Cognitive Control in Attention Deficit / Hyperactivity Disorder

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Björn Albrecht

aus Detmold

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Anleiter: Prof. Dr. Aribert Rothenberger

Referent: Prof. Dr. Marcus Hasselhorn

Korreferent: Prof. Dr. Dietmar Grube

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A bear, starting from the point P, walked one mile due south. Then he changed direction and walked one mile due east. Then he turned again to the left and walked one mile due north, and arrived exactly at the point P he started from. What was the colour of the bear?

(G. Polya, How to Solve It)

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1. Introduction

1.1. Cognitive Control: Conflicts, Errors, and the Brain

1.1.1. Cognitive Control is Present in Everyday Life

One of the most salient features of the human brain is its information processing capacity. In everyday life, a lot of different information about e.g. location, look, touch, sound and smell of objects in space and time, not to say of human behaviour and language needs to be processed and updated in order to form a stable representation of the world. Most of this information needs to be processed in parallel and is in some way expressed in behaviour. However, the more the situation becomes tricky, the more these parallel processing capabilities are stressed.

Control processes are necessary if rapid changes in the environment require adaptation. Suppose you wish to cross a street, the traffic lights turn green and you begin walking. Unfortunately, a car driver did not pay attention and crosses your way, but fortunately, a monitoring and control process in the brain may help both the car driver and yourself to avoid an accident! Since a bike crash several years ago, I am convinced that this cognitive control mechanism is highly developed, but represents also a painful limitation of our abilities.

Thus, stopping of ongoing performance is relevant in everyday life and may avoid many accidents if it works properly. Cognitive control is also active when you move to Great Britain or Australia and ride a bike (particularly if you usually live in the rest of the world or stayed there for some time), when you speak a foreign language and try to avoid falling back into your native speech, or even when you go shopping (for the latter see Shallice & Burgess, 1991). Admittedly, it appears to be difficult to assess these functions in everyday life, but important aspects can be studies in more controlled laboratory situations.

More than seventy years ago, a striking phenomenon highly suitable for experimentation was observed. Reading is usually a well-learned and automatized ability that proceeds with very little effort. Thus, it may be easy to read the colour words in Figure 1 on the next page, and one may do that within a couple of seconds:

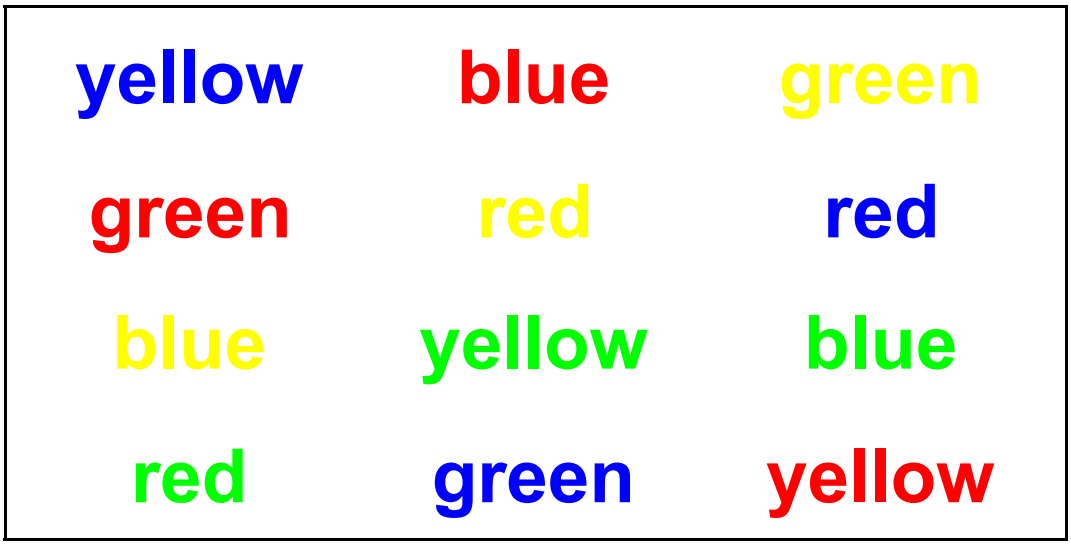

Figure 1: Material used in the Stroop-Test. Naming the colours is more difficult than reading the words (following Stroop, 1935)

But if instead the colour of the printing ink has to be named, the task becomes a lot more challenging, and you may notice a considerable lower response speed and more performance errors (Stroop, 1935).

A possible explanation of this so called Stroop-Effect is that reading the words is more habitual and produces the stronger, faster, and thus predominant response, which is in conflict or interferes with the weaker representation of the colour name. If the predominant response needs to be performed, everything is easy, and very little cognitive control is required. But in the other case, the weaker response requires effort to win over the predominant word-reading, it needs "top-down" processing (MacLeod, 1991). Thus, the task is usually asymmetrical; interference is strong for one, but not for the other demand. However, with training in colour naming, which results in shorter times to name the colour of a certain patch, interference was also found for word reading (MacLeod & Dunbar, 1988).

1.1.2. A Model of Cognitive Control and Executive Functions

The following outline of *cognitive control* is based on the work of Posner and Petersen (1990), theories of prefrontal cortex functions (Alexander *et al.*, 1990; Miller & Cohen, 2001) and a system model by Cohen et al. (2004). A general assumption of these

approaches is that information is represented in patterns of neuronal activity, and information processing occurs as the flow of activity in the brain.

In a systematic theory based mainly on findings from neuroimaging studies, Posner and colleagues have distinguished three neuronal networks of attention (Fan *et al.*, 2005; Posner & Rothbart, 2007). *Alerting* is regarded as a function modulated by norepinephrine in the locus coeruleus (LC) and the right frontal and parietal cortex that maintains sensitivity to incoming information. *Orienting* involves attention shifts towards certain stimuli, which is associated with acetylcholine and activity in the superior parietal cortex and temporal parietal junction, and for visual events also with the frontal eye fields (Corbetta & Shulman, 2002). Of particular importance for the current studies is the role of *executive attention*, which is regarded as a mechanism that mainly resolves conflict between the activities of different neuronal representations that compete for expression in behaviour. Following Posner, executive attention involves mostly dopaminergic modulations in midline frontal areas, particularly the anterior cingulate cortex (ACC), the prefrontal cortex, basal ganglia and lateral ventral areas (Posner & Rothbart, 2007). Figure 2 shows a summary of the attention networks model.

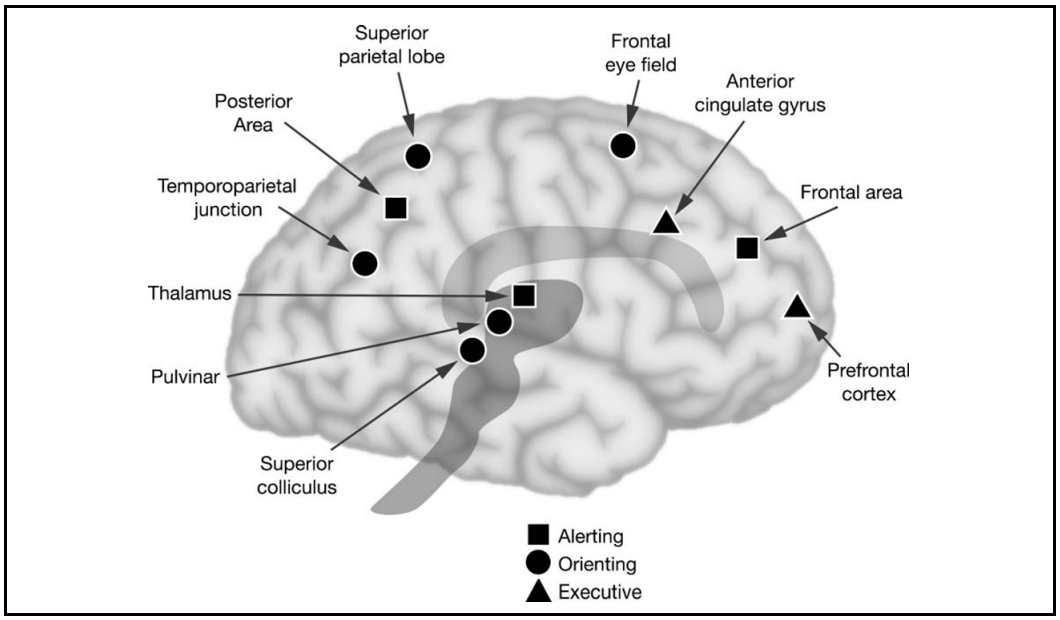

Figure 2: The anatomy of attention networks for alerting (squares), orienting (circles) and executive functions (triangles) (from Posner & Rothbart (2007), p. 6).

In order to deal efficiently with the environment, a number of interrelated functions are required. It is crucial to maintain a short term *working memory* representation of actual goals, demands and rules, which may be implemented via recurrent connectivity mediated by dopamine and NMDA-receptors within the prefrontal cortex (PFC) (Durstewitz *et al.*, 2000; Verma & Moghaddam, 1996; Wang, 1999). This representation needs *adaptive updating* in order to avoid stereotypy and perseveration, symptoms frequently reported following damage of the PFC in humans. There is some evidence that such updating may be due to a reward-driven gating mechanism initialized by dopaminergic input from the ventral tegmental area (VTA) (Pirot *et al.*, 1992; Schultz *et al.*, 1997). Thus, these mechanisms allow for *maintaining and updating representations*.

Cognitive control is required when such representations within PFC compete for expression, i.e. when actual requirements interfere with automatisms or when task demands conflict. Under such circumstances, a top-down acting *performance monitoring* system is required that represents the amount of conflict and signals the need for executive attentional control, i.e. the need for stronger activation of representations relevant for task performance within PFC. It is proposed that such a system relies on activity in the ACC (Cohen *et al.*, 2004).

However, if a person's capabilities fall short of reaching a certain goal, the model described so far would predict that a weakening performance goes along with increasing conflict, which in turn signals stronger activation of task-conducive activities. Consequently, if no regulatory mechanism is present, performance monitoring may turn into compulsivity. Following Usher et al. (1999), the balance between effort and outcome may further be regulated by activity in the LC in order to switch the modus operandi from effortful engagement in a task ("exploitation") towards exploration of new goals (Usher *et al.*, 1999).

