0,90	5,38	0,95	6,05	0,70
NoGo P300 (V) GFP	4,50	0,85	5,55	0,59	6,89	0,70	5,44	0,58	4,68	0,55	5,38	0,61
Go P300 (L) GFP	326,69	11,34	317,29	7,64	313,56	8,76	337,65	9,65	346,43	12,99	322,72	5,27
NoGo P300 (L) GFP	376,50	17,76	377,71	12,69	382,78	10,71	365,71	10,03	385,79	12,59	340,94	7,62
Go P300 (V) Pz	13,46	1,61	15,28	1,47	14,77	1,32	15,69	1,52	15,64	1,70	16,02	1,51
NoGo P300 (V) Cz	7,13	1,76	10,97	1,27	12,71	1,16	11,48	1,35	11,31	1,24	12,64	1,79
Go P300 (L) Pz	334,56	11,54	316,29	7,32	337,17	10,25	339,18	14,12	324,29	13,26	322,94	6,88
NoGo P300 (L) Cz	417,94	7,82	403,76	10,56	396,72	8,79	412,76	8,75	394,21	9,85	397,94	11,18
NGA	0,30	0,15	0,38	0,14	0,34	0,10	0,13	0,08	0,05	0,12	0,18	0,12
Centroid (Go)	4,00	0,17	4,31	0,06	4,09	0,12	4,18	0,09	3,67	0,13	4,12	0,08
Centroid (NoGo)	3,70	0,21	3,93	0,14	3,75	0,13	4,05	0,14	3,62	0,14	3,94	0,17

Table S8 Influence of DAT-Genotype on Go- and NoGo-Components in Diagnostic Groups during Continuous Performance Task (T1)

LPHN3 (T1)	Risk haplotype						No risk haplotype					
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
	m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
Go N200 (V)	-5,74	1,17	-4,02	0,68	-4,08	0,94	-2,63	0,88	-1,82	0,48	-2,73	0,97
NoGo N200 (V)	-7,19	1,17	-5,44	0,90	-6,97	1,08	-4,90	1,13	-5,09	0,88	-4,78	0,90
Go N200 (L)	307,00	4,39	292,32	6,37	304,00	5,44	306,44	6,16	291,77	10,07	301,21	6,46
NoGo N200 (L)	313,78	5,32	296,18	5,84	297,21	7,85	296,90	7,71	285,27	9,24	282,50	8,84
Go P300 (V) GFP	6,70	1,00	5,08	0,79	6,62	0,54	5,08	0,97	6,83	0,90	6,08	0,74
NoGo P300 (V) GFP	5,09	0,76	4,71	0,51	6,51	0,68	4,71	0,72	5,50	0,75	5,80	0,66
Go P300 (L) GFP	324,87	5,78	330,41	10,51	320,12	8,75	341,12	13,93	337,45	13,60	316,37	5,87
NoGo P300 (L) GFP	353,81	9,77	386,94	12,04	358,59	11,02	390,69	16,89	386,64	15,04	364,79	10,15
Go P300 (V) Pz	14,02	1,85	12,78	1,37	17,27	1,43	15,23	1,39	17,58	1,48	13,72	1,30
NoGo P300 (V) Cz	8,30	1,53	11,05	1,18	13,13	0,93	10,59	1,81	11,42	1,62	12,27	1,84
Go P300 (L) Pz	325,25	12,15	323,65	8,51	323,24	10,37	347,00	13,91	317,64	15,27	336,16	7,18
NoGo P300 (L) Cz	412,19	8,94	407,65	9,26	393,94	7,58	419,63	8,09	388,00	11,80	400,37	11,59
NGA	0,08	0,09	0,38	0,11	0,27	0,11	0,36	0,14	0,04	0,20	0,26	0,11
Centroid (Go)	4,31	0,06	4,05	0,13	4,13	0,10	3,85	0,16	3,94	0,14	4,08	0,10
Centroid (NoGo)	4,23	0,13	3,66	0,14	3,86	0,17	3,50	0,20	3,90	0,16	3,83	0,14

Table S9 Influence of LPHN3-Genotype on Go- and NoGo-Components in Diagnostic Groups during Continuous Performance Task (T1)

B 4 Working Memory: Amplitudes and Latencies (T1)

COMT (T1)			no Met allele						at least one Met allele					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Amplitudes			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-target	**N100**	-4,20	0,74	-4,55	0,79	-5,34	0,77	-5,69	0,60	-5,05	0,59	-4,30	0,50
		P150	8,04	1,64	5,66	1,12	7,86	1,33	5,12	0,85	6,80	1,08	4,92	0,78
		N300	-4,00	1,37	-4,22	1,13	-3,20	1,76	-5,21	0,82	-4,00	0,94	-4,28	0,92
		P450	4,07	0,76	6,11	0,66	5,90	0,82	4,61	0,55	4,60	0,48	3,56	0,48
	tar	**P100**	7,42	1,70	15,16	2,39	12,81	2,24	13,78	1,65	14,31	1,49	13,47	1,74
		P300	8,93	2,27	16,41	1,73	12,89	1,60	15,05	2,05	15,22	1,45	11,17	1,13
2-back	Non-target	**N100**	-3,45	0,71	-5,86	0,51	-5,70	0,70	-5,35	0,60	-5,56	0,73	-4,39	0,55
		P150	7,33	1,48	5,78	1,14	6,93	1,46	5,99	1,20	6,34	1,12	4,17	0,72
		N300	-3,63	1,44	-4,60	0,74	-3,51	1,82	-4,39	0,91	-3,75	0,96	-3,73	0,64
		P450	3,05	0,49	4,15	0,50	4,67	0,57	4,16	0,64	3,69	0,49	3,09	0,46
	tar	**P100**	6,91	1,85	15,39	1,81	13,21	2,21	14,07	2,18	14,70	1,82	13,53	1,88
		P300	11,49	2,81	17,15	1,28	17,18	2,21	15,99	2,67	15,56	1,78	12,13	1,31

			no Met allele						at least one Met allele					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Latencies			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-target	**N100**	125,67	5,12	115,33	7,07	123,67	3,96	125,10	2,36	121,83	2,97	127,19	3,79
		P150	205,86	5,92	197,03	6,81	197,00	6,20	206,40	5,34	192,56	4,07	205,28	3,67
		N300	346,72	8,42	325,52	11,10	324,45	12,10	333,23	6,98	330,18	7,27	330,33	4,93
	tar	**P100**	134,08	3,13	123,88	3,01	126,47	3,41	125,90	4,36	126,49	3,91	122,67	3,77
		P300	292,92	6,38	322,18	14,40	311,72	10,20	322,19	10,42	333,28	11,89	317,88	7,04
2-back	Non-target	**N100**	123,39	3,45	113,45	7,28	117,43	4,24	130,43	3,07	124,19	2,85	124,89	3,36
		P150	207,19	5,28	193,79	5,74	188,93	5,10	201,93	4,38	190,15	5,01	194,56	4,00
		N300	354,39	7,40	340,67	5,62	357,93	9,30	345,70	5,51	345,51	3,73	346,65	4,90
	tar	**P100**	128,67	5,41	118,48	4,08	121,28	6,04	128,67	2,30	125,28	3,58	122,00	3,11
		P300	304,08	10,47	324,42	11,55	323,17	7,18	326,43	11,93	306,58	6,74	321,00	5,82

Table S10 Influence of COMT-Genotype on Amplitudes and Latencies of Target and non-Target Components in Diagnostic Groups during n-Back Task (T1)

DAT 1 (T1)			other						10/10					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Amplitudes			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-target	N100	-5,14	0,80	-5,24	0,62	-5,07	0,67	-5,52	0,60	-4,47	0,72	-4,37	0,55
		P150	5,45	1,26	6,18	1,03	5,77	1,14	6,66	1,09	6,76	1,34	6,20	0,95
		N300	-4,71	1,16	-4,88	1,04	-4,11	1,30	-5,30	0,92	-3,10	0,98	-3,70	1,18
		P450	3,75	0,55	4,92	0,67	4,29	0,63	5,04	0,65	5,25	0,40	4,52	0,67
	tar	P100	8,26	1,58	15,85	1,89	13,22	2,15	14,81	1,67	13,16	1,59	13,25	1,80
		P300	7,87	1,51	16,25	1,79	11,93	1,37	17,43	1,89	14,88	1,29	11,67	1,27
2-back	Non-target	N100	-4,53	0,79	-5,00	0,63	-5,13	0,58	-5,02	0,56	-6,44	0,84	-4,67	0,66
		P150	6,10	1,44	6,21	1,24	5,59	1,35	6,62	1,12	6,10	1,13	4,86	0,76
		N300	-4,00	1,12	-3,84	0,75	-4,01	1,03	-4,44	1,04	-4,23	1,26	-3,36	1,13
		P450	3,39	0,58	4,02	0,59	3,24	0,39	4,19	0,65	3,61	0,43	4,03	0,60
	tar	P100	6,69	1,40	16,12	2,00	14,16	2,02	2,20	13,58	1,78	12,89	2,00	2,20
		P300	9,71	2,10	16,07	1,95	14,20	2,04	2,69	16,09	1,64	13,71	1,52	2,69

			other						10/10					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Latencies			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-target	N100	125,73	3,33	122,18	4,21	119,61	2,84	126,29	3,57	116,96	4,27	130,98	4,22
		P150	208,27	5,14	197,75	4,48	193,53	5,45	206,35	6,33	189,46	5,38	209,27	3,33
		N300	339,53	8,11	328,70	7,42	315,25	8,92	337,40	6,88	328,73	10,01	338,62	5,69
	tar	P100	131,21	6,30	128,22	2,63	126,95	4,12	128,33	1,46	122,75	5,18	121,95	3,60
		P300	296,79	6,32	341,41	12,59	314,48	9,84	321,44	12,41	316,50	13,14	316,57	7,12
2-back	Non-target	N100	130,55	3,49	121,54	4,14	123,14	2,89	125,75	3,04	119,96	4,69	121,33	4,28
		P150	209,06	4,49	189,82	6,13	188,78	5,04	198,71	4,49	193,04	4,40	195,48	3,94
		N300	347,12	5,23	340,37	3,96	344,39	7,23	351,52	7,02	348,29	4,76	356,00	5,90
	tar	P100	130,85	4,32	127,74	2,96	124,05	3,05	127,78	2,24	117,83	4,63	120,13	4,43
		P300	316,30	14,90	315,37	8,91	321,24	7,91	317,11	9,30	308,96	8,00	322,13	5,40

Table S11 Influence of DAT1-Genotype on Amplitudes and Latencies of Target and non-Target Components in Diagnostic Groups during n-Back Task (T1)

LPHN3 (T1)			Risk haplotype						No risk haplotype					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Amplitudes			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-target	**N100**	-4,91	0,72	-4,96	0,75	-5,64	0,72	-5,30	0,65	-4,39	0,53	-3,82	0,42
		P150	6,47	1,17	6,47	1,20	6,64	1,15	6,02	1,20	7,10	1,28	5,43	0,91
		N300	-5,69	1,14	-4,34	1,16	-5,90	1,50	-4,03	0,91	-3,49	0,90	-2,07	0,76
		P450	3,92	0,62	4,73	0,57	4,40	0,49	4,79	0,63	5,46	0,65	4,44	0,77
	tar	**P100**	12,83	2,93	15,83	2,05	13,38	1,66	10,52	1,18	14,00	1,53	13,09	2,20
		P300	14,29	3,40	12,57	1,57	13,54	1,17	11,81	1,56	18,35	1,21	10,01	1,32
2-back	Non-target	**N100**	-4,51	0,70	-5,31	0,83	-5,66	0,69	-4,74	0,67	-6,05	0,73	-4,17	0,53
		P150	6,91	1,19	6,28	1,19	6,09	1,09	6,17	1,38	7,04	1,31	4,37	0,96
		N300	-4,93	1,38	-4,05	1,20	-5,47	1,22	-3,47	0,87	-4,10	0,79	-2,01	0,82
		P450	3,42	0,77	3,55	0,51	3,85	0,49	3,99	0,53	4,36	0,64	3,52	0,57
	tag	**P100**	12,55	3,08	15,99	2,24	12,70	1,72	10,72	1,98	14,10	1,63	14,13	2,31
		P300	15,78	3,94	14,68	2,02	14,92	1,36	13,37	2,11	17,08	1,81	12,91	2,01

			Risk haplotype						No risk haplotype					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Latencies			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-target	**N100**	127,10	4,13	120,52	3,30	125,11	3,97	123,93	2,80	117,81	5,90	126,60	3,99
		P150	211,02	5,76	191,54	5,03	204,63	4,86	202,44	5,37	194,90	5,20	200,07	4,48
		N300	336,19	7,52	331,85	8,99	330,13	6,89	339,93	7,85	322,88	9,59	326,40	8,23
	tar	**P100**	122,74	6,52	127,65	2,75	125,75	4,68	133,13	2,14	127,43	4,12	122,27	2,82
		P300	321,04	16,37	336,71	13,77	314,00	6,16	304,97	6,06	324,86	15,09	317,41	9,87
2-back	Non-target	**N100**	125,05	3,32	123,22	3,38	122,04	3,64	129,93	3,30	117,95	6,07	122,23	3,96
		P150	205,00	4,45	191,35	5,80	197,35	3,78	203,06	4,97	191,29	5,86	188,10	4,77
		N300	349,88	6,79	348,00	3,91	353,44	7,28	348,24	5,98	338,17	5,25	348,43	5,99
	tar	**P100**	130,00	3,18	127,96	3,69	120,04	5,03	127,74	3,44	119,19	3,61	123,45	2,91
		P300	314,07	9,35	309,88	7,97	315,57	4,27	321,23	13,40	315,14	11,06	327,96	7,72

Table S12 Influence of LPHN3-Genotype on Amplitudes and Latencies of Target and non-Target Components in Diagnostic Groups during n-Back Task (T1)

B 5 Sensory Gating

COMT	no Met allele						at least one Met allele					
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
	m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
Conditioning P50 (V)	6,70	1,87	5,58	0,88	7,45	1,31	3,37	0,64	3,27	1,39	6,03	0,91
Testing P50 (V)	0,39	0,99	1,84	0,75	1,48	0,74	1,54	0,36	0,79	0,54	1,05	0,37
Conditioning P50 (L)	60,86	2,27	57,80	1,53	60,77	2,65	59,80	1,79	61,00	6,73	60,15	2,01
Testing P50 (L)	56,57	1,69	58,20	4,59	57,62	3,00	56,20	4,07	59,00	1,73	56,40	2,19
P50 Suppression (%)	78,21	13,14	60,82	13,86	81,73	12,31	53,83	6,57	82,24	6,91	83,02	9,17

Table S13 Modulation of P50 Sensory Gating Amplitudes and Latencies and Suppression Ratio by COMT-Genotype

DAT1	other						10/10					
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
	m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
Conditioning P50 (V)	4,80	1,22	4,82	1,56	6,89	1,18	4,66	1,51	4,34	1,02	6,34	0,99
Testing P50 (V)	0,83	0,73	0,56	0,66	1,25	0,52	1,40	0,46	2,02	0,60	1,20	0,52
Conditioning P50 (L)	60,00	1,83	58,50	6,19	57,67	2,91	60,57	2,21	59,80	2,75	62,67	1,45
Testing P50 (L)	59,00	3,35	61,25	3,09	56,47	2,25	52,57	3,21	56,40	3,82	57,22	2,66
P50 Suppression (%)	63,41	11,50	88,30	9,76	80,89	10,99	64,53	6,31	55,98	9,92	83,86	9,93

Table S14 Modulation of P50 Sensory Gating Amplitudes and Latencies and Suppression Ratio by DAT1-Genotype

LPHN3	Risk haplotype						No risk haplotype					
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
	m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
Conditioning P50 (V)	2,73	0,47	5,27	1,29	6,52	1,15	6,54	1,47	3,66	0,98	6,65	1,02
Testing P50 (V)	1,49	0,36	0,82	0,57	0,66	0,50	0,69	0,82	2,06	0,77	1,75	0,50
Conditioning P50 (L)	62,13	1,70	59,00	4,82	60,38	2,75	58,56	2,02	59,50	3,52	60,41	1,73
Testing P50 (L)	56,13	3,90	60,00	2,70	57,94	2,67	56,56	3,25	56,75	4,91	55,88	2,34
P50 Suppression (%)	46,43	7,08	85,39	8,10	99,18	10,52	79,38	9,26	51,54	11,45	66,82	8,66

Table S15 Modulation of P50 Sensory Gating Amplitudes and Latencies and Suppression Ratio by LPHN3-Genotype

B 6 Catamnestic Re-Examination of Sub-Sample

		$ADHD_{unmed}$	$ADHD_{med}$	Controls			Chi^2	*p*
COMT	**No Met**	4	8	8	20	50	1.150	.563
	Met	10	9	11	30			
DAT	**10/10**	7	9	12	28	50	.664	.717
	other	7	8	7	22			
LPHN3	**Risk**	6	8	11	25	47	.857	.651
	No risk	8	6	8	22			

Table S16 Comparison of binary genotype frequencies between diagnostic groups (T2)

							Group Differences (Genotypes)		Hardy-Weinberg	
			$ADHD_{unmed}$	$ADHD_{med}$	Controls		Total N	Chi^2	*p*	Chi^2	*p*
COMT		**CC**	4	8	9	20	50	1.583	.812	.688	.407
		CG	7	7	7	21					
		GG	3	2	4	9					
DAT1		**9/9**	2	2	0	4	50	2.811	.590	.000	.986
		9/10	5	6	7	18					
		10/10	7	9	12	20					
		10/11	0	0	0	0					
LPHN3	**rs6551665**	**AA**	6	6	5	17	46	2.047	.727	.659	.417
		AG	6	6	12	24					
		GG	1	2	2	5					
	rs2345039	**CC**	2	3	4	9	46	3.481	.481	.007	.935
		CG	7	9	7	23					
		GG	4	2	8	14					
	rs1947274	**AA**	7	6	5	18	48	4.816	.307	.739	.390
		AC	6	6	13	25					
		CC	1	3	1	5					

Table S17 Comparison of genotype frequencies between diagnostic groups and calculation of Hardy-Weinberg-Equilibrium (T2)

B 6.1 Behavioural Parameters (T2)

COMT (T2)	CPT					1-back					2-back				
	no Met		Met		*p*	no Met		Met		*p*	no Met		Met		*p*
	m	SE	m	SE		m	SE	m	SE		m	SE	m	SE	
Miss	1,33	0,34	1,93	0,47	0,649	4,29	0,85	5,60	0,84	0,293	16,95	1,50	18,90	1,86	0,701
False Alarm	0,88	0,31	0,32	0,14	0,107	4,48	2,32	1,97	0,55	0,162	11,71	5,06	7,90	1,69	0,651
Reaction times	450,87	24,36	484,52	22,07	0,344	403,88	29,74	421,99	25,79	0,497	543,48	26,70	536,65	29,06	0,985
SD (RT)	342,16	68,07	316,38	48,44	0,787	240,96	23,13	226,32	13,88	0,886	383,19	23,16	326,54	16,89	0,075

all *ps* 2-tailed

Table S18 Influence of COMT-Genotype on Error Rates, Response Times and RTV (T2)

DAT1 (T2)	CPT					1-back					2-back				
	10/10		other		*p*	10/10		other		*p*	10/10		other		*p*
	m	SE	m	SE		m	SE	m	SE		m	SE	m	SE	
Miss	1,71	0,45	1,67	0,40	0,584	4,68	0,82	5,52	0,92	0,462	17,50	1,51	18,83	2,11	0,864
False Alarm	0,63	0,19	0,39	0,24	0,187	2,00	0,58	4,22	2,12	0,287	7,25	1,64	12,17	4,68	0,403
Reaction times	446,26	20,28	510,39	25,96	0,053	382,11	24,42	454,01	29,42	0,042	515,54	27,13	568,59	29,58	0,212
SD (RT)	335,32	50,97	312,70	63,39	0,787	230,32	18,49	234,82	16,41	0,902	345,03	16,11	355,76	24,97	0,985

all *ps* 2-tailed

Table S19 Influence of DAT1-Genotype on Error Rates, Response Times and RTV (T2)

LPHN3 (T2)	CPT					1-back					2-back				
	Risk		No Risk		*p*	Risk		No Risk		*p*	Risk		No Risk		*p*
	m	SE	m	SE		m	SE	m	SE		m	SE	m	SE	
Miss	1,22	0,30	1,70	0,44	0,470	3,76	0,78	6,04	0,90	0,025	17,72	1,90	19,13	1,84	0,569
False Alarm	0,39	0,18	0,74	0,27	0,280	1,44	0,21	4,87	2,18	0,225	6,92	1,29	11,65	4,89	0,633
Reaction times	456,10	23,67	489,88	26,28	0,233	393,64	26,19	431,25	31,41	0,183	523,48	28,22	558,03	32,65	0,219
SD (RT)	447,12	66,85	216,34	25,63	0,034	205,29	9,63	255,62	23,63	0,078	317,71	15,34	383,65	23,47	0,014

all *ps* 2-tailed

Table S20 Influence of LPHN3-Genotype on Error Rates, Response Times and RTV (T2)

Group (T2)	CPT						
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		*p*
	m	SE	m	SE	m	SE	
Miss	1,79	0,60	2,12	0,62	1,13	0,35	-
False Alarm	1,07	0,34	0,24	0,14	0,36	0,25	$ADHD_{unmed}$ vs. $ADHD_{med}$: $p = .020$, $ADHD_{unmed}$ vs. KG : $p = .039$
Reaction times	459,81	34,80	497,42	25,77	452,59	26,04	
SD (RT)	283,23	59,72	303,28	61,42	393,10	82,27	

	1-back						
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		*p*
	m	SE	m	SE	m	SE	
Miss	6,07	1,24	4,82	1,24	4,47	0,72	
False Alarm	6,27	3,30	1,71	0,46	1,58	0,28	
Reaction times	403,93	45,32	450,71	23,96	390,54	31,14	
SD (RT)	243,14	22,54	269,28	25,34	190,79	12,78	$ADHD_{unmed}$ vs. KG : $p = .071$, $ADHD_{med}$ vs. KG : $p = .014$

	2-back						
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		*p*
	m	SE	m	SE	m	SE	
Miss	20,60	2,03	17,41	2,90	16,74	1,43	
False Alarm	14,00	7,27	8,12	1,71	7,11	1,80	
Reaction times	591,69	44,45	551,14	25,48	487,77	31,95	$ADHD_{unmed}$ vs. KG : $p = .064$
SD (RT)	364,55	33,26	354,34	23,29	334,28	19,13	

all *p*s 2-tailed

Table S21 Influence of Diagnostic Group on Error Rates, Response Times and RTV (T2)

B 6.2 Response Inhibition at T2

COMT (T2)	no Met allele						at least one Met allele					
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
	m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
Go N200 (V)	-5,50	1,29	-0,41	1,21	-0,99	1,18	-3,90	1,21	-0,69	1,07	-5,78	2,12
NoGo N200 (V)	-4,94	0,27	-3,50	0,94	-2,85	1,12	-6,22	1,11	-2,71	0,84	-5,65	2,13
Go N200 (L)	317,33	14,73	284,93	12,12	287,88	4,35	286,25	6,45	273,06	15,42	311,50	6,26
NoGo N200 (L)	288,17	14,68	265,25	9,64	257,13	10,52	278,15	7,21	272,50	11,41	287,17	18,02
Go P300 (V) GFP	6,02	1,25	4,96	0,70	6,97	1,11	4,06	0,82	3,69	1,02	5,47	2,20
NoGo P300 (V) GFP	6,53	0,21	5,10	1,26	7,17	0,54	3,48	0,80	3,03	0,80	5,10	1,81
Go P300 (L) GFP	355,67	32,54	324,71	11,11	316,50	18,35	334,10	8,98	332,00	14,52	315,67	12,45
NoGo P300 (L) GFP	363,00	35,37	361,38	14,74	378,00	30,38	358,30	14,19	392,13	20,67	333,33	4,37
Go P300 (V) Pz	15,05	0,75	12,47	1,70	15,07	1,91	12,77	2,39	12,39	2,97	13,47	5,80
NoGo P300 (V) Cz	9,27	3,92	11,25	2,45	11,49	2,42	7,49	2,48	5,50	1,07	5,29	4,23
Go P300 (L) Pz	337,00	5,29	298,71	4,68	291,50	7,97	303,40	9,39	319,25	6,17	321,33	24,21
NoGo P300 (L) Cz	392,00	5,51	383,88	13,65	389,75	27,76	387,80	14,05	388,38	12,46	388,67	6,06
NGA	-0,03	0,26	0,37	0,32	0,12	0,31	0,22	0,19	0,48	0,32	-0,10	0,08
Centroid (Go)	3,86	0,39	3,70	0,21	4,04	0,24	4,00	0,12	3,96	0,08	4,35	0,12
Centroid (NoGo)	3,89	0,32	3,45	0,24	3,91	0,20	3,77	0,21	3,47	0,36	4,45	0,07

Table S22 Influence of COMT-Genotype on Go- and NoGo-Components in Diagnostic Groups during Continuous Performance Task (T2)

DAT1 (T2)	other						10/10					
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
	m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
Go N200 (V)	-6,26	1,21	-2,16	0,99	-5,90	2,36	-1,94	0,92	0,84	0,96	-1,90	1,56
NoGo N200 (V)	-7,18	1,08	-4,01	0,96	-3,69	0,89	-4,46	1,20	-2,20	0,69	-4,19	1,64
Go N200 (L)	311,00	6,61	290,71	12,62	299,25	19,25	272,92	5,01	268,00	14,26	297,50	5,81
NoGo N200 (L)	284,21	8,28	281,94	11,30	289,25	20,25	276,08	10,18	255,81	7,11	262,30	12,18
Go P300 (V) GFP	5,02	1,04	4,82	0,87	6,72	0,74	3,92	0,98	3,81	0,94	6,17	1,52
NoGo P300 (V) GFP	4,62	1,17	3,18	0,74	7,77	0,03	3,67	0,79	4,95	1,33	5,68	1,10
Go P300 (L) GFP	335,71	14,37	326,86	17,22	301,50	23,50	343,00	13,96	330,13	9,16	322,00	12,78
NoGo P300 (L) GFP	362,43	20,98	389,88	22,71	338,50	10,50	355,83	15,32	363,63	12,13	367,00	25,72
Go P300 (V) Pz	14,63	1,34	15,00	2,41	14,95	1,89	11,73	3,78	10,18	2,26	14,16	3,48
NoGo P300 (V) Cz	6,96	1,91	6,04	1,00	15,63	1,91	9,00	4,03	10,70	2,64	6,11	2,31
Go P300 (L) Pz	318,29	10,09	322,14	6,13	310,00	33,00	302,83	13,73	298,75	4,24	302,00	13,30
NoGo P300 (L) Cz	397,71	13,61	399,75	15,98	365,00	13,00	378,33	17,31	372,50	5,88	399,00	19,34
NGA	0,28	0,28	0,37	0,31	0,46	0,44	0,04	0,09	0,49	0,33	-0,14	0,14
Centroid (Go)	3,98	0,18	4,05	0,12	4,37	0,02	3,95	0,18	3,65	0,15	4,09	0,21
Centroid (NoGo)	3,70	0,27	3,75	0,25	3,91	0,46	3,92	0,21	3,17	0,31	4,23	0,14

Table S23 Influence of DAT1-Genotype on Go- and NoGo-Components in Diagnostic Groups during Continuous Performance Task (T2)