1.1.3. Cognitive Control Revisited with Event-Related Potentials

Event-Related Potentials

The electroencephalogram (EEG) is a continuous record of brain electric potentials from electrodes on the scalp (Nunez & Srinivasan, 2006). The physiological basis of the EEG

are not the short-lasting action-potentials (1-2 ms) that would hardly summarize in time to create a sizable effect, but rather the longer-lasting (10-100 ms) post-synaptic de- or hyperpolarizations following excitatory or inhibitory postsynaptic potentials. For example, an excitatory postsynaptic potential (EPSP) leads predominantly to a local influx of positive Na^+ cations and thus to a local current sink and a distal current source (see Figure 3); inhibitory postsynaptic potentials (IPSP) generate conversely a local current source and distal sinks. Anatomical data suggest that EPSPs are most common in the superficial apical dendrites of the pyramidal cells whilst IPSPs occur mostly nearby the cell bodies in the deeper layers of the cortex (Braitenberg & Schüz, 1991; Nunez & Srinivasan, 2006) – both neural activities lead to relative current sinks at the surface of the scalp.

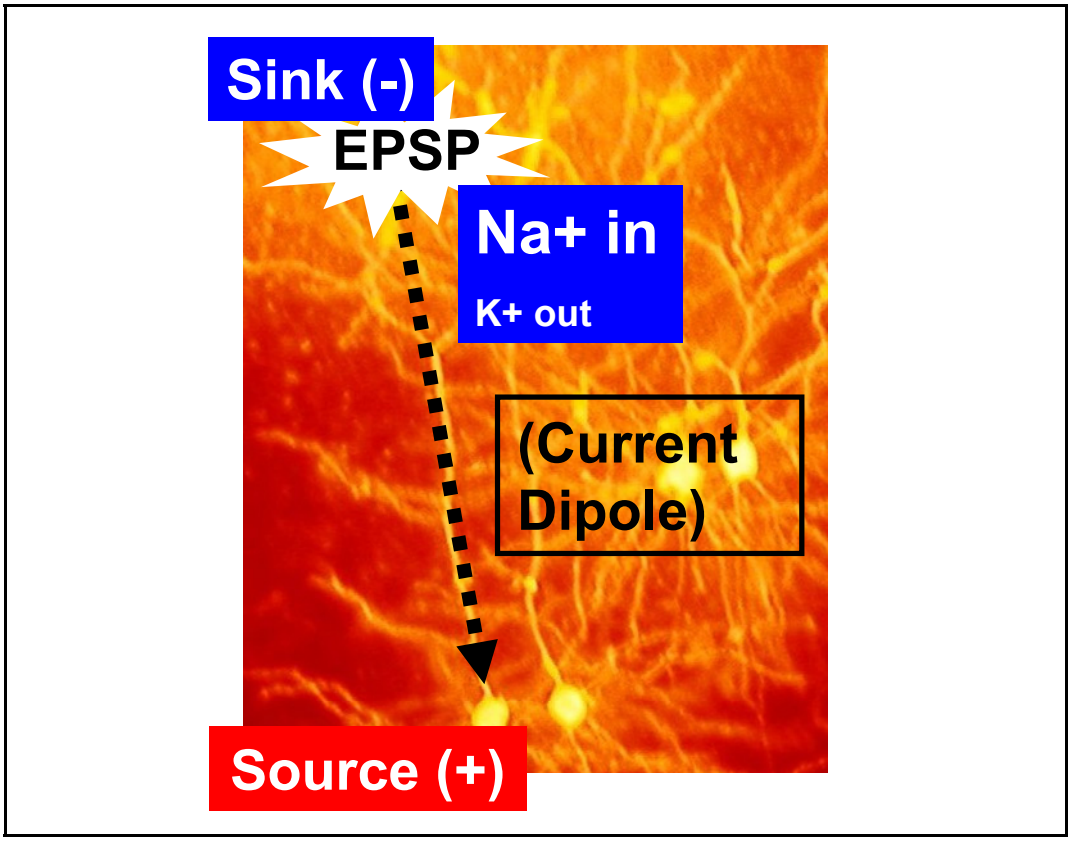

Figure 3: Electrical dipoles generated by postsynaptic potentials at the pyramidal cells are the physiological basis of the EEG (adapted from R.D. Pascual-Marqui 2009, personal communication).

Activity of a single neuron would not create a sufficiently large potential at the scalp, but since a) pyramidal cells are arranged perpendicular to the cortex surface and b) neurons

tend to be synchronously active in a given region, the dipole moment vectors may add-up to produce detectable scalp potentials – which is recorded in the EEG. However, the recorded brain activity may be contaminated with electrical artefacts generated by eye-movements, muscle activity or phase drifts due to electrode polarization, etc., which must be controlled for in subsequent data processing (Picton *et al.*, 2000).

The spontaneous EEG contains information about underlying brain activity with respect to frequency and coherency between recording locations. This allows inferences to certain mental states, e.g. discriminating relaxation from more activated and focused states, or the distinction of sleep stages (Rothenberger, 2009). The next step is to investigate brain activity that is correlated in time with certain events such as the presentation of stimuli. Since spontaneous activity recorded in the EEG has a mean voltage over time of null, it cancels out if a sufficient number of EEG-segments are averaged. The same happens if the segments contain an event at a fixed time; remaining activity would have a stable relationship in time with the event – that is an event-related potential (ERP). It may contain earlier exogenous potentials that reflect predominantly physical features of the eliciting event as well as endogenous potentials which may reflect systematic higher-order information processing. Such ERPs can be characterized by latency, amplitude, frequency and topography of significant components. If the EEG is recorded with many electrodes in high spatial resolution, microstates with relatively stable brain maps can be determined (Lehmann, 1987). And in conjunction with a number of structural assumptions, approximate source localisations can be calculated (Fuchs *et al.*, 2002; Jurcak *et al.*, 2007; Pascual-Marqui, 2002).

Event-Related Potentials and Cognitive Control

Several aspects of cognitive control can be assessed in high temporal resolution using ERPs. According to Posner's model of attention networks, alerting and orienting are associated with activity in posterior brain regions. Both networks should be activated in the Continuous Performance Test (CPT) by the cue stimulus that signals the potential need for a response in the following trial. sLORETA source localisation of the Cue-P3 from healthy children (maximal amplitudes about 500 ms after Cue-onset in children, latencies in adults are considerably shorter) confirms this view (see Figure 4, above).

Cued distractors in the CPT do not require execution of a prepared response and evoke a Nogo-P3a maximal at fronto-central sites. Several authors suggest that it reflects response inhibition (Fallgatter & Strik, 1999; Pfefferbaum *et al.*, 1985), but i.e. since Nogo-P3a latency (e.g. around 400 ms in children) seems too late with respect to Go reaction times, it may rather initiate termination of motor activation (Falkenstein *et al.*, 1999; Kopp *et al.*, 1996). Clearly, these aspects are interrelated, and thus Nogo-P3a is regarded here as a feature of terminal response control, closely related to activity of the executive attention network described by Posner & Rothbart (2007). Nogo-P3a may be generated in medial or anterior cingulate cortex, premotor areas and frontal areas, probably following dopaminergic input from basal ganglia (Beste *et al.*, 2008; Kiefer *et al.*, 1998; Verleger *et al.*, 2006; Weisbrod *et al.*, 2000). A recent study suggests that this may similarly be the case in children (Albrecht et al., in preparation; see Figure 4, below).

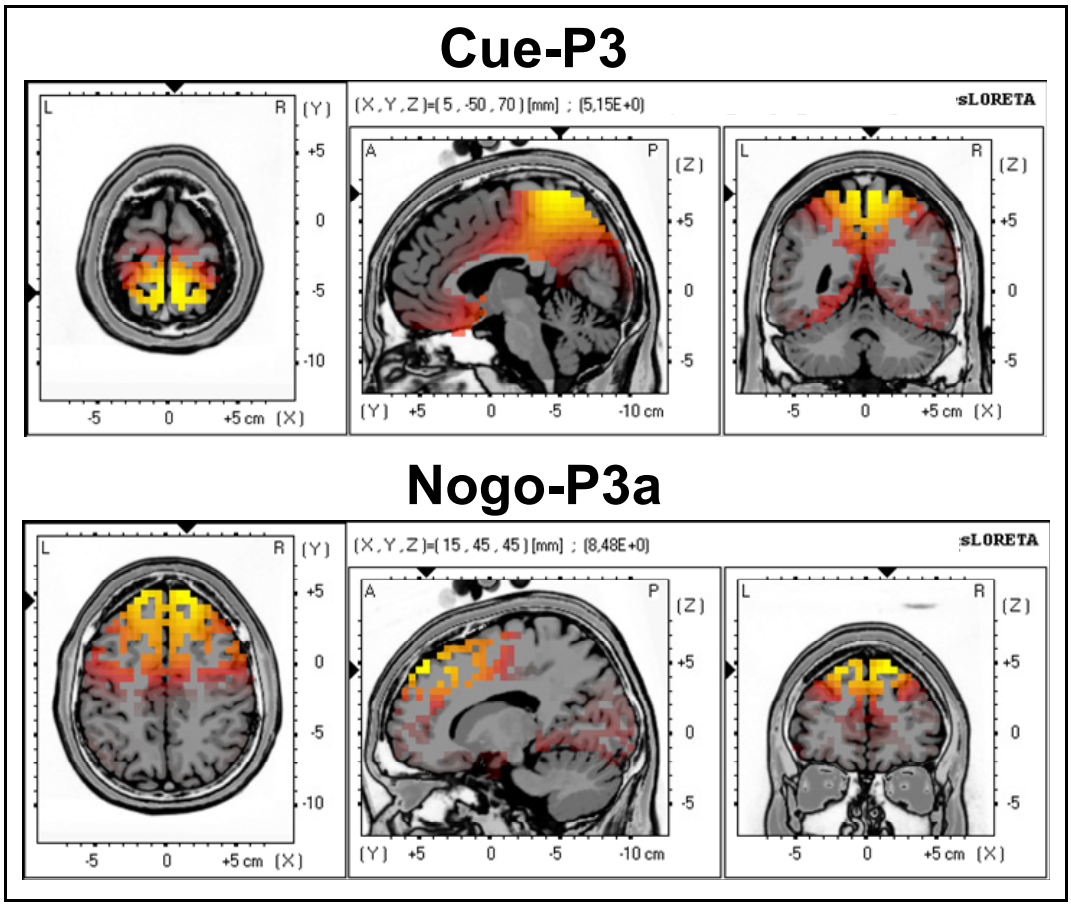

Figure 4: The CPT activates both posterior alerting and orienting networks following the cue as indicated by Cue-P3 and terminal response control after cued distractors reflected in the Nogo-P3a (sLORETA source localisation from grand average ERPs of healthy children; from Albrecht et al., in preparation).