LPHN3 (T2)	Risk haplotype						No risk haplotype					
	$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
	m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
Go N200 (V)	-4,33	1,49	1,82	0,77	-5,78	2,12	-4,19	1,34	-1,74	1,05	-0,99	1,18
NoGo N200 (V)	-5,81	1,13	-2,38	0,69	-5,65	2,13	-6,06	1,43	-3,24	1,08	-2,85	1,12
Go N200 (L)	300,86	10,80	270,67	20,08	311,50	6,26	284,75	7,17	280,64	12,84	287,88	4,35
NoGo N200 (L)	280,36	6,93	272,50	9,69	287,17	18,02	280,58	11,82	264,94	12,78	257,13	10,52
Go P300 (V) GFP	4,54	0,99	4,15	1,18	5,47	2,20	4,48	1,11	3,75	0,83	6,97	1,11
NoGo P300 (V) GFP	4,25	1,20	5,06	1,64	5,10	1,81	4,11	0,80	3,52	0,96	7,17	0,54
Go P300 (L) GFP	338,43	13,71	325,00	14,08	315,67	12,45	339,83	15,04	337,29	15,33	316,50	18,35
NoGo P300 (L) GFP	362,43	22,21	383,67	20,17	333,33	4,37	355,83	12,68	387,00	17,81	378,00	30,38
Go P300 (V) Pz	12,36	2,14	12,46	2,72	13,47	5,80	14,39	3,29	11,92	3,01	15,07	1,91
NoGo P300 (V) Cz	6,45	1,99	10,43	2,66	5,29	4,23	9,59	3,90	7,53	2,20	11,49	2,42
Go P300 (L) Pz	323,29	10,52	300,17	5,89	321,33	24,21	297,00	11,28	318,00	7,80	291,50	7,97
NoGo P300 (L) Cz	379,71	5,90	383,17	8,72	388,67	6,06	399,33	22,57	389,25	17,26	389,75	27,76
NGA	0,10	0,29	0,67	0,41	-0,10	0,08	0,25	0,07	0,40	0,30	0,12	0,31
Centroid (Go)	3,94	0,18	3,65	0,16	4,35	0,12	4,00	0,17	3,90	0,16	4,04	0,24
Centroid (NoGo)	3,84	0,29	2,98	0,36	4,45	0,07	3,76	0,18	3,59	0,24	3,91	0,20

Table S24 Influence of LPHN3-Genotype on Go- and NoGo-Components in Diagnostic Groups during Continuous Performance Task (T2)

B 6.3 Working Memory at T2

COMT (T2)			no Met allele						at least one Met allele					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Amplitudes			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-	N100	-3,44	0,96	-3,63	0,77	-3,47	0,37	-3,43	0,65	-3,19	1,03	-3,65	1,07
		P150	6,00	1,20	5,00	1,14	6,71	1,74	3,44	0,78	5,53	1,39	4,06	1,68
		N300	-2,34	1,52	-0,79	0,71	-2,10	1,37	-2,98	0,88	-1,43	0,93	-2,41	0,92
		P450	4,45	1,40	3,67	0,86	3,40	0,56	2,79	0,47	3,05	0,99	3,43	0,65
	tar	P100	8,16	3,09	9,47	1,91	14,37	2,09	6,76	1,43	4,59	1,37	10,22	2,03
		P300	12,06	2,99	12,86	2,08	14,54	1,98	11,46	2,07	5,60	1,55	11,57	1,41
2-back	Non-	N100	-3,03	0,95	-3,65	0,66	-3,50	0,30	-3,70	0,63	-3,40	0,85	-2,95	1,00
		P150	6,63	2,04	4,53	0,84	7,20	1,40	3,67	0,92	5,29	1,80	2,80	0,80
		N300	-3,71	1,63	-1,97	0,50	-2,25	1,20	-2,85	0,71	-1,61	1,09	-2,67	1,01
		P450	3,04	0,65	2,71	0,52	3,27	0,46	2,26	0,37	2,93	0,79	2,54	0,62
	tar	P100	6,44	2,68	10,32	1,26	15,50	2,23	7,57	1,54	6,46	1,69	12,19	2,00
		P300	8,45	2,45	9,80	2,28	15,28	2,10	9,94	2,01	8,60	1,91	14,54	1,66

			no Met allele						at least one Met allele					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Latencies			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-	N100	116,83	7,09	115,17	4,51	114,95	5,85	121,33	4,09	112,92	4,64	111,33	6,18
		P150	185,92	9,26	193,08	11,55	186,24	10,00	189,87	8,25	182,08	7,71	195,83	5,90
		N300	316,58	25,22	310,79	14,32	299,10	21,44	317,90	13,37	322,63	13,25	321,33	14,37
	tar	P100	103,50	15,10	111,42	7,74	124,10	4,09	115,93	6,28	114,00	8,99	122,27	5,99
		P300	339,17	16,94	328,25	23,40	314,67	11,63	320,13	6,54	312,08	4,86	332,13	15,47
2-back	Non-	N100	114,83	10,37	115,17	3,55	119,81	4,12	122,53	4,34	110,42	6,10	117,67	5,07
		P150	190,58	7,08	180,63	6,06	190,33	6,28	187,44	6,77	182,46	6,69	183,19	5,46
		N300	312,25	22,13	339,29	11,83	358,81	8,30	315,89	11,65	340,71	8,97	355,86	7,90
	tar	P100	126,00	5,26	120,75	3,59	114,95	3,97	124,00	4,70	120,19	7,74	119,87	4,90
		P300	313,83	15,73	326,08	6,55	305,52	5,07	331,78	10,77	324,29	17,93	331,07	13,93

Table S25 Influence of COMT-Genotype on Amplitudes and Latencies of Target and non-Target Components in Diagnostic Groups during n-Back Task (T2)

DAT1 (T2)			other						10/10					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Amplitudes			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-	N100	-3,54	0,77	-4,41	0,93	-2,62	0,30	-3,33	0,75	-2,41	0,72	-4,14	0,75
		P150	5,81	0,95	5,06	1,38	6,28	2,49	2,54	0,62	5,47	1,16	4,99	1,37
		N300	-2,85	0,93	-1,88	0,95	-1,17	0,69	-2,75	1,21	-0,33	0,57	-2,91	1,24
		P450	4,45	0,73	3,22	0,97	3,86	0,72	2,08	0,46	3,49	0,89	3,14	0,50
	tar	P100	7,17	2,19	8,57	1,52	8,77	1,17	7,14	1,57	5,82	1,97	15,40	1,95
		P300	11,67	2,01	10,20	2,14	15,65	1,94	11,59	2,78	8,48	2,31	11,62	1,60
2-back	Non-	N100	-3,56	0,79	-4,44	0,71	-2,48	0,50	-3,46	0,72	-2,60	0,64	-3,64	0,73
		P150	6,44	1,18	4,78	1,68	5,61	1,23	2,41	0,89	5,04	1,07	4,65	1,41
		N300	-3,99	0,91	-2,96	0,84	-2,03	1,06	-2,08	0,90	-0,61	0,59	-2,70	1,05
		P450	3,21	0,36	3,29	0,64	2,62	0,17	1,66	0,31	2,35	0,65	3,07	0,60
	tar	P100	1,90	9,54	1,48	11,08	1,26	1,90	5,23	1,46	7,62	1,68	16,43	2,23
		P300	1,99	10,46	2,00	14,33	1,33	1,99	7,15	2,19	8,16	2,16	15,46	2,24

			other						10/10					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Latencies			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-	N100	120,86	4,63	119,83	2,99	103,73	5,19	119,24	5,46	108,25	4,86	119,25	4,90
		P150	191,05	8,24	186,46	9,12	173,53	9,72	186,43	10,08	188,71	10,86	201,38	4,76
		N300	335,00	8,84	324,96	7,54	282,93	17,45	300,05	19,62	308,46	17,73	325,88	16,55
	tar	P100	105,43	11,31	124,86	5,86	126,40	6,53	119,33	4,04	103,26	8,01	121,14	3,44
		P300	322,19	11,39	332,48	25,16	326,67	9,42	328,95	8,04	310,59	7,97	318,57	14,96
2-back	Non-	N100	118,48	6,67	117,75	3,85	115,07	3,38	122,19	5,42	107,83	5,44	120,78	4,53
		P150	197,19	5,46	181,38	7,45	179,33	8,80	178,17	7,08	181,71	5,11	190,89	3,92
		N300	316,00	13,65	338,00	10,87	345,33	13,18	313,33	16,17	342,00	10,07	364,00	3,64
	tar	P100	128,38	4,48	119,05	4,40	114,00	5,51	120,22	5,41	121,75	6,55	119,14	3,55
		P300	318,38	11,44	336,48	17,14	311,47	10,43	335,44	13,87	315,42	5,86	319,52	10,36

Table S26 Influence of DAT1-Genotype on Amplitudes and Latencies of Target and non-Target Components in Diagnostic Groups during n-Back Task (T2)

LPHN3 (T2)			Risk haplotype						No risk haplotype					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Amplitudes			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-	N100	-3,28	0,79	-2,92	0,73	-3,88	0,76	-3,55	0,73	-3,70	1,22	-3,03	0,54
		P150	3,84	0,70	5,13	1,00	5,48	1,68	4,42	1,16	6,56	1,47	5,49	1,95
		N300	-3,26	1,36	-1,30	0,87	-3,08	0,94	-2,45	0,85	-0,06	0,70	-0,90	1,42
		P450	3,44	0,71	3,12	1,04	2,85	0,44	3,14	0,79	4,20	0,95	4,33	0,64
	tar	P100	7,19	1,99	7,09	2,39	10,83	1,09	7,12	1,67	7,51	1,75	13,93	2,50
		P300	10,29	1,69	10,28	2,65	12,72	1,49	13,41	3,17	7,66	2,46	13,72	2,09
2-back	Non-	N100	-3,34	0,70	-3,43	0,55	-3,93	0,74	-3,64	0,77	-3,38	0,99	-2,29	0,49
		P150	4,36	1,22	4,27	1,15	5,41	1,40	4,72	1,37	6,44	1,73	4,44	1,46
		N300	-3,83	1,28	-3,25	0,78	-3,66	0,85	-2,66	0,78	-0,07	0,66	-0,86	1,10
		P450	2,56	0,58	3,11	0,79	2,67	0,44	2,46	0,41	2,75	0,68	3,23	0,70
	tar	P100	7,08	1,86	8,07	1,99	11,63	1,57	7,45	1,81	9,63	1,37	15,35	2,15
		P300	7,26	1,41	10,55	2,38	15,36	1,96	13,03	2,79	5,88	1,13	14,71	1,84

			other						10/10					
			$ADHD_{unmed}$		$ADHD_{med}$		Controls		$ADHD_{unmed}$		$ADHD_{med}$		Controls	
Latencies			m	SE	m	SE	m	SE	m	SE	m	SE	m	SE
1-back	Non-	N100	117,22	4,78	113,52	3,87	113,00	5,78	122,17	4,99	111,90	5,77	113,73	6,15
		P150	186,50	11,59	176,33	6,56	195,71	7,64	190,42	7,45	195,43	11,80	182,60	9,34
		N300	305,89	19,92	315,43	11,95	320,13	18,85	326,25	13,63	315,29	18,43	292,13	15,49
	tar	P100	108,83	10,34	109,43	8,52	128,80	5,55	117,11	4,12	108,57	8,48	119,43	3,64
		P300	328,00	8,01	306,76	9,72	348,53	10,73	322,33	12,41	336,76	24,59	302,95	8,45
2-back	Non-	N100	117,22	4,76	112,86	3,92	119,25	4,28	122,67	6,51	110,48	6,77	118,06	5,10
		P150	179,67	9,51	176,48	7,79	192,67	4,51	193,88	5,17	185,14	6,06	178,89	6,57
		N300	317,53	11,67	331,05	13,95	359,92	5,22	313,04	15,18	349,86	7,84	353,89	11,40
	tar	P100	129,42	3,34	121,62	7,58	117,07	5,71	116,93	6,44	117,78	4,96	116,95	3,66
		P300	320,00	11,29	312,29	8,31	334,27	10,43	336,27	14,59	339,22	18,81	303,24	6,69

Table S27 Influence of DAT1-Genotype on Amplitudes and Latencies of Target and non-Target Components in Diagnostic Groups during n-Back Task (T2)

	Time	Condition	Time*Condition	Additional effects
N200 Amplitudes	T1 > T2	Go < NoGo		
Group	$F_{1, 27}$ = 15.03, *p* = .001	$F_{1, 27}$ = 23.86, *p* < .001	$F_{1, 27}$ = 4.39, *p* = .046	-
COMT	$F_{1, 28}$ = 16.36, *p* < .001	$F_{1, 28}$ = 25.25, *p* < .001	$F_{1, 28}$ = 4.10, *p* = .013	-
DAT	$F_{1, 28}$ = 16.47, *p* < .001	$F_{1, 28}$ =28.15 , *p* < .001	$F_{1, 28}$ =5.79 , *p* = .053	DAT1, condition*DAT1
LPHN3	$F_{1, 26}$ = 13.00, *p* = .001	$F_{1, 26}$ = , *p* < .001	$F_{1, 26}$ = 4.02, *p* = .056	-
N200 Latencies	T1 > T2	Go > NoGo		
Group	$F_{1, 27}$ = 73.01, *p* < .001	$F_{1, 27}$ = 3.63, *p* = .067	$F_{1, 27}$ = 7.08 , *p* = .023	-
COMT	$F_{1, 28}$ =75.03 , *p* < .001	$F_{1, 28}$ = 4.59, *p* = .041	$F_{1, 28}$ = 7.83, *p* = .020	-
DAT	$F_{1, 28}$ = 87.64, *p* < .001	$F_{1, 28}$ = 3.32, *p* = .079	$F_{1, 28}$ = 6.06, *p* = .056	time*DAT1
LPHN3	$F_{1, 26}$ = 73.18, *p* < .001	$F_{1, 26}$ = 2.91, *p* = .100	$F_{1, 26}$ =4.69 , *p* = .040	-
Repeated Measures ANOVA with factors 'time and 'condition'				
N200 amplitude	$F_{1, 29}$ = 17.61, *p* < .001	$F_{1, 29}$ = 28.31, *p* < .001	$F_{1, 29}$ = 4.720, *p* = .038	
			T1 p < .001 T2 p = .002	**Go < NoGo**
			Go p = .001 NoGo p < .001	**T1 > T2**
N200 latency	$F_{1, 29}$ = 82.03, *p* < .001	$F_{1, 29}$ = 3.30, *p* = .080	$F_{1, 29}$ = 6.51, *p* = .016	
			T1 p = .833 T2 p = .013	**Go > NoGo**
			Go p = .001 NoGo p < .001	**T1 > T2**

Table S28 Developmental Effects on Response Inhibition Related Components (N200)

References

Achenbach TM, Edelbrock CS (1983) Manual for the Child Behavior Checklist and Revised Child Behavior Profile. Burlington: Quee City Printers Inc.

Adler LA, Sutton VK, Moore RJ, Dietrich AP, Reimherr FW, Sangal RB, Saylor KE, Secnik K, Kelsey DK, Allen AJ (2006) Quality of life assessment in adult patients with attention-deficit/hyperactivity disorder treated with atomoxetine. J Clin Psychopharmacol 26:648-652.

Adler LE, Pachtman E, Franks RD, Pecevich M, Waldo MC, Freedman R (1982) Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. Biol Psychiatry 17:639-654.

Adler LE, Pang K, Gerhardt G, Rose GM (1988) Modulation of the gating of auditory evoked potentials by norepinephrine: pharmacological evidence obtained using a selective neurotoxin. Biol Psychiatry 24:179-190.

Alderson RM, Rapport MD, Hudec KL, Sarver DE, Kofler MJ (2010) Competing core processes in attention-deficit/hyperactivity disorder (ADHD): do working memory deficiencies underlie behavioral inhibition deficits? J Abnorm Child Psychol 38:497-507.

Almasy L, Blangero J (2001) Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. Am J Med Genet 105:42-44.

Amenedo E, Diaz F (1998) Automatic and effortful processes in auditory memory reflected by event-related potentials. Age-related findings. Electroencephalogr Clin Neurophysiol 108:361-369.

Ando J, Ono Y, Wright MJ (2001) Genetic structure of spatial and verbal working memory. Behavior Genetics 31:615-624.

Arcos-Burgos M, Castellanos FX, Pineda D, Lopera F, Palacio JD, Palacio LG, Rapoport JL, Berg K, Bailey-Wilson JE, Muenke M (2004) Attention-deficit/hyperactivity disorder in a population isolate: linkage to loci at 4q13.2, 5q33.3, 11q22, and 17p11. Am J Hum Genet 75:998-1014.

Arcos-Burgos M, Jain M, Acosta MT, Shively S, Stanescu H, Wallis D, Domene S, Velez JI, Karkera JD, Balog J, Berg K, Kleta R, Gahl WA, Roessler E, Long R, Lie J, Pineda D, Londono AC, Palacio JD, Arbelaez A, Lopera F, Elia J, Hakonarson H, Johansson S, Knappskog PM, Haavik J, Ribases M, Cormand B, Bayes M, Casas M, Ramos-Quiroga JA, Hervas A, Maher BS, Faraone SV, Seitz C, Freitag CM, Palmason H, Meyer J, Romanos M, Walitza S, Hemminger U, Warnke A, Romanos J, Renner T, Jacob C, Lesch KP, Swanson J, Vortmeyer A, Bailey-Wilson JE, Castellanos FX, Muenke M (2010) A common variant of the latrophilin 3 gene, LPHN3, confers susceptibility to ADHD and predicts effectiveness of stimulant medication. Mol Psychiatry 15:1053-1066.

Arnold LE (1996) Sex differences in ADHD: conference summary. J Abnorm Child Psychol 24:555-569.

Arnsten AF (1997) Catecholamine regulation of the prefrontal cortex. J Psychopharmacol 11:151-162.

Arnsten AF, Dudley AG (2005) Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: Relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder. Behav Brain Funct 1:2.

Arnsten AFT (2001) Dopaminergic and noradrenergic influences on cognitive functions mediated by prefrontal cortex. In: Stimulant Drugs and ADHD: Basic and Clinical Neuroscience(Solanto, M. V. et al., eds), pp 185-208 London: Oxford University Press.

Backman L, Ginovart N, Dixon RA, Wahlin TB, Wahlin A, Halldin C, Farde L (2000) Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am J Psychiatry 157:635-637.

Baddeley A (1992) Working memory. Science 255:556-559.

Baddeley A (2000) The episodic buffer: a new component of working memory? Trends Cogn Sci 4:417-423.

Baddeley AD, Hitch GJ (1974) Working memory. In: The Psychology of Learning and Motivation(Bower, G. A., ed), pp 47-89 New York: Academic Press.

Baker K, Baldeweg T, Sivagnanasundaram S, Scambler P, Skuse D (2005) COMT Val108/158 Met modifies mismatch negativity and cognitive function in 22q11 deletion syndrome. Biol Psychiatry 58:23-31.

Banaschewski T, Brandeis D, Heinrich H, Albrecht B, Brunner E, Rothenberger A (2003) Association of ADHD and conduct disorder--brain electrical evidence for the existence of a distinct subtype. J Child Psychol Psychiatry 44:356-376.

Banaschewski T, Brandeis D, Heinrich H, Albrecht B, Brunner E, Rothenberger A (2004) Questioning inhibitory control as the specific deficit of ADHD--evidence from brain electrical activity. Journal of Neural Transmission 111:841-864.

Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ (2007) Long-term school outcomes for children with attention-deficit/hyperactivity disorder: A population-based perspective. J Dev Behav Pediatr 28:265-273.

Barkley R, Murphy KR, Fischer M (2007) ADHD in adults: What the science says. New York: Guilford.

Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 121:65-94.

Barkley RA, Edwards G, Laneri M, Fletcher K, Metevia L (2001) Executive functioning, temporal discounting, and sense of time in adolescents with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). J Abnorm Child Psychol 29:541-556.

Barkley RA, Fischer M, Smallish L, Fletcher K (2004) Young adult follow-up of hyperactive children: antisocial activities and drug use. J Child Psychol Psychiatry 45:195-211.

Barkley RA, Fischer M, Smallish L, Fletcher K (2006a) Young Adult Outcome of Hyperactive Children: Adaptive Functioning in Major Life Activities. J Am Acad Child Adolesc Psychiatry 45:192-202.

Barkley RA, Smith KM, Fischer M, Navia B (2006b) An examination of the behavioral and neuropsychological correlates of three ADHD candidate gene polymorphisms (DRD4 7+, DBH TaqI A2, and DAT1 40 bp VNTR) in hyperactive and normal children followed to adulthood. Am J Med Genet B Neuropsychiatr Genet 141B:487-498.

Barnett JH, Heron J, Ring SM, Golding J, Goldman D, Xu K, Jones PB (2007) Gender-specific effects of the catechol-O-methyltransferase Val108/158Met polymorphism on cognitive function in children. Am J Psychiatry 164:142-149.

Barnett JH, Scoriels L, Munafo MR (2008) Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. Biol Psychiatry 64:137-144.

Barry RJ, Johnstone SJ, Clarke AR (2003) A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. Clin Neurophysiol 114:184-198.

Bedard AC, Schulz KP, Cook EH, Jr., Fan J, Clerkin SM, Ivanov I, Halperin JM, Newcorn JH (2010) Dopamine transporter gene variation modulates activation of striatum in youth with ADHD. NeuroImage 53:935-942.

Bekker EM, Kenemans JL, Verbaten MN (2005) Source analysis of the N2 in a cued Go/NoGo task. Brain Res Cogn Brain Res 22:221-231.

Bellgrove MA, Domschke K, Hawi Z, Kirley A, Mullins C, Robertson IH, Gill M (2005) The methionine allele of the COMT polymorphism impairs prefrontal cognition in children and adolescents with ADHD. Exp Brain Res 163:352-360.

Bender S, Rellum T, Freitag C, Resch F, Rietschel M, Treutlein J, Jennen-Steinmetz C, Brandeis D, Banaschewski T, Laucht M (2012) Dopamine inactivation efficacy related to functional DAT1 and COMT variants influences motor response evaluation. PLoS ONE 7:e37814.

Berridge CW, Stalnaker TA (2002) Relationship between low-dose amphetamine-induced arousal and extracellular norepinephrine and dopamine levels within prefrontal cortex. Synapse 46:140-149.

Bertolino A, Blasi G, Latorre V, Rubino V, Rampino A, Sinibaldi L, Caforio G, Petruzzella V, Pizzuti A, Scarabino T, Nardini M, Weinberger DR, Dallapiccola B (2006) Additive effects of genetic variation in dopamine regulating genes on working memory cortical activity in human brain. J Neurosci 26:3918-3922.

Bertolino A, Fazio L, Di Giorgio A, Blasi G, Romano R, Taurisano P, Caforio G, Sinibaldi L, Ursini G, Popolizio T, Tirotta E, Papp A, Dallapiccola B, Borrelli E, Sadee W (2009) Genetically determined interaction between the dopamine transporter and the D2 receptor on prefronto-striatal activity and volume in humans. J Neurosci 29:1224-1234.

Berwid OG, Curko Kera EA, Marks DJ, Santra A, Bender HA, Halperin JM (2005) Sustained attention and response inhibition in young children at risk for Attention Deficit/Hyperactivity Disorder. J Child Psychol Psychiatry 46:1219-1229.

Bidwell LC, Willcutt EG, DeFries JC, Pennington BF (2007) Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. Biol Psychiatry 62:991-998.

Biederman J, Fried R, Petty CR, Wozniak J, Doyle AE, Henin A, Corkum L, Claudat K, Faraone SV (2011) Cognitive Development in Adults With Attention-Deficit/ Hyperactivity Disorder: A Controlled Study in Medication-Naive Adults Across the Adult Life Cycle. J Clin Psychiatry 72:11-16.

Biederman J, Mick E, Faraone SV, Braaten EB, Doyle A, Spencer T, Wilens TE, Frazier E, Johnson MA (2002) Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. Am J Psychiatry 159:36-42.

Biederman J, Petty CR, Ball SW, Fried R, Doyle AE, Cohen D, Henderson C, Faraone SV (2009) Are cognitive deficits in attention deficit/hyperactivity disorder related to the course of the disorder? A prospective controlled follow-up study of grown up boys with persistent and remitting course. Psychiatry Res 170:177-182.

Biederman J, Petty CR, Evans M, Small J, Faraone SV (2010a) How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. Psychiatry Res 177:299-304.

Biederman J, Petty CR, Monuteaux MC, Fried R, Byrne D, Mirto T, Spencer T, Wilens TE, Faraone SV (2010b) Adult psychiatric outcomes of girls with attention deficit hyperactivity disorder: 11-year follow-up in a longitudinal case-control study. Am J Psychiatry 167:409-417.

Bilder RM, Volavka J, Lachman HM, Grace AA (2004) The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology 29:1943-1961.

Birnbaum SG, Yuan PX, Wang M, Vijayraghavan S, Bloom AK, Davis DJ, Gobeske KT, Sweatt JD, Manji HK, Arnsten AF (2004) Protein kinase C overactivity impairs prefrontal cortical regulation of working memory. Science 306:882-884.

Blanchard MM, Chamberlain SR, Roiser J, Robbins TW, Muller U (2011) Effects of two dopamine-modulating genes (DAT1 9/10 and COMT Val/Met) on n-back working memory performance in healthy volunteers. Psychol Med 41:611-618.

Bokura H, Yamaguchi S, Kobayashi S (2001) Electrophysiological correlates for response inhibition in a Go/NoGo task. Clin Neurophysiol 112:2224-2232.

Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK (2010) To act or not to act, that's the problem: primarily inhibition difficulties in adult ADHD. Neuropsychology 24:209-221.

Borger N, van der Meere J, Ronner A, Alberts E, Geuze R, Bogte H (1999) Heart rate variability and sustained attention in ADHD children. J Abnorm Child Psychol 27:25-33.

Brandeis D, van Leeuwen TH, Rubia K, Vitacco D, Steger J, Pascual-Marqui RD, Steinhausen HC (1998) Neuroelectric mapping reveals precursor of stop failures in children with attention deficits. Behav Brain Res 94:111-125.

Brinkman MJ, Stauder JE (2007) Development and gender in the P50 paradigm. Clin Neurophysiol 118:1517-1524.

Broyd SJ, Johnstone SJ, Barry RJ, Clarke AR, McCarthy R, Selikowitz M, Lawrence CA (2005) The effect of methylphenidate on response inhibition and the event-related potential of children with attention deficit/hyperactivity disorder. Int J Psychophysiol 58:47-58.

Bruder GE, Keilp JG, Xu H, Shikhman M, Schori E, Gorman JM, Gilliam TC (2005) Catechol-O-methyltransferase (COMT) genotypes and working memory: associations with differing cognitive operations. Biol Psychiatry 58:901-907.

Bunge SA, Ochsner KN, Desmond JE, Glover GH, Gabrieli JD (2001) Prefrontal regions involved in keeping information in and out of mind. Brain 124:2074-2086.

Bunge SA, Wright SB (2007) Neurodevelopmental changes in working memory and cognitive control. Curr Opin Neurobiol 17:243-250.

Bymaster FP, Katner JS, Nelson DL, Hemrick Luecke SK, Threlkeld PG, Heiligenstein JH, Morin SM, Gehlert DR, Perry KW (2002) Atomoxetine increases extracellular levels of norepinephrine

and dopamine in prefrontal cortex of rat: A potential mechanism for efficacy in attention deficit/hyperactivity disorder. [References]. Neuropsychopharmacology 27:699-711.

Caldu X, Vendrell P, Bartres-Faz D, Clemente I, Bargallo N, Jurado MA, Serra-Grabulosa JM, Junque C (2007) Impact of the COMT Val108/158 Met and DAT genotypes on prefrontal function in healthy subjects. NeuroImage 37:1437-1444.

Cardenas VA, Gill P, Fein G (1997) Human P50 suppression is not affected by variations in wakeful alertness. Biol Psychiatry 41:891-901.

Carlson CL, Mann M (2000) Attention-deficit/hyperactivity disorder, predominantly inattentive subtype. Child Adolesc Psychiatr Clin N Am 9:499-510, vi.

Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, Shaw D, Shehzad Z, Di Martino A, Biswal B, Sonuga-Barke EJ, Rotrosen J, Adler LA, Milham MP (2008) Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 63:332-337.

Castellanos FX, Tannock R (2002) Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3:617-628.

Chambers CD, Garavan H, Bellgrove MA (2009) Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev 33:631-646.

Cheon K-A, Ryu Y-H, Kim J-W, Cho D-Y (2005) The homozygosity for 10-repeat allele at dopamine transporter gene and dopamine transporter density in Korean children with attention deficit hyperactivity disorder: relating to treatment response to methylphenidate. Eur Neuropsychopharmacol 15:95-101.

Cheuk DK, Wong V (2006) Meta-analysis of association between a catechol-O-methyltransferase gene polymorphism and attention deficit hyperactivity disorder. Behavior Genetics 36:651-659.

Ciliax BJ, Drash GW, Staley JK, Haber S, Mobley CJ, Miller GW, Mufson EJ, Mash DC, Levey AI (1999) Immunocytochemical localization of the dopamine transporter in human brain. J Comp Neurol 409:38-56.

Clark CR, Orr RS, Wright E, Weber D (1998) Working memory updating to visual verbal stimuli: a high resolution ERP study. In: Brain Topography Today(Koga, Y. et al., eds), pp 173-178 Amsterdam: Elsevier Science.