Cognitive control as an important aspect of executive functioning comes also into play *when task demands conflict*. For instance, if a task requires responding to a certain stimulus but to withhold the response to another one, the stimulus-locked ERP usually shows a fronto-central negativity preceding the Nogo-P3a with a maximum at around 200 to 400 ms after onset of the stimulus. Its amplitude is larger for the Nogo than for the Go condition, particularly when the Nogo condition is rare. The same effect can be observed in the Flanker-Task when the target is primed with either incongruent compared to congruent distractors. The so called N2 and the N2-enhancement were originally attributed to (response) inhibition (Falkenstein *et al.*, 1999; Kok, 1999), but recent studies suggest that it reflects a more general monitoring process that is also present if no response needs to be inhibited (Donkers & van Boxtel, 2004; Nieuwenhuis *et al.*, 2003).

Cognitive control is probably also required *after errors*. Around forty years ago, Rabbitt reported that errors in simple choice reaction time tasks were executed faster than correct responses, but responses following errors were considerably slower. This phenomenon was thought to reflect that errors occur when "a subject attempts to respond faster than some limitation to his capacity allows" (p. 272), which is usually followed by some kind of remedial adaptation (Rabbitt, 1966). In the response-locked ERP, errors are generally accompanied by a negative component peaking approximately 40-120 ms after the erroneous response at fronto-central sites (error negativity or error related negativity, Ne) with sources in the anterior cingulate cortex and supplementary motor area (SMA) (Dehaene *et al.*, 1994; Falkenstein *et al.*, 1990; Gehring *et al.*, 1993; Holroyd *et al.*, 1998). It is frequently followed by a more parietal positive deflection (error positivity, Pe) within 200 to 500ms after the response (Falkenstein *et al.*, 2000).

The Ne is described in a variety of simple reaction-tasks (Falkenstein et al., 2000; Hogan *et al.*, 2005) or tasks with more complex demands such as mental rotation (Band & Kok, 2000), when errors of choice or commission-errors (Scheffers *et al.*, 1996) were made. It occurs when the response is given by hand, with foot (Holroyd et al., 1998) or with eye-movements (Nieuwenhuis *et al.*, 2001). Thus, several hypotheses ascribe Ne a crucial role in error detection and response monitoring such that it may reflect *mismatch* (Falkenstein et al., 1990; Gehring et al., 1993) or *conflict* (Carter *et al.*, 1998) *between error and required response*. Ne is susceptible to dopaminergic manipulations since dopamine agonists enhance and antagonists reduce its amplitude (de Bruijn *et al.*, 2004; de Bruijn *et*

al., 2006; Zirnheld *et al.*, 2004). Some studies suggest that N2 and Ne evoked by Go/Nogo- or Flanker-Tasks share similar electrical sources in the medial frontal cortex and may reflect the same process triggered by different aspects of task performance (Bekker *et al.*, 2005; Ridderinkhof *et al.*, 2002; Van Veen & Carter, 2002; Yeung & Cohen, 2006). This hypothesis is also confirmed by sLORETA source localisations of healthy children's N2-enhancement following stimulus conflict and enhancement of response negativity after errors (Ne) minus correct responses of choice evoked by a Flanker-Task (see Figure 5).

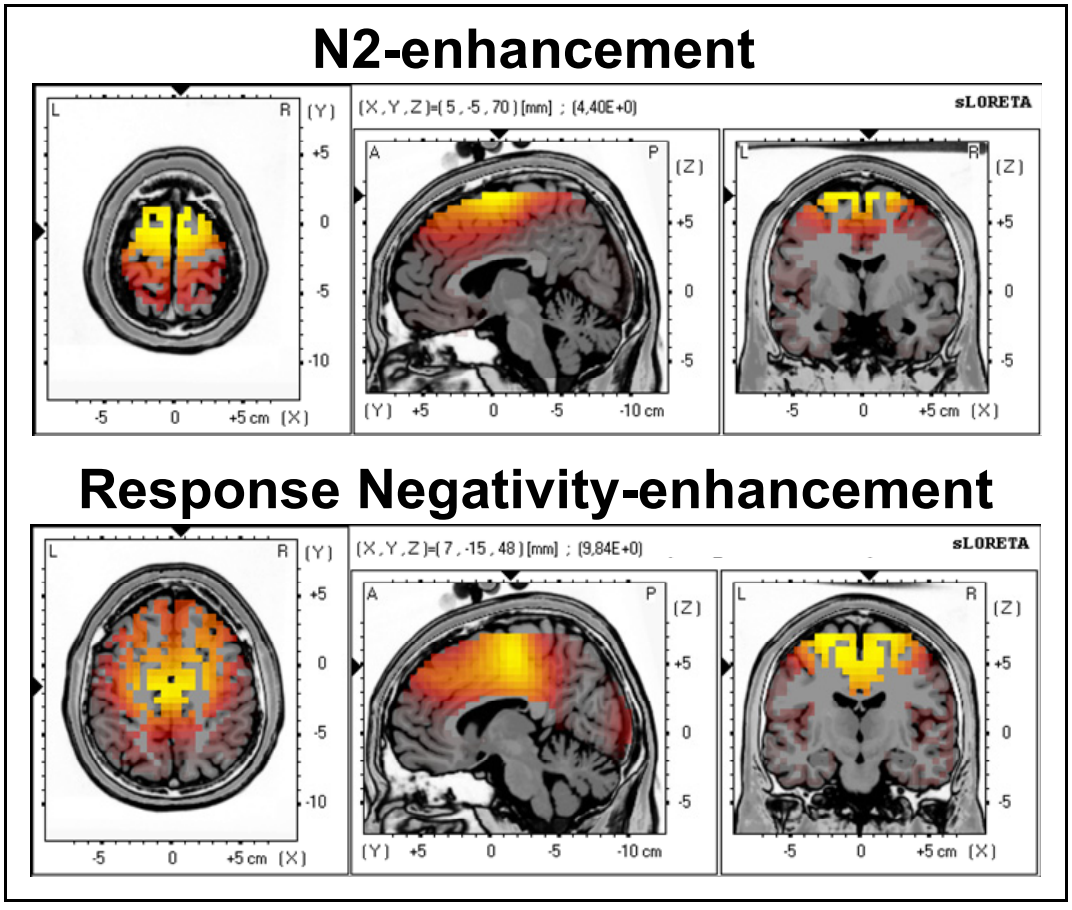

Figure 5: Healthy children's grand average N2-enhancement to processing conflict in absence of performance errors (above) and response negativity enhancement between Ne following errors and activity following correct responses (below). Both components share similar sources in SMA, ACC and dorsal PFC, which highlights the interplay of motor programming and action monitoring processes in cognitive control (from data reported previously by Albrecht et al. 2008a).

1.2. Attention Deficit / Hyperactivity Disorder

1.2.1. What is ADHD?

Attention Deficit / Hyperactivity Disorder (ADHD) is an early-onset psychiatric disorder, characterized by severe and age-inappropriate levels of pervasive Inattention, Hyperactivity and Impulsivity (APA, 1994). It occurs in about 5% of school-age children with a strong overrepresentation of boys (Polanczyk *et al.*, 2007). Whilst severity of hyperactivity and impulsivity may decrease with age, about one third of childhood ADHD cases persist into adulthood and lead to long-term educational and psycho-social disadvantages (Swanson *et al.*, 1998).

A meta analysis by Faraone et al. (2005) showed that 3/4 of variability in ADHD may be explained by genetics (heritability). However, only a small number of genes showed significant associations with ADHD on the basis of pooled odds ratios across studies (these were a) in the catecholaminergic system genes associated with the dopamine D4 and D5 receptors, the transporter, and the enzyme dopamine β-hydroxylase responsible for conversion of dopamine to norepinephrine; b) in the serotonergic system the transporter and 1B receptor genes; and moreover c) the gene encoding the Synaptosomal-Associated Protein 25, as also present in the hyperactive coloboma mouse), but the effects were rather small with odds-ratios ranging from 1.18 to 1.46 (Faraone *et al.*, 2005).

There are also neurobiological but nongenetic risks for the development of ADHD, such as prenatal exposure to alcohol, drugs and nicotine, low birth weight and traumatic brain injuries (Becker *et al.*, 2008; Max *et al.*, 1998; Mick *et al.*, 2002). Since arterial supply terminates in the anterior forebrain which is responsible for executive control, these regions and associated functions are particularly sensitive to perinatal hypoxia and toxins. Other possibly related factors are maternal stress during pregnancy and poor early caregiving (Schachar & Tannock, 2002; Stevens *et al.*, 2008; Uebel, 2007).