Cornish KM, Manly T, Savage R, Swanson J, Morisano D, Butler N, Grant C, Cross G, Bentley L, Hollis CP (2005) Association of the dopamine transporter (DAT1) 10/10-repeat genotype with ADHD symptoms and response inhibition in a general population sample. Mol Psychiatry 10:686-698.

Crichton A (2008) An Inquiry Into the Nature and Origin of Mental Derangement. J Atten Disord 12:200-204.

Cummins TD, Hawi Z, Hocking J, Strudwick M, Hester R, Garavan H, Wagner J, Chambers CD, Bellgrove MA (2012) Dopamine transporter genotype predicts behavioural and neural measures of response inhibition. Mol Psychiatry 17:1086-1092.

Da Fonseca D, Seguier V, Santos A, Poinso F, Deruelle C (2009) Emotion understanding in children with ADHD. Child Psychiatry Hum Dev 40:111-121.

Daffner KR, Ryan KK, Williams DM, Budson AE, Rentz DM, Wolk DA, Holcomb PJ (2006) Age-related differences in attention to novelty among cognitively high performing adults. Biological Psychology 72:67-77.

de Frias CM, Annerbrink K, Westberg L, Eriksson E, Adolfsson R, Nilsson LG (2005) Catechol O-methyltransferase Val158Met polymorphism is associated with cognitive performance in nondemented adults. J Cogn Neurosci 17:1018-1025.

De Luca CR, Wood SJ, Anderson V, Buchanan JA, Proffitt TM, Mahony K, Pantelis C (2003) Normative data from the CANTAB. I: development of executive function over the lifespan. J Clin Exp Neuropsychol 25:242-254.

DeFrance JF, Smith S, Schweitzer FC, Ginsberg L, Sands S (1996) Topographical analyses of attention disorders of childhood. Int J Neurosci 87:41-61.

DeVito EE, Blackwell AD, Clark L, Kent L, Dezsery AM, Turner DC, Aitken MR, Sahakian BJ (2009) Methylphenidate improves response inhibition but not reflection-impulsivity in children with attention deficit hyperactivity disorder (ADHD). Psychopharmacology (Berl) 202:531-539.

Diamond A, Briand L, Fossella J, Gehlbach L (2004) Genetic and neurochemical modulation of prefrontal cognitive functions in children. Am J Psychiatry 161:125-132.

Doehnert M, Brandeis D, Imhof K, Drechsler R, Steinhausen HC (2010) Mapping attention-deficit/hyperactivity disorder from childhood to adolescence--no neurophysiologic evidence for a developmental lag of attention but some for inhibition. Biol Psychiatry 67:608-616.

Doehnert M, Brandeis D, Schneider G, Drechsler R, Steinhausen HC (2012) A neurophysiological marker of impaired preparation in an 11-year follow-up study of attention-deficit/hyperactivity disorder (ADHD). J Child Psychol Psychiatry.

Donkers FC, van Boxtel GJ (2004) The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. Brain Cogn 56:165-176.

Draeger S, Prior M, Sanson A (1986) Visual and auditory attention performance in hyperactive children: competence or compliance. J Abnorm Child Psychol 14:411-424.

Drechsler R, Brandeis D, Foldenyi M, Imhof K, Steinhausen HC (2005) The course of neuropsychological functions in children with attention deficit hyperactivity disorder from late childhood to early adolescence. J Child Psychol Psychiatry 46:824-836.

Dresler T, Ehlis A-C, Heinzel S, Renner TJ, Reif A, Baehne CG, Heine M, Boreatti-Hümmer A, Jacob CP, Lesch K-P, Fallgatter AJ (2010) Dopamine transporter (SLC6A3) genotype impacts neurophysiological correlates of cognitive response control in an adult sample of patients with ADHD. Neuropsychopharmacology 35:2193-2202.

Dumontheil I, Roggeman C, Ziermans T, Peyrard-Janvid M, Matsson H, Kere J, Klingberg T (2011) Influence of the COMT genotype on working memory and brain activity changes during development. Biol Psychiatry 70:222-229.

Durston S, Fossella JA, Casey BJ, Hulshoff Pol HE, Galvan A, Schnack HG, Steenhuis MP, Minderaa RB, Buitelaar JK, Kahn RS, van Engeland H (2005) Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. Mol Psychiatry 10:678-685.

Durukan I, Yucel M, Erdem M, Kara K, Oz O, Karaman D, Odabasi Z (2011) P50 Sensory Gating in Children and Adolescents with ADHD and Effects of Methylphenidate Administration on P50 Sensory Gating. Bulletin of Clinical Psychopharmacology 21:42-48.

Dykiert D, Der G, Starr JM, Deary IJ (2012) Age differences in intra-individual variability in simple and choice reaction time: systematic review and meta-analysis. PLoS ONE 7:e45759.

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR (2001) Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A 98:6917-6922.

Ehlis A-C (2008) Hirnelektrische Hypofrontalität bei schizophrenen Patienten und ihre Bedeutung für die Auswahl der neuroleptischen Medikation. Würzburg: Universitätsbibliothek der Universität Würzburg.

Ehlis AC, Reif A, Herrmann MJ, Lesch KP, Fallgatter AJ (2007) Impact of catechol-O-methyltransferase on prefrontal brain functioning in schizophrenia spectrum disorders. Neuropsychopharmacology 32:162-170.

Eisenberg J, Mei-Tal G, Steinberg A, Tartakovsky E, Zohar A, Gritsenko I, Nemanov L, Ebstein RP (1999) Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): association of the high-enzyme activity Val allele with ADHD impulsive-hyperactive phenotype. Am J Med Genet 88:497-502.

Epstein JN, Erkanli A, Conners CK, Klaric J, Costello JE, Angold A (2003) Relations between Continuous Performance Test performance measures and ADHD behaviors. J Abnorm Child Psychol 31:543-554.

Falkenstein M, Hoormann J, Hohnsbein J (1999) ERP components in Go/Nogo tasks and their relation to inhibition. Acta Psychol (Amst) 101:267-291.

Falkenstein M, Hoormann J, Hohnsbein J (2002) Inhibition-related ERP components: variation with modality, age, and time-on-task. Journal of Psychophysiology 16:167-175.
Fallgatter AJ (2001) Electrophysiology of the prefrontal cortex in healthy controls and schizophrenic patients: a review. Journal of Neural Transmission 108:679-694.
Fallgatter AJ, Aranda DR, Bartsch AJ, Herrmann MJ (2002a) Long-term reliability of electrophysiologic response control parameters. J Clin Neurophysiol 19:61-66.
Fallgatter AJ, Baehne CG, Ehlis A-C, Plichta MM, Richter MM, Herrmann M, J., , Conzelmann A, Pauli P, Jacob C, Lesch K-P (2009) Impact of COMT genotype on prefrontal brain functioning in adult ADHD. Kognitive Neurophysiologie des Menschen 2:33-56.
Fallgatter AJ, Bartsch AJ, Herrmann MJ (2002b) Electrophysiological measurements of anterior cingulate function. Journal of Neural Transmission 109:977-988.
Fallgatter AJ, Bartsch AJ, Zielasek J, Herrmann MJ (2003) Brain electrical dysfunction of the anterior cingulate in schizophrenic patients. Psychiatry Res 124:37-48.
Fallgatter AJ, Brandeis D, Strik WK (1997) A robust assessment of the NoGo-anteriorisation of P300 microstates in a cued Continuous Performance Test. Brain Topogr 9:295-302.
Fallgatter AJ, Ehlis A-C, RÃ¶sler M, Strik WK, Blocher D, Herrmann MJ (2005) Diminished prefrontal brain function in adults with psychopathology in childhood related to attention deficit hyperactivity disorder. Psychiatry Research: Neuroimaging 138:157-169.
Fallgatter AJ, Ehlis AC, Seifert J, Strik WK, Scheuerpflug P, Zillessen KE, Herrmann MJ, Warnke A (2004) Altered response control and anterior cingulate function in attention-deficit/hyperactivity disorder boys. Clin Neurophysiol 115:973-981.
Fallgatter AJ, Mueller TJ, Strik WK (1999) Age-related changes in the brain electrical correlates of response control. Clin Neurophysiol 110:833-838.
Fallgatter AJ, Muller TJ (2001) Electrophysiological signs of reduced prefrontal response control in schizophrenic patients. Psychiatry Res 107:19-28.
Fallgatter AJ, Strik WK (1999) The NoGo-anteriorization as a neurophysiological standard-index for cognitive response control. Int J Psychophysiol 32:233-238.
Faraone SV, Biederman J, Mick E (2006) The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med 36:159-165.
Faraone SV, Biederman J, Weber W, Russell RL (1998) Psychiatric, neuropsychological, and psychosocial features of DSM-IV subtypes of attention-deficit/hyperactivity disorder: results from a clinically referred sample. J Am Acad Child Adolesc Psychiatry 37:185-193.
Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P (2005) Molecular Genetics of Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry 57:1313-1323.
Faraone SV, Spencer T, Aleardi M, Pagano C, Biederman J (2004) Meta-analysis of the efficacy of methylphenidate for treating adult attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 24:24-29.
Feifel D, Minassian A, Perry W (2009) Prepulse inhibition of startle in adults with ADHD. Journal of Psychiatric Research 43:484-489.
Finn AS, Sheridan MA, Kam CL, Hinshaw S, D'Esposito M (2010) Longitudinal evidence for functional specialization of the neural circuit supporting working memory in the human brain. J Neurosci 30:11062-11067.
Fisher T, Aharon-Peretz J, Pratt H (2011) Dis-regulation of response inhibition in adult Attention Deficit Hyperactivity Disorder (ADHD): An ERP study. Clin Neurophysiol In Press, Corrected Proof.
Fjell AM, Walhovd KB (2004) Life-span changes in P3a. Psychophysiology 41:575-583.
Flory K, Molina BSG, Pelham WE, Gnagy E, Smith B (2006) Childhood ADHD Predicts Risky Sexual Behavior in Young Adulthood. J Clin Child Adolesc Psychol 35:571-577.
Ford JM, Gray M, Whitfield SL, Turken AU, Glover G, Faustman WO, Mathalon DH (2004) Acquiring and inhibiting prepotent responses in schizophrenia: event-related brain potentials and functional magnetic resonance imaging. Arch Gen Psychiatry 61:119-129.
Franke B, Vasquez AA, Johansson S, Hoogman M, Romanos J, Boreatti-Hummer A, Heine M, Jacob CP, Lesch KP, Casas M, Ribases M, Bosch R, Sanchez-Mora C, Gomez-Barros N, Fernandez-Castillo N, Bayes M, Halmoy A, Halleland H, Landaas ET, Fasmer OB, Knappskog PM, Heister AJ,

Kiemeney LA, Kooij JJ, Boonstra AM, Kan CC, Asherson P, Faraone SV, Buitelaar JK, Haavik J, Cormand B, Ramos-Quiroga JA, Reif A (2010) Multicenter analysis of the SLC6A3/DAT1 VNTR haplotype in persistent ADHD suggests differential involvement of the gene in childhood and persistent ADHD. Neuropsychopharmacology 35:656-664.

Freitas AL, Azizian A, Leung HC, Squires NK (2007) Resisting recently acted-on cues: compatibility of Go/NoGo responses to response history modulates (frontal P3) event-related potentials. Psychophysiology 44:2-10.

Friedman D (1990) Cognitive event-related potential components during continuous recognition memory for pictures. Psychophysiology 27:136-148.

Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S (2001) The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. Pharmacogenomics J 1:152-156.

Gainetdinov RR, Caron MG (2000) An animal model of attention deficit hyperactivity disorder. Mol Med Today 6:43-44.

Gallinat J, Bajbouj M, Sander T, Schlattmann P, Xu K, Ferro EF, Goldman D, Winterer G (2003) Association of the G1947A COMT (Val(108/158)Met) gene polymorphism with prefrontal P300 during information processing. Biol Psychiatry 54:40-48.

Gamo NJ, Wang M, Arnsten AF (2010) Methylphenidate and atomoxetine enhance prefrontal function through alpha2-adrenergic and dopamine D1 receptors. J Am Acad Child Adolesc Psychiatry 49:1011-1023.

Gaspar PA, Ruiz S, Zamorano F, Altayo M, Perez C, Bosman CA, Aboitiz F (2011) P300 amplitude is insensitive to working memory load in schizophrenia. BMC Psychiatry 11:29.

Gaub M, Carlson CL (1997) Gender differences in ADHD: a meta-analysis and critical review. J Am Acad Child Adolesc Psychiatry 36:1036-1045.

Geurts HM, Verté S, Oosterlaan J, Roeyers H, Sergeant JA (2004) How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? J Child Psychol Psychiatry 45:836-854.

Ghisolfi ES, Heldt E, Zanardo AP, Strimitzer IM, Jr., Prokopiuk AS, Becker J, Cordioli AV, Manfro GG, Lara DR (2006) P50 sensory gating in panic disorder. Journal of Psychiatric Research 40:535-540.

Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR (2003) Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch Gen Psychiatry 60:889-896.

Goldman-Rakic PS (1996) Regional and cellular fractionation of working memory. Proc Natl Acad Sci U S A 93:13473-13480.

Goldman-Rakic PS, Castner SA, Svensson TH, Siever LJ, Williams GV (2004) Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. Psychopharmacology (Berl) 174:3-16.

Gomarus HK, Wijers AA, Minderaa RB, Althaus M (2009) ERP correlates of selective attention and working memory capacities in children with ADHD and/or PDD-NOS. Clin Neurophysiol 120:60-72.

Goos LM, Crosbie J, Payne S, Schachar R (2009) Validation and extension of the endophenotype model in ADHD patterns of inheritance in a family study of inhibitory control. Am J Psychiatry 166:711-717.

Gottwald B, Mihajlovic Z, Wilde B, Mehdorn HM (2003) Does the cerebellum contribute to specific aspects of attention? Neuropsychologia 41:1452-1460.

Grady SR, Murphy KL, Cao J, Marks MJ, McIntosh JM, Collins AC (2002) Characterization of nicotinic agonist-induced [(3)H]dopamine release from synaptosomes prepared from four mouse brain regions. J Pharmacol Exp Ther 301:651-660.

Griffith J, Hoffer LD, Adler LE, Zerbe GO, Freedman R (1995) Effects of sound intensity on a midlatency evoked response to repeated auditory stimuli in schizophrenic and normal subjects. Psychophysiology 32:460-466.