Classification

Following the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association, the diagnosis of ADHD combined-type requires the presence of six out of nine *Inattention symptoms* (i.e. “Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities“, “Often has

difficulty sustaining attention in tasks or play activities", "Is often easily distracted by extraneous stimuli", etc.) and six out of nine *Hyperactive-Impulsive symptoms* (e.g. "Often leaves seat in classroom or in other situations in which remaining seated is expected", "Is often 'on the go' or often acts as if 'driven by a motor'", "Often blurts out answers before questions have been completed", etc.). If only one domain is present, the ADHD diagnosis of predominantly inattentive or predominantly hyperactive-impulsive subtype is possible (APA, 1994). Diagnoses according to the World Health Organization's International Classification of Diseases 10 (ICD-10; WHO, 2004) requires the concurrent presence of at least six inattentive, three hyperactive and one impulsive symptom and do thus not permit symptomatic subtyping. Moreover, the ICD-10 diagnosis is generally more rigorous, and consequently prevalence rates for ADHD are considerably lower (1-2%) as compared to DSM-IV's (~ 5%).

Further, the two classification schemes deal differently with comorbidity; that is if the patient meets the criteria for another psychiatric disorder. Whereas DSM-IV allows diagnosis of multiple disorders, this is not feasible in ICD-10. However, if criteria for both ADHD and Oppositional Defiant / Conduct Disorder are fulfilled, ICD-10 requires the diagnosis of "Hyperkinetic Conduct Disorder" (WHO, 2004).

Comorbidity

Co-occurrence of symptoms from other psychiatric disorders above chance is not an exception, but the rule in ADHD. As described by Schachar & Tannock (2002), more than half of the children with ADHD also meet criteria for at least one comorbid disorder. The most frequent comorbidities are Oppositional Defiant Disorder (ODD, in 35-50% of the patients with ADHD) and the later development of Conduct Disorder (CD, ~25%), Anxiety (25%) and Depressive Disorder (15%), and Learning Disability (15-40%) or Language Impairment (15-70%). In each of the cases, it remains an open question whether the comorbidity is due to referral bias in clinical populations (i.e. patients with more than one disorder are preferred for service), whether ADHD increases the risk for a second disorder, whether the disorders share common causes or whether the comorbidity is essentially a separate clinical entity (Schachar & Tannock, 2002).

1.2.2. Models of ADHD

Theoretical accounts of ADHD can be subdivided into approaches that favour cognitive, motivational and combined explanations. Although there are also not so subtle differences between the theories, the following section dwells on the similarities within each category.

Cognitive Theories

Central to cognitive theories on ADHD is the role of *executive functions*, which are described as higher-order top-down processes that manage a wide array of cognitive functions in order to adapt flexibly to novel or changing situations. Executive functions include working memory, verbal fluency, set shifting, etc. that are engaged in planning, organizing and controlling goal directed behaviour. It is further thought that these control processes are located within the prefrontal cortex, which makes cognitive theories of ADHD essentially applied theories of PFC functions (Barkley, 1997; Castellanos & Tannock, 2002; Pennington & Ozonoff, 1996; Sergeant, 2005). Thus, executive functions are closely related to cognitive control and particularly executive attention, as described in previous chapters.

One such cognitive dysfunction model of ADHD is described by Barkley (1997) on the basis of theories about neuropsychological functions of the prefrontal cortex (Fuster, 1989; Gray, 1991). It is assumed that the core deficit of ADHD is *behavioural inhibition*, which is further subdivided into three sub-components. Generally, inhibition of an event may be conceptualized as something that reduces the probability of that event. Following Barkley, behavioural inhibition is required for the proper functioning in four distinct domains of executive functions (see Figure 6). Consequently, *working memory* as required when events should be held in mind for the organization of behaviour may be compromised, impaired *self-regulation of affect, motivation and arousal* may result in difficulties to maintain an alert and productive state during performance, hindered *internalization of speech* may result in lower problem-solving and reasoning capabilities, and finally impaired *reconstitution* may limit the capability to analyze and synthesize new behaviour (Barkley, 1997).

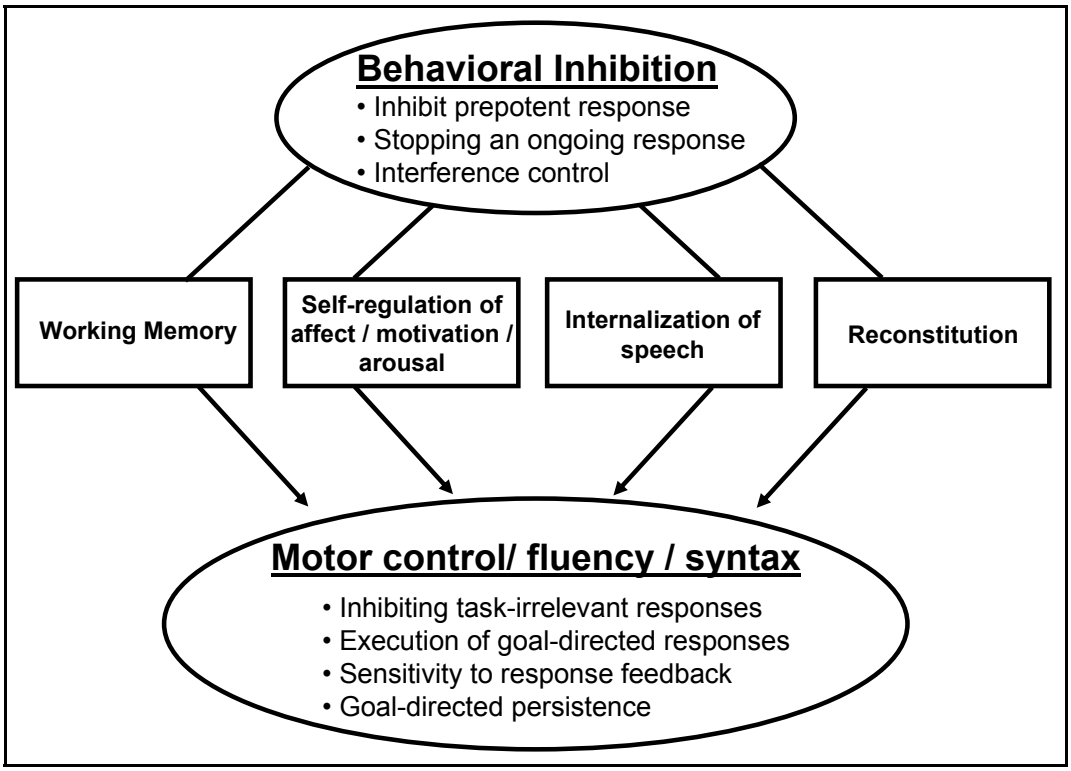

Figure 6: Behavioural inhibition as the core deficit in ADHD (adapted from Barkley, 1997). The model provides an important step in ADHD research, but the idea of a core deficit is empirically proved wrong.

Predictions of cognitive theories are supported by numerous studies with tasks tapping executive functions, but ADHD appears to be nevertheless a neuropsychologically heterogeneous construct (Doyle, 2006; Tannock, 1998): critical for Cognitive Theories of ADHD is that impairments in executive functions are present in many, perhaps the majority of ADHD patients, but not in each and every case. Moreover, also a number of control subjects do show cognitive impairments but not ADHD, indicating that cognitive impairments are probably not the core deficit of the disorder (Nigg *et al.*, 2005). Moreover, deficits in executive functions appear not to be specific in ADHD, since other externalising disorders do also display impaired performance in tasks tapping executive functions (Sergeant *et al.*, 2002).

Taken together, cognitive theories do provide an important and partially successful account for understanding the problems of many patients suffering from ADHD, but not all cases share the same common cognitive impairments.

Motivation

Diminished performance in cognitive tasks may follow motivational problems, thus overt performance has to be differentiated from non-overt ability. Although this interpretation is not necessarily neglected by purely cognitive theories, motivational theories of ADHD stress the impact of sub-optimal reward processes and do not claim cognitive impairments per se.

A model proposed by Sagvolden and colleagues (1998) claims that ADHD is characterized by a steeper gradient between the delay of a reinforcer and its effect on the probability that the reinforced action will be repeated, both prospective and retrospectively (Sagvolden *et al.*, 1998). Figure 7 shows a prediction of this model. Following that, ADHD requires immediate reinforcement of actions and during learning, an effect also utilized in behavioural therapy (Döpfner & Sobanski, 2009).

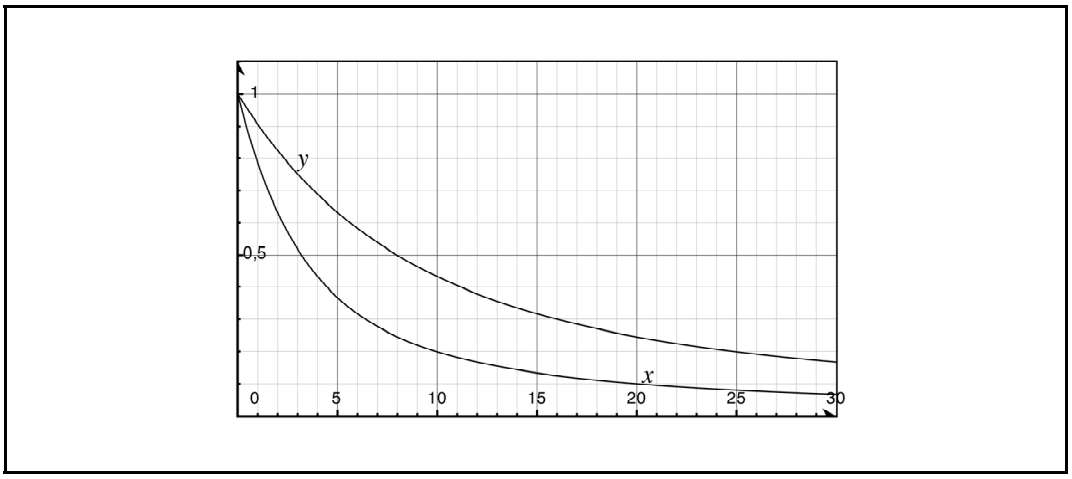

Figure 7: The behaviour of patients with ADHD may be explained by a steeper delay of reinforcement gradient. The function is also used as a model of response strength in behaviourism and is basically the integral of the well known decay function $f_{(t)}=N_0*e^{-\lambda t}$ from t=0 to t, divided by t: $N_{(t)}=N_0*(1-e^{-\lambda t})*(\lambda t)^{-1}$, where N_0 is the effect of a immediate reinforcer, t is some unit of time and λ the decay constant (adapted from (Killeen, 2001)). For the graph above, N_0 is set to 1, with λ=0.5 in the steeper and λ=0.2 for the moderate gradient. Thus, we get a quantifiable model which hypothesizes higher values for λ in ADHD as compared to Controls.

Another approach by Sonuga-Barke focuses on delay aversion in ADHD, i.e. it was found that children with ADHD display hypersensitivity to delay and may thus exhibit difficulties

in maintaining work over extended periods of time which may be regarded as inattention and overactivity (Sonuga-Barke *et al.*, 2004; Sonuga-Barke *et al.*, 1994).

Motivational theories are supported by reports that children with ADHD seem to be highly sensitive to reward (Douglas & Parry, 1994), and some studies found improved performance in tasks tapping executive functions if incentives were given within due time (Sagvolden *et al.*, 2005; Slusarek *et al.*, 2001). In a recent study with a Go/Nogo-task tapping response control (see section 2.4.), we detected that a motivational dysfunction does show familial effects in ADHD, but that even under immediate reinforcement regime children with ADHD still show cognitive impairments (Uebel *et al.*, 2009).

Multiple Pathways

The problems of cognitive and motivational theories of ADHD arise when they are regarded as competitive rather than complementary. Approaches that consider multiple developmental pathways may bridge the gap (Nigg *et al.*, 2004; Sonuga-Barke, 2005).

One such theory was described by Sonuga-Barke (2005). In this theory, the cognitive branch of executive functions is related to basal-ganglia and thalamocortical pathways as described similarly in the theory of cognitive control outlined in chapter one. The proposed circuit links the (dorso-lateral) prefrontal cortex via excitatory dopaminergic connections to the dorsal striatum, and further via inhibitory dopaminergic connections via the dorsal neostriatum (particularly the caudate nucleus) and dorsomedial thalamus with excitatory glutaminergic (norepinephrine) cells back to the prefrontal cortex (Alexander *et al.*, 1990; Sonuga-Barke, 2005). Since dopamine is a key modulator in this circuit, this may explain why pharmacological treatment with stimulants effectively reduces cognitive problems in many patients with ADHD and may further support performance and motor inhibition (Jonkman *et al.*, 1997; Lawrence *et al.*, 2005; Moll *et al.*, 2000).

Impairments of reinforcement, learning and motivation have been associated with the orbito-frontal cortex connected via dopaminergic and norepinephrinergic neurons with the anterior cingulate (ACC) as part of a frontal circuit mediated by the amygdala that further includes the ventral pallidum, the ventral striatum (nucleus accumbens) and the thalamus (Alexander et al., 1990; McClure *et al.*, 2004; Sonuga-Barke, 2005). Structural predictions of the model have been tested in animal studies, e.g. lesions in the nucleus accumbens led

to persistent impulsive choice of small immediate over large delayed rewards in rats (Cardinal *et al.*, 2001). Studies showed similar response style also in children with ADHD (Marco *et al.*, 2009)

Taken together, ADHD symptoms may derive from individually heterogeneous impairments in executive functions or reward processing and motivation due to dysfunctions in fronto-striatal dopaminergic networks which control attentional processes (Barkley, 1997; Pennington & Ozonoff, 1996; Sergeant, 2005; Sonuga-Barke, 2005).

1.3. Unresolved Issues

The situation in psychiatry now appears to be similar to the situation in physics during the discovery of subatomic particles. Experiments beginning in the 1950s with hadron colliders revealed several hundreds of new subatomic particles. Later, it was found that this ever growing array of "strongly interacting particles" could be classified by a few characteristics of even smaller elements and their interactions (Feynman, 1974).

Subatomic particles of psychiatry are potentially where the current classification systems like DSM-IV show heterogeneity within and overlap between characteristics of disorders. This may explain why molecular genetics so far can hardly explain disorders like ADHD in spite of high heritability, and why it is difficult to differentiate for example ADHD from ODD/CD on the level of functional impairments: these disorders are classified concerning their symptoms, but the classification may be heterogeneous concerning underlying neuronal dysfunctions. A possible solution for this predicament may be the search for endophenotypes, which are intermediate phenotypes defined by heritable, quantitative indices of risk for the disorder associated closely with biological factors. Endophenotypes may help to understand the complex relationships between genetics, environmental factors and behaviour, and may serve as useful intermediate constructs that explain the heterogeneity of the ADHD phenotype (Buitelaar, 2005; Doyle *et al.*, 2005; Gottesman & Gould, 2003).

This thesis addresses some of these questions. It is argued that cognitive control is very important in every day life, and that ADHD may at least partly follows impairments of related brain functions. The second chapter covers several studies in which aspects of cognitive control in childhood ADHD are assessed.

In the first experiment, the ability to inhibit prepotent responses is assessed in children with ADHD, ODD/CD, children with comorbid ADHD+ODD/CD and controls in order to test whether this important aspect of cognitive control is shared among these externalising disorders, and whether particularly the comorbidity of the two forms a separate clinical entity. The second experiment tests whether a widely accepted notion of ADHD as a disorder with particular interference liability as seen in task performance holds if a number of problematic confounds in frequently used study designs are ruled out. The third experiment tests whether cognitive control in terms of action monitoring and error processing is familially-driven in ADHD, and may thus represent an endophenotype for the disorder. The fourth and last experiment is about the particular role motivation plays in task performance of children with ADHD.

2. Original Publications

This chapter contains the following original articles which were at the submission date of the thesis published or accepted for publication: Please note that the fourth is given in the final edition published online March 2010.

1. Albrecht, B., Banaschewski, T., Brandeis, D., Heinrich, H., & Rothenberger, A. (2005). Response inhibition deficits in externalizing child psychiatric disorders: an ERP-study with the Stop-task. *Behavioral and Brain Functions, 1*, 22.
2. Albrecht, B., Rothenberger, A., Sergeant, J., Tannock, R., Uebel, H., & Banaschewski, T. (2008). Interference control in attention-deficit/hyperactivity disorder: differential Stroop effects for colour-naming versus counting. *Journal of Neural Transmission, 115*(2), 241-247.
3. Albrecht, B., Brandeis, D., Uebel, H., Heinrich, H., Mueller, U. C., Hasselhorn, M., Steinhausen, H.C., Rothenberger, A., Banaschewski, T. (2008). Action monitoring in boys with attention-deficit/hyperactivity disorder, their nonaffected siblings, and normal control subjects: evidence for an endophenotype. Biological Psychiatry, 64(7), 615-625.
4. Uebel, H., Albrecht, B., Asherson, P., Börger, N. A., Butler, L., Chen, W., Christiansen, H., Heise, H., Kuntsi, J., Schäfer, U., Andreou, P. Manor, I., Marco, R. Miranda, A., Mulligan, A., Oades, R.D., van der Meere, J., Faraone, S.V., Rothenberger, A., Banaschewski, T. (2010). Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD. *Journal of Child Psychology and Psychiatry, 51, 210-8.*

2.1. Response inhibition Deficits in Externalizing Child Psychiatric Disorders: An ERP-Study with the Stop-Task

Response inhibition is arguably an important feature of every day performance, and a number of theories suppose that children with ADHD and ODD/CD may show impairments (Barkley, 1997; Quay, 1993). There is a further debate whether the frequent comorbidity of ADHD and ODD/CD symptoms should be considered as a simple additive model of the disorder as suggested by the American Psychiatric Association's Diagnostic and Statistical Manual IV (DSM-IV, APA, 1994), or whether it reflects a separate clinical entity as proposed by the World Health Organization in their International Classification of Diseases 10 (ICD-10, WHO, 2004).

The current manuscript (Albrecht *et al.*, 2005) describes performance and electrophysiological parameters of children with these disorders and healthy controls in a simple two-choice reaction-time task that requires stopping of an already ongoing response due to an auditory stop-signal. As a main characteristic of the task, stopping becomes more difficult with increasing stop-signal delays. Pilot tests with a comparable sample revealed that a sufficient number of correct and failed stop trials occurred at stop-signal delays around 250 ms, which was analysed using event-related potentials. It was confirmed that successful stopping goes along with a right-frontal negative deflection in the ERP that is markedly reduced in children with ADHD and ODD/CD, but not in comorbid ADHD+ODD/CD, which was also paralleled by an estimated parameter of the speed of the inhibition process (stop signal reaction time).

These, and earlier reported findings with the Continuous Performance Test (Banaschewski *et al.*, 2003) as well as genetics (Christiansen *et al.*, 2008; Faraone *et al.*, 1997) support that comorbid symptoms of ADHD and ODD/CD may form a separate pathological entity with distinct neuropsychological and -physiological impairments compared to both ADHD and ODD/CD as considered in the ICD-10 classification system.

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Response inhibition deficits in externalizing child psychiatric disorders: An ERP-study with the Stop-task

Björn Albrecht*[1], Tobias Banaschewski[1], Daniel Brandeis[2], Hartmut Heinrich[3,4] and Aribert Rothenberger[1]

Address: [1]Child and Adolescent Psychiatry, University of Göttingen, Germany, [2]Child and Adolescent Psychiatry, University of Zürich, Switzerland, [3]Child and Adolescent Psychiatry, University of Erlangen, Germany and [4]Heckscher-Klinik, München, Germany

Email: Björn Albrecht* - balbrec@gwdg.de; Tobias Banaschewski - tbanasc@gwdg.de; Daniel Brandeis - brandeis@kjpd.unizh.ch; Hartmut Heinrich - hheinri@arcor.de; Aribert Rothenberger - arothen@gwdg.de

* Corresponding author

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Abstract

Background: Evidence from behavioural studies suggests that impaired motor response inhibition may be common to several externalizing child psychiatric disorders, although it has been proposed to be the core-deficit in AD/HD. Since similar overt behaviour may be accompanied by different covert brain activity, the aim of this study was to investigate both brain-electric-activity and performance measures in three groups of children with externalizing child psychiatric disorders and a group of normal controls.