Groom MJ, Scerif G, Liddle PF, Batty MJ, Liddle EB, Roberts KL, Cahill JD, Liotti M, Hollis C (2010) Effects of Motivation and Medication on Electrophysiological Markers of Response Inhibition in

Children with Attention-Deficit/Hyperactivity Disorder: Development of Inhibitory Control in Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry 67:624-631.
Grossman MH, Emanuel BS, Budarf ML (1992) Chromosomal mapping of the human catechol-O-methyltransferase gene to 22q11.1----q11.2. Genomics 12:822-825.
Halmoy A, Fasmer OB, Gillberg C, Haavik J (2009) Occupational outcome in adult ADHD: Impact of symptom profile, comorbid psychiatric problems, and treatment: A cross-sectional study of 414 clinically diagnosed adult ADHD patients. J Atten Disord 13:175-187.
Han C, Wang Y, Wang X, Y. L (2010) Effect of variable number of tandem repeats polymorphism in the human dopamine transporter gene on conflict information processing according to event-related potential. Neural Regeneration Research 5:1196-1200.
Hawi Z, Millar N, Daly G, Fitzgerald M, Gill M (2000) No association between catechol-O-methyltransferase (COMT) gene polymorphism and attention deficit hyperactivity disorder (ADHD) in an Irish sample. Am J Med Genet 96:282-284.
Hawk LW, Jr., Yartz AR, Pelham WE, Jr., Lock TM (2003) The effects of methylphenidate on prepulse inhibition during attended and ignored prestimuli among boys with attention-deficit hyperactivity disorder. Psychopharmacology (Berl) 165:118-127.
Hazy TE, Frank MJ, O'Reilly RC (2006) Banishing the homunculus: making working memory work. Neuroscience 139:105-118.
Heinz A, Goldman D, Jones DW, Palmour R, Hommer D, Gorey JG, Lee KS, Linnoila M, Weinberger DR (2000) Genotype influences in vivo dopamine transporter availability in human striatum. Neuropsychopharmacology 22:133-139.
Heinzel S, Dresler T, Baehne CG, Heine M, Boreatti-Hummer A, Jacob CP, Renner TJ, Reif A, Lesch KP, Fallgatter AJ, Ehlis AC (2012) COMT x DRD4 Epistasis Impacts Prefrontal Cortex Function Underlying Response Control. Cerebral Cortex.
Hervey AS, Epstein JN, Curry JF (2004) Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychology 18:485-503.
Hess C, Reif A, Strobel A, Boreatti-Hummer A, Heine M, Lesch KP, Jacob CP (2009) A functional dopamine-beta-hydroxylase gene promoter polymorphism is associated with impulsive personality styles, but not with affective disorders. Journal of Neural Transmission 116:121-130.
Holmes J, Gathercole SE, Place M, Alloway TP, Elliott JG, Hilton KA (2010) The Diagnostic Utility of Executive Function Assessments in the Identification of ADHD in Children. Child and Adolescent Mental Health 15:37-43.
Hoza B, Gerdes AC, Mrug S, Hinshaw SP, Bukowski WM, Gold JA, Arnold LE, Abikoff HB, Conners CK, Elliott GR, Greenhill LL, Hechtman L, Jensen PS, Kraemer HC, March JS, Newcorn JH, Severe JB, Swanson JM, Vitiello B, Wells KC, Wigal T (2005) Peer-Assessed Outcomes in the Multimodal Treatment Study of Children With Attention Deficit Hyperactivity Disorder. J Clin Child Adolesc Psychol 34:74-86.
Jacob C, Romanos J, Dempfle A, Heine M, Windemuth-Kieselbach C, Kruse A, Reif A, Walitza S, Romanos M, Strobel A, Brocke B, Schäfer H, Schmidtke A, Böning J, Lesch KP (2007) Co-morbidity of adult attention-deficit/hyperactivity disorder with focus on personality traits and related disorders in a tertiary referral center. Eur Arch Psychiatry Clin Neurosci 257:309-317.
Jerger K, Biggins C, Fein G (1992) P50 suppression is not affected by attentional manipulations. Biol Psychiatry 31:365-377.
Jerome L, Habinski L, Segal A (2006) Attention-deficit/hyperactivity disorder (ADHD) and driving risk: a review of the literature and a methodological critique. Curr Psychiatry Rep 8:416-426.
Johnson MR, Adler LE (1993) Transient impairment in P50 auditory sensory gating induced by a cold-pressor test. Biol Psychiatry 33:380-387.
Johnstone SJ, Barry RJ, Anderson JW (2001) Topographic distribution and developmental timecourse of auditory event-related potentials in two subtypes of attention-deficit hyperactivity disorder. Int J Psychophysiol 42:73-94.

Johnstone SJ, Clarke AR (2009) Dysfunctional response preparation and inhibition during a visual Go/No-go task in children with two subtypes of attention-deficit hyperactivity disorder. Psychiatry Res 166:223-237.

Karama S, Grizenko N, Sonuga-Barke E, Doyle A, Biederman J, Mbekou V, Polotskaia A, Ter-Stepanian M, De Guzman R, Bellingham J, Sengupta S, Joober R (2008) Dopamine transporter 3'UTR VNTR genotype is a marker of performance on executive function tasks in children with ADHD. BMC Psychiatry 8:45.

Karatekin C (2004) A test of the integrity of the components of Baddeley's model of working memory in attention-deficit/hyperactivity disorder (ADHD). J Child Psychol Psychiatry 45:912-926.

Karayanidis F, Robaey P, Bourassa M, De Koning D, Geoffroy G, Pelletier G (2000) ERP differences in visual attention processing between attention-deficit hyperactivity disorder and control boys in the absence of performance differences. Psychophysiology 37:319-333.

Karl A, Malta LS, Maercker A (2006) Meta-analytic review of event-related potential studies in post-traumatic stress disorder. Biological Psychology 71:123-147.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N (1997) Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980-988.

Kawarai T, Kawakami H, Yamamura Y, Nakamura S (1997) Structure and organization of the gene encoding human dopamine transporter. Gene 195:11-18.

Keage HA, Clark CR, Hermens DF, Williams LM, Kohn MR, Clarke S, Lamb C, Crewther D, Gordon E (2008) ERP indices of working memory updating in AD/HD: differential aspects of development, subtype, and medication. J Clin Neurophysiol 25:32-41.

Kebir O, Joober R (2011) Neuropsychological endophenotypes in attention-deficit/hyperactivity disorder: a review of genetic association studies. Eur Arch Psychiatry Clin Neurosci 261:583-594.

Kemner C, Verbaten MN, Koelega HS, Buitelaar JK, van der Gaag RJ, Camfferman G, van Engeland H (1996) Event-related brain potentials in children with attention-deficit and hyperactivity disorder: effects of stimulus deviancy and task relevance in the visual and auditory modality. Biol Psychiatry 40:522-534.

Kempton S, Vance A, Maruff P, Luk E, Costin J, Pantelis C (1999) Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. Psychol Med 29:527-538.

Kereszturi E, Tarnok Z, Bognar E, Lakatos K, Farkas L, Gadoros J, Sasvari-Szekely M, Nemoda Z (2008) Catechol-O-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children. Am J Med Genet B Neuropsychiatr Genet 147B:1431-1435.

Kieling C, Genro JP, Hutz MH, Rohde LA (2008) The -1021 C/T DBH polymorphism is associated with neuropsychological performance among children and adolescents with ADHD. Am J Med Genet B Neuropsychiatr Genet 147B:485-490.

Kinsbourne M (1973) Minimal brain dysfunction as a neurodevelopmental lag. Annals of the New York Academy of Sciences 205:268-273.

Kirley A, Lowe N, Hawi Z, Mullins C, Daly G, Waldman I, McCarron M, O'Donnell D, Fitzgerald M, Gill M (2003) Association of the 480 bp DAT1 allele with methylphenidate response in a sample of Irish children with ADHD. Am J Med Genet B Neuropsychiatr Genet 121B:50-54.

Klassen AF, Miller A, Fine S (2004) Health-Related Quality of Life in Children and Adolescents Who Have a Diagnosis of Attention-Deficit/Hyperactivity Disorder. Pediatrics 114:e541-e547.

Kok A (2001) On the utility of P3 amplitude as a measure of processing capacity. Psychophysiology 38:557-577.

Kondo H, Morishita M, Osaka N, Osaka M, Fukuyama H, Shibasaki H (2004) Functional roles of the cingulo-frontal network in performance on working memory. NeuroImage 21:2-14.

Kooij JS, Boonstra AM, Vermeulen SH, Heister AG, Burger H, Buitelaar JK, Franke B (2008) Response to methylphenidate in adults with ADHD is associated with a polymorphism in SLC6A3 (DAT1). Am J Med Genet B Neuropsychiatr Genet 147B:201-208.

Kuntsi J, Rogers H, Swinard G, Borger N, van der Meere J, Rijsdijk F, Asherson P (2006) Reaction time, inhibition, working memory and 'delay aversion' performance: genetic influences and their interpretation. Psychol Med 36:1613-1624.

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM (1996) Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 6:243-250.

Lambek R, Shevlin M (2011) Working memory and response inhibition in children and adolescents: age and organization issues. Scand J Psychol 52:427-432.

Lange M, Norton W, Coolen M, Chaminade M, Merker S, Proft F, Schmitt A, Vernier P, Lesch KP, Bally-Cuif L (2012) The ADHD-susceptibility gene lphn3.1 modulates dopaminergic neuron formation and locomotor activity during zebrafish development. Mol Psychiatry.

Lavric A, Pizzagalli DA, Forstmeier S (2004) When 'go' and 'nogo' are equally frequent: ERP components and cortical tomography. Eur J Neurosci 20:2483-2488.

Lawrence CA, Barry RJ, Clarke AR, Johnstone SJ, McCarthy R, Selikowitz M, Broyd SJ (2005) Methylphenidate effects in attention deficit/hyperactivity disorder: electrodermal and ERP measures during a continuous performance task. Psychoparmacology 183:81-91.

Levy F, Swanson JM (2001) Timing, space and ADHD: the dopamine theory revisited. Aust N Z J Psychiatry 35:504-511.

Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM (2004) Striatal contributions to working memory: a functional magnetic resonance imaging study in humans. Eur J Neurosci 19:755-760.

Li CS, Yan P, Bergquist KL, Sinha R (2007) Greater activation of the "default" brain regions predicts stop signal errors. NeuroImage 38:640-648.

Li S, Kim KY, Kim JH, Park MS, Bahk JY, Kim MO (2004) Chronic nicotine and smoking treatment increases dopamine transporter mRNA expression in the rat midbrain. Neurosci Lett 363:29-32.

Lijffijt M, Lane SD, Meier SL, Boutros NN, Burroughs S, Steinberg JL, Moeller FG, Swann AC (2009a) P50, N100, and P200 sensory gating: relationships with behavioral inhibition, attention, and working memory. Psychophysiology 46:1059-1068.

Lijffijt M, Moeller FG, Boutros NN, Burroughs S, Lane SD, Steinberg JL, Swann AC (2009b) The Role of Age, Gender, Education, and Intelligence in P50, N100, and P200 Auditory Sensory Gating. J Psychophysiol 23:52-62.

Lijffijt M, Moeller FG, Boutros NN, Steinberg JL, Meier SL, Lane SD, Swann AC (2009c) Diminished P50, N100 and P200 auditory sensory gating in bipolar I disorder. Psychiatry Res 167:191-201.

Liotti M, Pliszka SR, Perez R, 3rd, Luus B, Glahn D, Semrud-Clikeman M (2007) Electrophysiological correlates of response inhibition in children and adolescents with ADHD: influence of gender, age, and previous treatment history. Psychophysiology 44:936-948.

Loo SK, Specter E, Smolen A, Hopfer C, Teale PD, Reite ML (2003) Functional effects of the DAT1 polymorphism on EEG measures in ADHD. J Am Acad Child Adolesc Psychiatry 42:986-993.

Lopez V, Lopez-Calderon J, Ortega R, Kreither J, Carrasco X, Rothhammer P, Rothhammer F, Rosas R, Aboitiz F (2006) Attention-deficit hyperactivity disorder involves differential cortical processing in a visual spatial attention paradigm. Clin Neurophysiol 117:2540-2548.

Lu BY, Martin KE, Edgar JC, Smith AK, Lewis SF, Escamilla MA, Miller GA, Canive JM (2007) Effect of catechol O-methyltransferase val(158)met polymorphism on the p50 gating endophenotype in schizophrenia. Biol Psychiatry 62:822-825.

Majic T, Rentzsch J, Gudlowski Y, Ehrlich S, Juckel G, Sander T, Lang UE, Winterer G, Gallinat J (2011) COMT Val108/158Met genotype modulates human sensory gating. NeuroImage 55:818-824.

Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D (2002) A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry 159:652-654.

Manor I, Gutnik I, Ben-Dor DH, Apter A, Sever J, Tyano S, Weizman A, Zalsman G (2010) Possible association between attention deficit hyperactivity disorder and attempted suicide in adolescents: A pilot study. Eur Psychiatry 25:146-150.

Marshall PJ, Bar-Haim Y, Fox NA (2004) The development of P50 suppression in the auditory event-related potential. Int J Psychophysiol 51:135-141.

Martinussen R, Hayden J, Hogg-Johnson S, Tannock R (2005) A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 44:377-384.

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR (2003) Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A 100:6186-6191.

McEvoy LK, Pellouchoud E, Smith ME, Gevins A (2001) Neurophysiological signals of working memory in normal aging. Brain Res Cogn Brain Res 11:363-376.

Meegan DV, Purc-Stephenson R, Honsberger MJ, Topan M (2004) Task analysis complements neuroimaging: an example from working memory research. NeuroImage 21:1026-1036.

Mehta MA, Goodyer IM, Sahakian BJ (2004) Methylphenidate improves working memory and set-shifting in AD/HD: relationships to baseline memory capacity. J Child Psychol Psychiatry 45:293-305.

Mill J, Asherson P, Browes C, D'Souza U, Craig I (2002) Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. Am J Med Genet 114:975-979.

Millar A, Smith D, Choueiry J, Fisher D, Albert P, Knott V (2011) The moderating role of the dopamine transporter 1 gene on P50 sensory gating and its modulation by nicotine. Neuroscience 180:148-156.

Mills S, Langley K, Van den Bree M, Street E, Turic D, Owen MJ, O'Donovan MC, Thapar A (2004) No evidence of association between Catechol-O-Methyltransferase (COMT) Val158Met genotype and performance on neuropsychological tasks in children with ADHD: a case-control study. BMC Psychiatry 4:15.