Methods: A Stop-task was used to measure specific aspects of response inhibition in 10 children with attention-deficit hyperactivity disorder (AD/HD), 8 children with oppositional defiant disorder/conduct disorder (ODD/CD), 11 children with comorbid AD/HD+ODD/CD and 11 normal controls. All children were between 8 and 14 years old. Event-related potentials and behavioural responses were recorded. An initial go-signal related microstate, a subsequent Stop-signal related N200, and performance measures were analyzed using ANCOVA with age as covariate.

Results: Groups did not differ in accuracy or reaction time to the Go-stimuli. However, all clinical groups displayed reduced map strength in a microstate related to initial processing of the Go-stimulus compared to normal controls, whereas topography did not differ. Concerning motor response inhibition, the AD/HD-only and the ODD/CD-only groups displayed slower Stop-signal reaction times (SSRT) and Stop-failure reaction time compared to normal controls. In children with comorbid AD/HD+ODD/CD, Stop-failure reaction-time was longer than in controls, but their SSRT was not slowed. Moreover, SSRT in AD/HD+ODD/CD was faster than in AD/HD-only or ODD/CD-only. The AD/HD-only and ODD/CD-only groups displayed reduced Stop-N200 mean amplitude over right-frontal electrodes. This effect reached only a trend for comorbid AD/HD+ODD/CD.

Conclusion: Following similar attenuations in initial processing of the Go-signal in all clinical groups compared to controls, distinct Stop-signal related deficits became evident in the clinical groups. Both children with AD/HD and ODD/CD showed deficits in behavioural response-inhibition accompanied by decreased central conflict signalling or inhibition processes. Neither behavioural nor neural markers of inhibitory deficits as found in AD/HD-only and ODD/CD-only were additive. Instead, children with comorbid AD/HD+ODD/CD showed similar or even less prominent inhibition deficits than the other clinical groups. Hence, the AD/HD+ODD/CD-group may represent a separate clinical entity.

Background

Attention-deficit hyperactivity disorder (AD/HD) is characterised by symptoms of severe inattention, overactivity and impulsiveness. With its prevalence of 3–5% in school-age-children, AD/HD is one of the most common disorders in child and adolescent psychiatry [1]. According to Barkley's theory of AD/HD [2,3], deficient behavioural inhibition is the core deficit of the disorder, and may lead to impairments of executive functions. Behavioural inhibition may be separated into three interrelated processes called 'inhibition of the initial prepotent response to an event', 'stopping of an ongoing response' and 'interference control'.

Several behavioural studies reported deficits of response-inhibition in children with AD/HD ([4-8]; for a review see [9]). However, impaired behavioural response inhibition is also observed in children with other disruptive disorders such as ODD/CD [9], which is the most prevalent comorbidity of AD/HD and poses significant additional clinical and public health problems. In addition, further deficits which are not likely to result from deficient inhibition are present in children with AD/HD, as evident from their poor performance in a variety of executive functions tasks such as the Continuous Performance Test (CPT) [10,11], Wisconsin Card-Sorting-Task [12-14], Tower-of-Hanoi [13,14] and Stroop-Test [12,15]; for a review see [16,17].

In a more neurophysiologically oriented theory covering both ADHD and ODD/CD, Quay [18,19] following Gray [20] argued that the behavioural activation system (BAS, sensitive to reward) and the behavioural inhibition system (BIS, sensitive to punishment) may reflect distinct pathways for inhibition deficits. Children with AD/HD may suffer from an underactive BIS while their BAS seems to be unimpaired, whereas children with ODD/CD should have an overactive BAS that dominates their (unimpaired) BIS. Therefore, according to Quay's theory both AD/HD and ODD/CD groups should display deficits in inhibition, but for very different reasons. If comorbid AD/HD+ODD/CD is an additive combination of AD/HD and ODD/CD, this group should display the worst impairment in response inhibition because an overactive BAS may be combined with a weak BIS. Concerning response control, results from a recent neurophysiological study with the CPT-task are consistent with this prediction, and indicate that such deficits are indeed particularly pronounced in this comorbid group [21]. Deficits in executive functioning in general, and inhibition deficits in particular are also explained by other neurophysiological theories focusing on either AD/HD or ODD/CD. For ODD/CD [22-24], it has been argued that deficits of the prefrontal cortex leads to reduced orienting and arousal, both of which predispose individuals to stimulation-seeking, disinhibition and attention deficits, and thereby to antisocial behaviour.

The ‚Stop-signal paradigm'[25] allows investigating well defined response inhibition processes directly. Generally, the subjects perform a simple or a two choice reaction task. In some of the trials, a Stop-signal follows the go-stimulus at a given delay and requires the inhibition of the ongoing response. The longer the Stop-signal-delay (SSD), the more difficult it becomes to inhibit the response. The „horse race" model of the Stop-task, which assumes a race between the reaction to the primary task and the reaction to the Stop signal, further allows to estimate the "virtual" reaction time to the Stop-signal (SSRT) as a measure for response inhibition performance [25]. In a meta-analysis of the Stop-task, Oosterlaan et al. [26] reported that behavioural studies showed consistently slower SSRT for children with ADHD, but also for children with CD compared to controls, Comparisons between AD/HD and CD as well as between AD/HD+CD and AD/HD revealed no differences. However, inferences based on performance data only may have limited validity, because differences in covert brain mechanisms may lead to similar overt performance [21,27].

A more direct access to brain functions is provided by non-invasive methods such as functional magnetic resonance imaging (fMRI) [28] or event related potentials (ERP) [29]. Briefly, in the blood-oxygenation-level-dependent (BOLD) fMRI, changes in cerebral blood-flow and metabolism related to neuronal activation are measured with high spatial but low temporal resolution reflecting the underlying hemodynamic process. ERPs are voltage topographies and fluctuations recorded on the scalp which reflect neural activation to an event such as the presentation of a stimulus or a response. A major advantage of the ERP technique is the high temporal resolution in the range of milliseconds which allows to measure brain-electrical correlates of information-processing in realtime. A number of studies therefore used electrophysiological or fMRI measures of response inhibition processes in AD/HD [7,27,30-32].

An ERP-study of Brandeis et al. [27] revealed that in AD/HD children, successful Stops differed from Stop-failures with topographic alterations in a microstate which reflected mainly processing of the go-stimulus, whereas normal controls differed at a slightly later stage of processing with increased global-field-power (GFP, the spatial standard deviation of voltages) in Stop-failures compared to correct Stops. Rubia et al. [30] reported that during their fMRI-study, decreased right-inferior-prefrontal activation in AD/HD occurred solely in the Stop-task, and thus hypothesized the "brake system of the brain" [30] to be located right-prefrontal. Pliszka et al. [7] reported for

Table 1: Performance Data

		Group						
		Controls (N) N = 11	AD/HD (A) N = 10	AD/HD+ODD/CD (AO) N = 11	ODD/CD (O) N = 8	ANCOVA (covariate "age")		
Measure		**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**$F_{(3,35)}$**	**p**	**Planned contrasts**
Go-reaction-time (ms)		598 (81.6)	583 (46.2)	594 (52.7)	649 (109.9)	1.97	.14	
SD of Go-reaction- time		161 (43.2)	157.6 (28.4)	155.5 (25.6)	188.5 (49.7)	1.76	.17	
Percentage of correct Go-trials		88.4 (.08)	82.8 (.09)	79.9 (.11)	84.0 (.08)	1.43	.25	
Stop-failure reaction-time (ms)		450 (37.6)	492 (50.5)	502 (50.2)	477 (57.5)	3.70*	.02	N < A*, AO*, O*/A = AO = O
SSRT at 250 ms SSD (ms)		245 (33.9)	272 (47.4)	256 (53.1)	274 (49.8)	3.41*	.03	N < A*, O*/N = AO/AO < A*, O*
Inhibition-function (percentage of Stop failures)	100 ms SSD	3.9 (5.5)	11.0 (9.9)	9.1 (9.9)	5.8 (5.0)	Group: $F_{(3,35)}$ = 1.50, p = .21		
	250 ms SSD	30.0 (11.1)	40.3 (16.1)	29.9 (9.6)	27.9 (13.2)			
	700 ms SSD	88.8 (12.0)	89.8 (7.0)	90.8 (6.3)	84.3 (12.5)	Group*SSD: $F_{(6,70)}$ = 1.61, ε = .95, p = .16		

* one-tailed, p < .05

Table 2: Analyses of Microstates

	Microstate					
	I	**II**	**III**	**IV**	**V**	**VI**
Correct Go: GFP[a]	1.25	4.53* C>A*, AO*, O*	.88	.88	1.67	
Correct Go: Topography[b]	1.21	1.15	.66	1.29	1.63+	
Successful Stop: GFP	.74	4.28* C>A*, AO*, O*	.70	2.33+ C>AO+, O*	.51	.83
Successful Stop: Topography	.62	1.06	1.16	1.33	1.18	1.52

* $p < .05$, for comparisons: one-tailed
+ $p < .10$, for comparisons: one-tailed
[a] $F_{(3,35)}$, covariate "age"
[b] multivariate Pillai's-trace $F_{(12,102)}$, covariate "age"

normal controls a negative wave 200 ms after onset of the Stop-signal (Stop-N200) over right inferior frontal electrodes which was reduced in ADHD-children. For both groups, this N200 after successful inhibitions was positively correlated with inhibition performance whereas correlations for Stop-N200 to Stop-failures were not that clear. Following Kok [33], the N200 to the Stop-signal could either reflect a 'red flag' or a subsequent "(action-) inhibitory process, emanating from structures in the prefrontal cortex" [33]. A second finding was that at right-frontal electrode-sites 250–500 ms post Go-signal-onset the control-group displayed greater positivity to failed than successful Stop-trials whereas in the ADHD-group successful trials did not differ from failed ones. This preparatory activity in failed Stop-trials was more positive in controls than in ADHD patients. Further, Dimoska et al. [32] found, despite worse Go-task- and inhibition-performance in AD/HD compared to controls, different activation-patterns at an early stage of processing the Stop-signal. Again, a decreased N200 to the Stop-signal of successful Stops for AD/HD was found, whereas groups did not differ concerning Stop-N2 of Stop-failures. Following Pliszka et al. [7], the authors argued that this N200 would reflect activation of inhibitory processes. However, in contrast to Pliszka et al. their auditory evoked N200 was generally larger to failed than to successful Stops. Overtoom et al. [31] found slower SSRT and decreased inhibition performance for AD/HD compared to normal controls. Interestingly the study showed no N200-effects to the Stop-signal. This could be due to the use of an auditory Stop-signal, as Falkenstein et al. [34] found a Nogo-N2 which was smaller for auditory compared to visual stimuli despite similar performance in both modalities which could indicate that inhibition is related to a pre-motor level.