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50:381-425.

Mitchell RJ, Howlett S, Earl L, White NG, McComb J, Schanfield MS, Briceno I, Papiha SS, Osipova L, Livshits G, Leonard WR, Crawford MH (2000) Distribution of the 3' VNTR polymorphism in the human dopamine transporter gene in world populations. Hum Biol 72:295-304.

Mullis RJ, Holcomb PJ, Diner BC, Dykman RA (1985) The effects of aging on the P3 component of the visual event-related potential. Electroencephalogr Clin Neurophysiol 62:141-149.

Myerson J, Hale S, Rhee SH, Jenkins L (1999) Selective interference with verbal and spatial working memory in young and older adults. J Gerontol B Psychol Sci Soc Sci 54:P161-164.

Nagel IE, Chicherio C, Li SC, von Oertzen T, Sander T, Villringer A, Heekeren HR, Backman L, Lindenberger U (2008) Human aging magnifies genetic effects on executive functioning and working memory. Front Hum Neurosci 2:1.

Nandam LS, Hester R, Wagner J, Cummins TD, Garner K, Dean AJ, Kim BN, Nathan PJ, Mattingley JB, Bellgrove MA (2011) Methylphenidate but not atomoxetine or citalopram modulates inhibitory control and response time variability. Biol Psychiatry 69:902-904.

Nazari MA, Berquin P, Missonnier P, Aarabi A, Debatisse D, De Broca A, Wallois F (2010) Visual sensory processing deficit in the occipital region in children with attention-deficit / hyperactivity disorder as revealed by event-related potentials during cued continuous performance test. Neurophysiol Clin 40:137-149.

Nieuwenhuis S, Yeung N, van den Wildenberg W, Ridderinkhof KR (2003) Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. Cogn Affect Behav Neurosci 3:17-26.

Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJS (2005) Causal Heterogeneity in Attention-Deficit/Hyperactivity Disorder: Do We Need Neuropsychologically Impaired Subtypes? Biol Psychiatry 57:1224-1230.

Nittono H, Nageishi Y, Nakajima Y, Ullsperger P (1999) Event-related potential correlates of individual differences in working memory capacity. Psychophysiology 36:745-754.

Oh KS, Shin DW, Oh GT, Noh KS (2003) Dopamine transporter genotype influences the attention deficit in Korean boys with ADHD. Yonsei Med J 44:787-792.

Olincy A, Ross RG, Harris JG, Young DA, McAndrews MA, Cawthra E, McRae KA, Sullivan B, Adler LE, Freedman R (2000) The P50 auditory event-evoked potential in adult attention-deficit disorder: comparison with schizophrenia. Biol Psychiatry 47:969-977.

Oosterlaan J, Logan GD, Sergeant JA (1998) Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: a meta-analysis of studies with the stop task. J Child Psychol Psychiatry 39:411-425.

Overtoom CC, Verbaten MN, Kemner C, Kenemans JL, van Engeland H, Buitelaar JK, Camfferman G, Koelega HS (1998) Associations between event-related potentials and measures of attention and inhibition in the Continuous Performance Task in children with ADHD and normal controls. J Am Acad Child Adolesc Psychiatry 37:977-985.

Owen AM, McMillan KM, Laird AR, Bullmore E (2005) N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 25:46-59.

Palmason H, Moser D, Sigmund J, Vogler C, Hanig S, Schneider A, Seitz C, Marcus A, Meyer J, Freitag CM (2010) Attention-deficit/hyperactivity disorder phenotype is influenced by a functional catechol-O-methyltransferase variant. Journal of Neural Transmission 117:259-267.

Parish CL, Nunan J, Finkelstein DI, McNamara FN, Wong JY, Waddington JL, Brown RM, Lawrence AJ, Horne MK, Drago J (2005) Mice lacking the alpha4 nicotinic receptor subunit fail to modulate dopaminergic neuronal arbors and possess impaired dopamine transporter function. Mol Pharmacol 68:1376-1386.

Patel SH, Azzam PN (2005) Characterization of N200 and P300: selected studies of the Event-Related Potential. Int J Med Sci 2:147-154.

Patterson JV, Hetrick WP, Boutros NN, Jin Y, Sandman C, Stern H, Potkin S, Bunney WE, Jr. (2008) P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. Psychiatry Res 158:226-247.

Pelosi L, Blumhardt LD (1999) Effects of age on working memory: an event-related potential study. Brain Res Cogn Brain Res 7:321-334.

Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, Plessen KJ, Yu S (2009) An FMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. Am J Psychiatry 166:1286-1294.

Pliszka SR, Liotti M, Woldorff MG (2000) Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. Biol Psychiatry 48:238-246.

Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 164:942-948.

Polich J (1996) Meta-analysis of P300 normative aging studies. Psychophysiology 33:334-353.

Prox V, Dietrich DE, Zhang Y, Emrich HM, Ohlmeier MD (2007) Attentional processing in adults with ADHD as reflected by event-related potentials. Neurosci Lett 419:236-241.

Qian Q, Wang Y, Zhou R, Li J, Wang B, Glatt S, Faraone SV (2003) Family-based and case-control association studies of catechol-O-methyltransferase in attention deficit hyperactivity disorder suggest genetic sexual dimorphism. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 118B:103-109.

Quednow BB, Schmechtig A, Ettinger U, Petrovsky N, Collier DA, Vollenweider FX, Wagner M, Kumari V (2009) Sensorimotor gating depends on polymorphisms of the serotonin-2A receptor and catechol-O-methyltransferase, but not on neuregulin-1 Arg38Gln genotype: a replication study. Biol Psychiatry 66:614-620.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98:676-682.

Renner TJ (2007) Die Nogo-Anteriorisierung bei gesunden und zwangserkrankten Kindern und Jugendlichen. Würzburg: Universitätsbibliothek der Universität Würzburg.

Ribases M, Ramos-Quiroga JA, Sanchez-Mora C, Bosch R, Richarte V, Palomar G, Gastaminza X, Bielsa A, Arcos-Burgos M, Muenke M, Castellanos FX, Cormand B, Bayes M, Casas M (2011) Contribution of LPHN3 to the genetic susceptibility to ADHD in adulthood: a replication study. Genes Brain Behav 10:149-157.

Riccio CA, Waldrop JJ, Reynolds CR, Lowe P (2001) Effects of stimulants on the continuous performance test (CPT): implications for CPT use and interpretation. J Neuropsychiatry Clin Neurosci 13:326-335.

Rommelse NN, Altink ME, Arias-Vasquez A, Buschgens CJ, Fliers E, Faraone SV, Buitelaar JK, Sergeant JA, Franke B, Oosterlaan J (2008a) A review and analysis of the relationship between neuropsychological measures and DAT1 in ADHD. Am J Med Genet B Neuropsychiatr Genet 147B:1536-1546.

Rommelse NN, Altink ME, Oosterlaan J, Buschgens CJ, Buitelaar J, Sergeant JA (2008b) Support for an independent familial segregation of executive and intelligence endophenotypes in ADHD families. Psychol Med 38:1595-1606.

Rommelse NNJ, Altink ME, Martin NC, Buschgens CJM, Faraone SV, Buitelaar JK, Sergeant JA, Oosterlaan J (2008c) Relationship between endophenotype and phenotype in ADHD. Behavioral and Brain Functions.

Rommelse NNJ, Rommelse NNJ, Altink ME, Oosterlaan J, Beem L, Buschgens CJM, Buitelaar J, Sergeant JA (2008d) Speed, variability, and timing of motor output in ADHD: Which measures are useful for endophenotypic research? Behavior Genetics 38:121-132.

Rosvold HE, Mirsky AF, Sarason I, Bransome ED, Jr., Beck LH (1956) A continuous performance test of brain damage. J Consult Psychol 20:343-350.

Roussos P, Giakoumaki SG, Rogdaki M, Pavlakis S, Frangou S, Bitsios P (2008) Prepulse inhibition of the startle reflex depends on the catechol O-methyltransferase Val158Met gene polymorphism. Psychol Med 38:1651-1658.

Rubia K, Smith AB, Brammer MJ, Toone B, Taylor E (2005) Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. Am J Psychiatry 162:1067-1075.

Sambataro F, Reed JD, Murty VP, Das S, Tan HY, Callicott JH, Weinberger DR, Mattay VS (2009) Catechol-O-methyltransferase valine(158)methionine polymorphism modulates brain networks underlying working memory across adulthood. Biol Psychiatry 66:540-548.

Sander C, Arns M, Olbrich S, Hegerl U (2010) EEG-vigilance and response to stimulants in paediatric patients with attention deficit/hyperactivity disorder. Clin Neurophysiol 121:1511-1518.

Sartory G, Heine A, Müller BW, Elvermann-Hallner A (2002) Event- and Motor-Related Potentials During the Continuous Performance Task in Attention- Deficit/Hyperactivity Disorder. Journal of Psychophysiology 16:97-106.

Satterfield JH, Schell AM, Backs RW, Hidaka KC (1984) A cross-sectional and longitudinal study of age effects of electrophysiological measures in hyperactive and normal children. Biol Psychiatry 19:973-990.

Schachar R, Tannock R, Marriott M, Logan G (1995) Deficient inhibitory control in attention deficit hyperactivity disorder.

. J Abnorm Child Psychol 23:411-437.

Schecklmann M, Ehlis AC, Plichta MM, Dresler T, Heine M, Boreatti-Hummer A, Romanos M, Jacob C, Pauli P, Fallgatter AJ (2012) Working Memory and Response Inhibition as One Integral Phenotype of Adult ADHD? A Behavioral and Imaging Correlational Investigation. J Atten Disord.

Scherk H, Backens M, Schneider-Axmann T, Kraft S, Kemmer C, Usher J, Reith W, Falkai P, Meyer J, Gruber O (2009) Dopamine transporter genotype influences N-acetyl-aspartate in the left putamen. World J Biol Psychiatry 10:524-530.

Seidman LJ (2006) Neuropsychological functioning in people with ADHD across the lifespan: Attention Deficit Hyperactivity Disorder From A Neurosciences And Behavioral Approach. Clinical Psychology Review 26:466-485.

Seidman LJ, Valera EM, Makris N (2005) Structural Brain Imaging of Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry 57:1263-1272.

Seifert J, Scheuerpflug P, Zillessen KE, Fallgatter A, Warnke A (2003) Electrophysiological investigation of the effectiveness of methylphenidate in children with and without ADHD. Journal of Neural Transmission 110:821-829.

Sergeant J (2000) The cognitive-energetic model: an empirical approach to Attention-Deficit Hyperactivity Disorder. Neurosci Biobehav Rev 24:7-12.

Sergeant J, van der Meere J (1990) Additive factor method applied to psychopathology with special reference to childhood hyperactivity. Acta Psychol (Amst) 74:277-295.

Sergeant JA (2005) Modeling Attention-Deficit/Hyperactivity Disorder: A Critical Appraisal of the Cognitive-Energetic Model. Biol Psychiatry 57:1248-1255.

Sergeant JA, Geurts H, Oosterlaan J (2002) How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? Behav Brain Res 130:3-28.

Shaikh M, Hall MH, Schulze K, Dutt A, Walshe M, Williams I, Constante M, Picchioni M, Toulopoulou T, Collier D, Rijsdijk F, Powell J, Arranz M, Murray RM, Bramon E (2011) Do COMT, BDNF and NRG1 polymorphisms influence P50 sensory gating in psychosis? Psychol Med 41:263-276.

Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL (2007) Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A 104:19649-19654.

Shaw P, Gilliam M, Liverpool M, Weddle C, Malek M, Sharp W, Greenstein D, Evans A, Rapoport J, Giedd J (2011) Cortical Development in Typically Developing Children With Symptoms of Hyperactivity and Impulsivity: Support for a Dimensional View of Attention Deficit Hyperactivity Disorder. Am J Psychiatry 168:143-151.

Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, Giedd J, Castellanos FX, Rapoport J (2006) Longitudinal Mapping of Cortical Thickness and Clinical Outcome in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. [References]. Arch Gen Psychiatry 63:540-549.

Shaw P, Sharp WS, Morrison M, Eckstrand K, Greenstein DK, Clasen LS, Evans AC, Rapoport JL (2009a) Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder. Am J Psychiatry 166:58-63.

Shaw P, Wallace GL, Addington A, Evans A, Rapoport J, Giedd JN (2009b) Effects of the Valsuperscript 158Met catechol-O-methytransferase polymorphism on cortical structure in children and adolescents. [References]. Mol Psychiatry 14:348-349.

Shook D, Brady C, Lee PS, Kenealy L, Murphy ER, Gaillard WD, VanMeter JW, Cook EH, Jr., Stein M, Vaidya CJ (2011) Effect of dopamine transporter genotype on caudate volume in childhood ADHD and controls. Am J Med Genet B Neuropsychiatr Genet 156B:28-35.

Singh KD, Fawcett IP (2008) Transient and linearly graded deactivation of the human default-mode network by a visual detection task. NeuroImage 41:100-112.

Slaats-Willemse D, Swaab-Barneveld H, de Sonneville L, van der Meulen E, Buitelaar J (2003) Deficient response inhibition as a cognitive endophenotype of ADHD. J Am Acad Child Adolesc Psychiatry 42:1242-1248.

Smith JL, Johnstone SJ, Barry RJ (2004) Inhibitory processing during the Go/NoGo task: an ERP analysis of children with attention-deficit/hyperactivity disorder. Clin Neurophysiol 115:1320-1331.

Smith JL, Johnstone SJ, Barry RJ (2007) Response priming in the Go/NoGo task: the N2 reflects neither inhibition nor conflict. Clin Neurophysiol 118:343-355.

Sobanski E, Banaschewski T, Asherson P, Buitelaar J, Chen W, Franke B, Holtmann M, Krumm B, Sergeant J, Sonuga Barke E, Stringaris A, Taylor E, Anney R, Ebstein RP, Gill M, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Steinhausen HC, Faraone SV (2010) Emotional lability in children and adolescents with attention deficit hyperactivity disorder (ADHD): Clinical correlates and familial prevalence. J Child Psychol Psychiatry 51:915-923.

Sonuga-Barke EJ (2003) The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. Neurosci Biobehav Rev 27:593-604.

Sonuga-Barke EJ, Castellanos FX (2007) Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci Biobehav Rev 31:977-986.

Sonuga-Barke EJS (2005) Causal Models of Attention-Deficit/Hyperactivity Disorder: From Common Simple Deficits to Multiple Developmental Pathways. Biol Psychiatry 57:1231-1238.

Stefanis NC, van Os J, Avramopoulos D, Smyrnis N, Evdokimidis I, Stefanis CN (2005) Effect of COMT Val158Met polymorphism on the Continuous Performance Test, Identical Pairs Version: tuning rather than improving performance. Am J Psychiatry 162:1752-1754.

Stein MA, Waldman ID, Sarampote CS, Seymour KE, Robb AS, Conlon C, Kim SJ, Cook EH (2005) Dopamine transporter genotype and methylphenidate dose response in children with ADHD. Neuropsychopharmacology 30:1374-1382.

Stige S, Fjell AM, Smith L, Lindgren M, Walhovd KB (2007) The development of visual P3a and P3b. Dev Neuropsychol 32:563-584.

Stollstorff M, Foss-Feig J, Cook EH, Jr., Stein MA, Gaillard WD, Vaidya CJ (2010) Neural response to working memory load varies by dopamine transporter genotype in children. NeuroImage 53:970-977.

Strachey L (1971) Elizabeth and Essex. London, UK: Cox & Wyman Ltd.

Strandburg RJ, Marsh JT, Brown WS, Asarnow RF, Higa J, Harper R, Guthrie D (1996) Continuous-processing--related event-related potentials in children with attention deficit hyperactivity disorder. Biol Psychiatry 40:964-980.

Strik WK, Fallgatter AJ, Brandeis D, Pascual-Marqui RD (1998) Three-dimensional tomography of event-related potentials during response inhibition: evidence for phasic frontal lobe activation. Electroencephalogr Clin Neurophysiol 108:406-413.

Sugita S, Ichtchenko K, Khvotchev M, Sudhof TC (1998) alpha-Latrotoxin receptor CIRL/latrophilin 1 (CL1) defines an unusual family of ubiquitous G-protein-linked receptors. G-protein coupling not required for triggering exocytosis. J Biol Chem 273:32715-32724.

Sunohara GA, Malone MA, Rovet J, Humphries T, Roberts W, Taylor MJ (1999) Effect of methylphenidate on attention in children with attention deficit hyperactivity disorder (ADHD): ERP evidence. Neuropsychopharmacology 21:218-228.

Szuromi B, Czobor P, Komlosi S, Bitter I (2011) P300 deficits in adults with attention deficit hyperactivity disorder: a meta-analysis. Psychol Med 41:1529-1538.

Tamnes CK, Fjell AM, Westlye LT, Ostby Y, Walhovd KB (2012) Becoming consistent: developmental reductions in intraindividual variability in reaction time are related to white matter integrity. J Neurosci 32:972-982.

Taylor MJ, Sunohara GA, Khan SC, Malone MA (1997) Parallel and serial attentional processes in ADHD: ERP evidence. Developmental Neuropsychology 13:531-539.

Taylor RN, Williams LT (1988) Developmental expression of platelet-derived growth factor and its receptor in the human placenta. Mol Endocrinol 2:627-632.

Tekok-Kilic A, Shucard JL, Shucard DW (2001) Stimulus modality and Go/NoGo effects on P3 during parallel visual and auditory continuous performance tasks. Psychophysiology 38:578-589.

Tian L, Jiang T, Liang M, Zang Y, He Y, Sui M, Wang Y (2008) Enhanced resting-state brain activities in ADHD patients: a fMRI study. Brain Dev 30:342-348.

Tregellas JR, Ellis J, Shatti S, Du YP, Rojas DC (2009) Increased hippocampal, thalamic, and prefrontal hemodynamic response to an urban noise stimulus in schizophrenia. Am J Psychiatry 166:354-360.

Tsai SJ, Yu YW, Chen TJ, Chen MC, Hong CJ (2003) Association analysis for dopamine D3 receptor, dopamine D4 receptor and dopamine transporter genetic polymorphisms and P300 event-related potentials for normal young females. Psychiatr Genet 13:51-53.

Turic D, Williams H, Langley K, Owen M, Thapar A, O'Donovan MC (2005) A family based study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD). Am J Med Genet B Neuropsychiatr Genet 133B:64-67.

Uebel H, Albrecht B, Asherson P, Borger NA, Butler L, Chen W, Christiansen H, Heise A, Kuntsi J, Schafer U, Andreou P, Manor I, Marco R, Miranda A, Mulligan A, Oades RD, van der Meere J, Faraone SV, Rothenberger A, Banaschewski T (2010) Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD. J Child Psychol Psychiatry 51:210-218.

Uekermann J, Kraemer M, Abdel-Hamid M, Schimmelmann BG, Hebebrand J, Daum I, Wiltfang J, Kis B (2010) Social cognition in attention-deficit hyperactivity disorder (ADHD). Neurosci Biobehav Rev 34:734-743.

Valera EM, Brown A, Biederman J, Faraone SV, Makris N, Monuteaux MC, Whitfield-Gabrieli S, Vitulano M, Schiller M, Seidman LJ (2010) Sex differences in the functional neuroanatomy of working memory in adults with ADHD. Am J Psychiatry 167:86-94.

Valera EM, Faraone SV, Biederman J, Poldrack RA, Seidman LJ (2005) Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 57:439-447.

Van der Stelt O, Geesken R, Gunning WB, Snel J, Kok A (1998) P3 scalp topography to target and novel visual stimuli in children of alcoholics. Alcohol 15:119-136.

Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF (2007) Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci 10:376-384.

Vogel EK, Luck SJ (2000) The visual N1 component as an index of a discrimination process. Psychophysiology 37:190-203.

Volkow ND, Wang G, Fowler JS, Logan J, Gerasimov M, Maynard L, Ding Y, Gatley SJ, Gifford A, Franceschi D (2001) Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. J Neurosci 21:RC121.

Volkow ND, Wang GJ, Fowler JS, Ding YS (2005) Imaging the effects of methylphenidate on brain dopamine: new model on its therapeutic actions for attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1410-1415.

Volkow ND, Wang GJ, Fowler JS, Telang F, Maynard L, Logan J, Gatley SJ, Pappas N, Wong C, Vaska P, Zhu W, Swanson JM (2004) Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. Am J Psychiatry 161:1173-1180.

Wåhlstedt C, Thorell L, Bohlin G (2009) Heterogeneity in ADHD: Neuropsychological Pathways, Comorbidity and Symptom Domains. J Abnorm Child Psychol 37:551-564.

Wallis D, Hill DS, Mendez IA, Abbott LC, Finnell RH, Wellman PJ, Setlow B (2012) Initial characterization of mice null for Lphn3, a gene implicated in ADHD and addiction. Brain Res 1463:85-92.

Wan L, Friedman BH, Boutros NN, Crawford HJ (2008) P50 sensory gating and attentional performance. Int J Psychophysiol 67:91-100.

Watter S, Geffen GM, Geffen LB (2001) The n-back as a dual-task: P300 morphology under divided attention. Psychophysiology 38:998-1003.

Weissman DH, Roberts KC, Visscher KM, Woldorff MG (2006) The neural bases of momentary lapses in attention. Nat Neurosci 9:971-978.

Wild-Wall N, Oades RD, Schmidt-Wessels M, Christiansen H, Falkenstein M (2009) Neural activity associated with executive functions in adolescents with attention-deficit/hyperactivity disorder (ADHD). Int J Psychophysiol 74:19-27.

Wilens TE, Biederman J, Faraone SV, Martelon M, Westerberg D, Spencer TJ (2009) Presenting ADHD symptoms, subtypes, and comorbid disorders in clinically referred adults with ADHD. J Clin Psychiatry 70:1557-1562.

Wilens TE, Dodson W (2004) A clinical perspective of attention-deficit/hyperactivity disorder into adulthood. J Clin Psychiatry 65:1301-1313.

Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF (2005) Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. Biol Psychiatry 57:1336-1346.

Williams TJ, Nuechterlein KH, Subotnik KL, Yee CM (2011) Distinct neural generators of sensory gating in schizophrenia. Psychophysiology 48:470-478.

Wodka EL, Mahone EM, Blankner JG, Larson JCG, Fotedar S, Denckla MB, Mostofsky SH (2007) Evidence that response inhibition is a primary deficit in ADHD. Journal of Clinical and Experimental Neuropsychology 29:345-356.

Woestenburg JC, Das-Smaal EA, Brand E, Kramer S (1992) Learning during visual search in children with attentional and learning problems: a trial-to-trial evaluation of RT and ERP measures. Journal of Psychophysiology 6:204-224.

Wolf RC, Plichta MM, Sambataro F, Fallgatter AJ, Jacob C, Lesch KP, Herrmann MJ, Schönfeldt-Lecuona C, Connemann BJ, Grön G, Vasic N (2009) Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. Hum Brain Mapp 30:2252-2266.

Yacubian J, Sommer T, Schroeder K, Glascher J, Kalisch R, Leuenberger B, Braus DF, Buchel C (2007) Gene-gene interaction associated with neural reward sensitivity. Proc Natl Acad Sci U S A 104:8125-8130.

Yadon CA, Bugg JM, Kisley MA, Davalos DB (2009) P50 sensory gating is related to performance on select tasks of cognitive inhibition. Cogn Affect Behav Neurosci 9:448-458.

Yee CM, White PM (2001) Experimental modification of P50 suppression. Psychophysiology 38:531-539.

Yee CM, Williams TJ, White PM, Nuechterlein KH, Ames D, Subotnik KL (2010) Attentional modulation of the P50 suppression deficit in recent-onset and chronic schizophrenia. J Abnorm Psychol 119:31-39.

Yong-Liang G, Robaey P, Karayanidis F, Bourassa M, Pelletier G, Geoffroy G (2000) Stimulus-response incompatibility effects on event-related potentials in children with attention-deficit hyperactivity disorder. Brain Cogn 43:211-215.

Yue C, Wu T, Deng W, Wang G, Sun X (2009) Comparison of visual evoked-related potentials in healthy young adults of different catechol-O-methyltransferase genotypes in a continuous 3-back task. Neuroreport 20:521-524.

Zelazo PD, Müller U (2002) Executive function in typical and atypical development. In: Handbook of childhood cognitive development(Goswami, U., ed), pp 445-469 Oxford: Blackwell.

Zillessen KE, Scheuerpflug P, Fallgatter AJ, Strik WK, Warnke A (2001) Changes of the brain electrical fields during the continuous performance test in attention-deficit hyperactivity disorder-boys depending on methylphenidate medication. Clin Neurophysiol 112:1166-1173.

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Curriculum Vitae

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Education

- **Department of Molecular Psychiatry, Würzburg (09/2008 - 2013)**

  at the Clinic and Policlinic for Psychiatry, Psychotherapy and Psychosomatics

  Dissertation "Neuropsychological Endophenotypes of Attention-Deficit/ Hyperactivity Disorder"

  Event-related potentials, topographical measures and behavioural parameters during tasks assessing response inhibition, working memory, sensory gating and reaction time variability as putative ADHD endophenotypes, interaction with genetic markers (COMT, DAT1, LPHN3)

  Associate member (2008-2012) and speaker (2010-2011) of the DFG research training group 1253/1: "Processing of affective stimuli: from the molecular basis to the emotional experience" (GK Emotions)

  Member of RTG 1156 (9/2008-11/2009) "From synaptic plasticity to behavioural modulation in genetic model organisms"

- **ERASMUS student at the University of Kent at Canterbury, UK (2005)**

- **University of Würzburg (2002-2008)**

  Studies in Psychology, Degree: Diploma
  (with focus on Clinical Psychology and Psychopathology)

  Diploma thesis „ Facial reactions when viewing emotional expressions of AIDS patients" at the Department for Psychology I

  Electromyographic recording of M. Corrugator supercilii, M. Zygomaticus major and M. Levator labii in reaction to emotional Facial expressions of computer-generated stigmatised vs. non-stigmatised persons

Research experience

- 2004-2006 student assistant to Dr. Peter Weyers (Department for Clinical and Biological Psychiatry, University of Würzburg
- 2007 student assistant to Prof. Schneider (Department for Developmental Psychology, University of Würzburg
- 2009-2010 BMBF multi-centre study on adult ADHD: external ratings accompanying therapeutic-pharmacological interventions and follow-up (Clinic for Psychiatry, Würzburg)
- since 2009 Longitudinal assessment of childhood ADHD (Clinic for Child and Adolescent Psychiatry, Würzburg)
- since 2010 SOSTA-Net multi-centre study evaluating a social skills training for autism spectrum disorders (Clinic for Child and Adolescent Psychiatry, Würzburg)
- since 12/2011 research assistant at the Clinic for Child and Adolescent Psychiatry in Würzburg

Clinical experience

- since 2010 Social skills training for autism spectrum disorders
- since 2010 Training in behavioural psychotherapy (AVM Institute, Würzburg)

Awards & Grants

- Young Scientist Award at the 3rd International Congress on ADHD
  Talk on the topic "EEG parameters during working memory and response inhibition tasks differentiate between medicated and unmedicated ADHD patients", Young Scientists Session des 3rd International Congress on ADHD.
- GSLS travel fellowship to attend the conference of the Society for Psychophysiological Research from September 19-23 2012 in New Orleans

Publications

- Grünblatt, E.*, Geissler, J.*, Jacob, C. et al. (2012). Pilot study: potential transcription markers for adult attention-deficit hyperactivity disorder in whole blood. *ADHD Attention Deficit and Hyperactivity Disorders*. 4(2). 77-4
- Geissler, J. & Lesch, K.-P. (2011). A lifetime of ADHD: Diagnosis, treatment and neurobiological mechanisms. *Expert Reviews of Neurotherapeutics.* 11(10), 1467-1484.

Other

- Member of the psychology students' representative body (Fachschaftsinitiative Psychologie, 2002-2006)

Affidavit

I hereby confirm that my thesis entitled 'Neurophysiological Endophenotypes of Attention-Deficit/Hyperactivity Disorder' is the result of my own work. I did not receive any help or support from commercial consultants. All sourcesand / or materials applied are listed and specified I the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Würzburg, January 2nd 2013
Place, Date Signature

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation 'Neuropsychologische Endophänotypen der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung' eigenständig, d.h. inbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters angefertigt und keine anderen als die von mir angegebenen Quelle und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Würzburg, 02.01.2013
Ort, Datum Unterschrift