There is an ongoing debate whether the Nogo-N200 reflects inhibitory processes per se [33-37], or conflict monitoring [38-40] which may initiate inhibition. We did not intend to distinguish between these two models. Both of them predict that the Stop-N200 is related to inhibition performance: while the inhibition theory relates diminished Stop-N200 amplitudes directly to an impaired central inhibition mechanism, the conflict-signal theory suggests that impaired triggering of the inhibitory mechanisms is responsible.

Taken together, studies strongly suggest difficulties in response inhibition paralleled by neurophysiological deviances for children with AD/HD compared to normal

Table 3: Electrophysiological Data

	Group						
	Controls (N) N = 11	**AD/HD (A) N = 10**	**AD/HD+ODD/ CD (AO) N = 11**	**ODD/CD (O) N = 8**	**ANCOVA (covariate "age")**		
Measure	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**$F_{(3,35)}$**	**p**	**Planned contrasts**
Go-Trial ROI[a] mean amplitude (μV)	-3.20 (1.68)	-2.64 (2.10)	-2.25 (2.36)	-1.98 (2.18)	.80	.50	
Stop-Trial ROI[a] mean amplitude (μV)	-5.36 (1.69)	-1.94 (4.00)	-2.89 (2.21)	-1.90 (4.20)	3.15	.04*	N<A*, AO*, O*/A = AO = O
Stop-N200 ROI[a] mean amplitude (μV)	-2.16 (1.60)	.69 (3.43)	-.63 (1.76)	.07 (2.02)	2.54	.07+	N<A*, AO+, O*/A = AO = O

* one-tailed, $p < .05$
+ one-tailed, $p < .10$
[a] Region of interest, mean of electrodes F4 and F8 at 420–500 ms post Go-signal onset

controls, but to our knowledge there is no such evidence for ODD/CD and comorbid AD/HD+ODD/CD. Thus, the aim of this study was threefold, as we intended (1) to replicate the neurophysiological finding of Brandeis et al. [27] and of Pliszka et al. [7] concerning both early pre-Stop-signal processing and the later Stop-N200-differences between controls and children with AD/HD; (2) to clarify whether children with ODD/CD and especially those with comorbid AD/HD+ODD/CD also display an inhibitory-deficit as hypothesized according to Quay's model, i.e. a slower SSRT and slower Stop-failure reaction-times paralleled at the neuronal level by a reduced Stop-N200-amplitude; and (3) we wanted to test whether an additive model of AD/HD and ODD/CD explains response-inhibition performance of children with comorbid AD/HD+ODD/CD.

Results

Behavioural data

The groups did not differ in terms of correct Go-reaction-times ($F_{(3,35)} = 1.97$, $p > .13$), standard deviation of Go-reaction-time ($F_{(3,35)} = 1.79$, $p > .17$), or accuracy as reflected by percentage of correct Go-trials ($F_{(3,35)} = 1.43$, $p > .25$, Table 1). A significant partial-correlation between IQ and percentage of correct go-trials was found ($r_{part} = .45$, $p < .01$). There were also no differences between inhibition-functions (group ($F_{(3,35)} = 1.60$, $p > .20$) and group*SSD ($F_{(6,70)} = 1.61$, $\varepsilon = .95$, $p > .16$)).

However, groups differed in their Stop-failure-reaction-times ($F_{(3,35)} = 3.70$, $p = .02$) with control children being faster than all clinical groups; no differences were found among the clinical groups. Stop-failure-reaction-time was correlated with IQ ($r_{part} = .43$, $p < .01$). There were also group-differences in SSRT ($F_{(3,35)} = 3.41$, $p > .03$) with slower SSRT for the pure AD/HD and ODD/CD groups compared to controls, but not for the comorbid AD/HD+ODD/CD which displayed faster SSRT than AD/HD and ODD/CD. In the 2*2 ANCOVA-design, there were no main effects for AD/HD ($F_{(1,35)} = .14$, $p > .71$) or ODD/CD ($F_{(1,35)} = .04$, $p > .85$) on SSRT; but an interaction-effect AD/HD*ODD/CD ($F_{(1,35)} = 10.21$, $p < .01$).

Brainmapping

For correct Go-trials, only the second microstate 200–272 ms post go-signal-onset revealed group-differences in GFP ($F_{(3,35)} = 4.53$, $p < .01$) with lower values for all clinical groups compared to controls (see Table 2). No differences in topography were found (Pillai-Spur $F_{(12,102)} = 1.15$, $p > .33$).

In successful Stops, groups again differed in the second microstate in GFP ($F_{(3,35)} = 4.28$, $p = .01$) with higher GFP for controls compared to all clinical groups whereas topography did not differ (Pillai-Spur $F_{(12,102)} = 1.06$, $p > .4$). The fourth microstate, related to the Stop-N200, revealed only an overall trend towards group-differences in GFP ($F_{(3,35)} = 2.33$, $p < .1$) with ODD/CD lower than controls; groups did not differ in topography (Pillai-Spur $F_{(12,102)} = 1.33$, $p > .2$).

Stop-N200

In the frontal region of interest, no main-effect of "condition" ($F_{(1,35)} = 1.1$, $p > .3$), but a trend for an interaction-effect "condition*group" ($F_{(3,35)} = 2.5$, $p = .07$) was found at the given time window 170–250 ms post Stop-signal-onset. Separate ANCOVAs for both levels of the "condition"-factor revealed that there were no amplitude differences between the groups for correct Go-trials ($F_{(3,35)} = .80$, $p = .50$), but significant differences of mean amplitude in ROI for successful Stop-trials ($F_{(3,35)} = 3.15$, $p < .04$). These differences were reflected by increased negativity in controls compared to all clinical groups which did not differ among themselves (see Table 3 and Figures 1, 2, and 3).

In order to clarify the interaction "condition*group" which reflects the Stop-N200, planned comparisons of the difference between mean amplitude of successful Stop and correct Go-trials were computed (Figure 4). The (difference-) Stop-N200 was increased for normal controls compared to pure AD/HD and ODD/CD, but there was just a trend for increased negativity in controls compared to comorbid AD/HD+ODD/CD. Again, clinical groups did not differ. The Stop-N200 analysed with the 2*2 ANCOVA revealed no main effects AD/HD or ODD/CD ($F(1,35) = 2.08$, $p = .16$ and $F(1,35) = .39$, $p = .54$, respectively) but again an interaction AD/HD*ODD/CD ($F(1,35) = 4.63$, $p < .04$). For the total sample, this Stop-N200 correlated positively with the speed of the inhibition process (rpart = .31, $p < .05$).

Discussion

The Stop-task was used to investigate inhibitory response control in children with AD/HD, ODD/CD and comorbid AD/HD+ODD/CD in comparison to normal controls. While processing the Go-signal, all clinical groups displayed reduced map strength in a microstate attributable to initial orienting, consistent with previous work [7,27]. A novel finding was that this Go-signal related reduction occurred on both correct Go-trials and successful Stops rather than just on Stop-failures, indicating a more general deficit than reported in previous work. Moreover, these earlier studies had reported a different topography of brain electrical activity with frontal positivity whereas in this work particularly in controls frontal negativity emerged. One explanation may be that participants in our sample showed less Stop-failures than for instance participants of Brandeis et al. [27] did: In this study, percentages of Stop-failures were 30% for controls and 40% for chil-

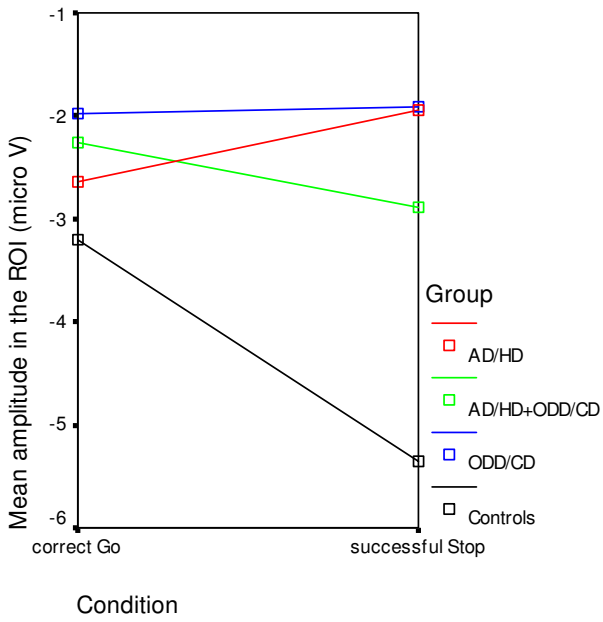

Figure 1
Mean Amplitudes in the region of interest. Mean amplitudes in the ROI for correct Go-trials and successful Stops. Normal controls (black), AD/HD (red), AD/HD+ODD/CD (green) and ODD/CD (blue).

dren with AD/HD but 48% and 51% respectively in Brandeis et al. [27]. This could have invoked the same inhibitory or conflict monitoring mechanism as reflected later on by the Stop-N200.

Normal control children displayed a right anterior negativity to the Stop-signal which could reflect response inhibition processes in the right prefrontal cortex [7,32,33], or the mechanism triggering such an inhibitory process. Although deciding between these alternatives is beyond the scope of this study, the right-frontal topography of this Stop-N200 [7] slightly favors the inhibition explanation, and differs from that of the "conflict" Nogo-N200 at fronto-central electrodes [21,39,40].

Not only the Stop-N200 effect, but also its attenuation in AD/HD children as first described by Pliszka et al. [7] could be replicated. It can not be attributed to differences in processing the primary-task at that stage, because group-amplitudes did not differ in this region of interest in Go-trials. Along with this, children with AD/HD performed poorer than normal controls in behavioural response inhibition. Their Stop-signal reaction-times and their reaction-times in Stop-failures were considerably slower than those of normal controls, indicating an even slower inhibitory process, consistent with the majority of previous work [8,9]. Alternative explanations such as 'clumsiness' or 'poor motor control' seems not to be valid since there was a lack of group-differences in other performance measures not related to behavioural inhibition, such as go-reaction-time or accuracy.

The lack of differences between inhibition functions could be due to the adaptive instructions. These were used in this version of the Stop-task to prevent extreme speed-accuracy-tradeoffs at the fixed medium stop signal delay. Such fixed Stop signal delays are advantageous for ERP studies, but suboptimal for deriving inhibition functions [41]. Still, we note that it is crucial for any Stop-task to balance between the strategies avoiding every Stop-failure or responding so fast that no stopping is possible either implicitly (with standard instructions like "respond as quickly and as accurately as possible to the primary stimulus, as well as to inhibit the response on the appearance of the Stop signal" [8]) or explicitly as is done here. The widely reported finding that children with AD/HD display more variable reaction-times could not be replicated here, maybe also because of the adaptive instructions.

Inhibition deficits were not limited to children with AD/HD, but also characterized children with ODD/CD, as predicted by the model of Quay. Their Stop-N200 was also reduced compared to normal controls, and did not differ from AD/HD and comorbid AD/HD+ODD/CD. The latter finding extends the commonality between AD/HD and ODD/CD to the neurophysiological level, which is in contrast to Quay's theory of conduct disorder postulating an intact behavioural inhibition system.

Surprisingly, children with comorbid AD/HD+ODD/CD tended to be somewhat less impaired than the other clinical groups. Their inhibition process (as reflected by SSRT) was not significantly slower than in normal controls, and was even faster than in the other clinical groups. However their Stop-failure reaction-times were slower compared to normal controls and similar to that of the other clinical groups. Hence, inhibition performance was by no means most impaired in comorbid AD/HD+ODD/CD. Although there was only a trend for decreased Stop-N200 mean amplitude compared to normal controls, no differences were found compared to the pure groups, which again stands in contrast to Quay's theory.

Consistent with this pattern, the 2*2 ANCOVA with between subject factors "AD/HD" and "ODD/CD" revealed no main- but strong interaction-effects for the most important measures of inhibition, indicating that effects of AD/HD and ODD/CD symptoms on response inhibition were not additive but sub-additive. This supports the conclusion of Banaschewski et al. using the CPT [42] who argue against the view that comorbid AD/HD+ODD/CD is a hybrid or a phenocopy of AD/HD or

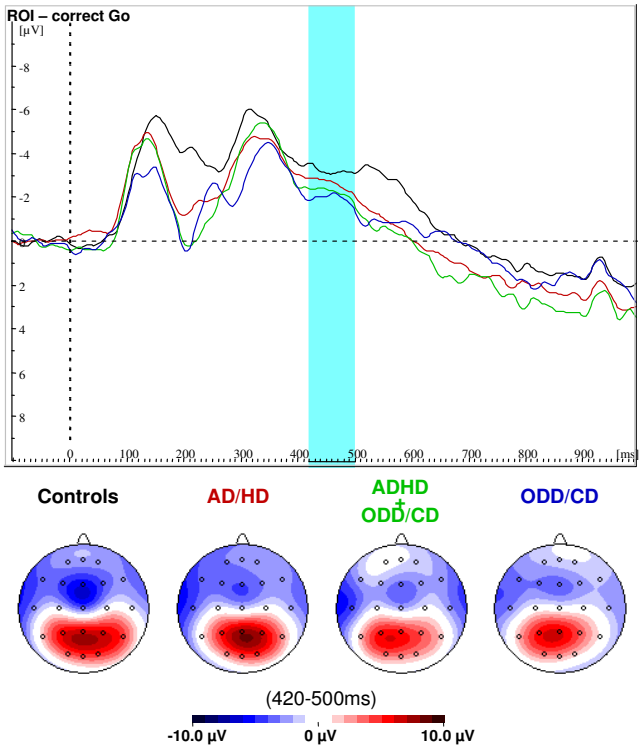

Figure 2
ERPs for correct Go-trials. Grand-average waveshapes from the region of interest (F4/F8), and spline-interpolated maps for correct Go-trials for normal controls (black), AD/HD (red), AD/HD+ODD/CD (green) and ODD/CD (blue). There were no group-differences and no negative peaks in the region and time window of interest.

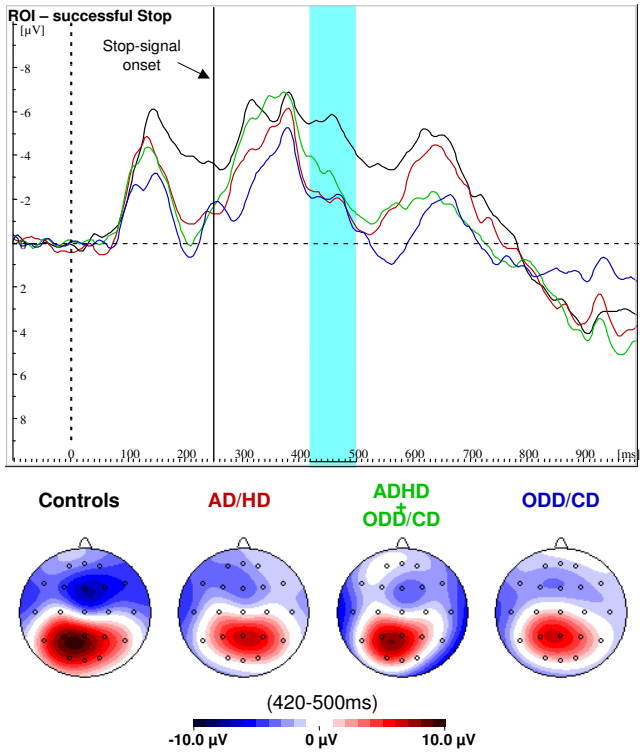

Figure 3
ERPs for successful Stop-trials. Grand-average waves in the region of interest and spline-interpolated maps for successful Stop-trials for normal controls (black), AD/HD (red), AD/HD+ODD/CD (green) and ODD/CD (blue). Only normal control children display a negative peak approximately 210 ms after onset of the Stop-signal.

ODD/CD. The present results suggest that this conclusion is not task specific.

However, since CPT and Stop-task were performed by partly the same sample of children, an independent replication with a larger sample size is needed to further support this view.

Although some evidence for inhibition deficits in AD/HD has been obtained using the CPT [43,44], it was also found that neither commission errors nor the Nogo-N200 enhancement had differed between the groups in the cued CPT [21,44]. We note that there are clear differences in what has to be inhibited in these two tasks: In the CPT, participants have to withhold a prepared but not yet initiated response and made only a few false alarms. In the Stop-task, participants have to stop an already ongoing response which often failed. These two types of inhibition have to be differentiated (see e.g., Barkley [2,3]).

Conclusion

While all clinical groups displayed similarly attenuated neural signs of go-signal processing, the subsequent response inhibition deficits further separated the clinical groups. Both children with AD/HD and ODD/CD-patients were found to be impaired in behavioural response inhibition. Also, both groups displayed reduced neuronal inhibition as reflected by smaller right-frontal Stop-N200 amplitudes; for AD/HD this is in agreement with Quay's model of psychopathology whereas for ODD/CD predictions of that model were violated. Hence, the inhibition-deficit concerning "stopping of an ongoing response" is by no means specific for AD/HD. In addition, the comorbid group with AD/HD+ODD/CD which should display the most severe deficits was found to be even somewhat less impaired than the "pure" groups, indicating that the comorbid condition may represent a separate disorder distinct from AD/HD and ODD/CD.

Limitations

The study is limited by its small sample size and by the fact, that another attention test was administered before-

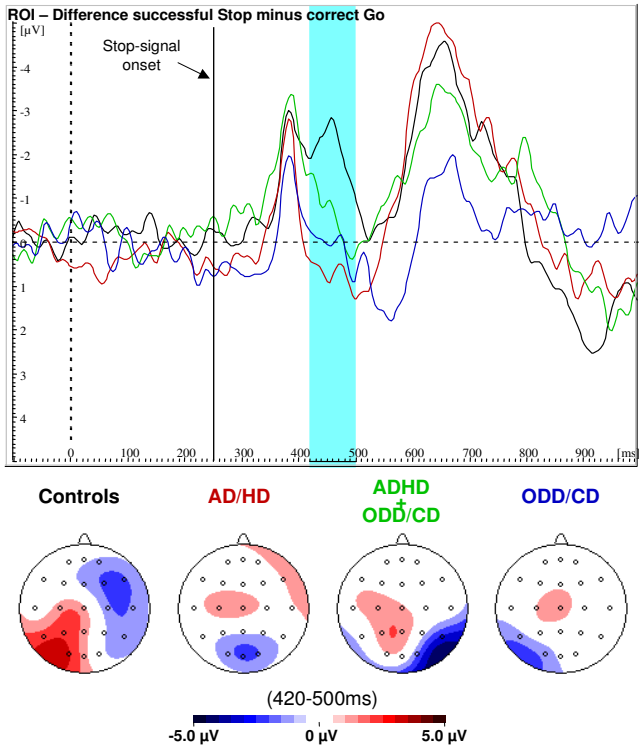

Figure 4

Difference ERPs (successful Stop minus correct Go). Difference waves and spline-interpolated difference maps between event-related potential grand means of successful Stop-correct Go-trials in the region of interest for normal controls (black), AD/HD (red), AD/HD+ODD/CD (green) and ODD/CD (blue). A clear Stop-signal N200 is present only for normal controls.

hand. Valid performance data concerning inhibition performance was only available for one fixed SSD. Since SSRT is only estimated from one fixed SSD with less than the optimal Stop-failure rate of 50% [41], its reliability and its sensitivity to group-differences is decreased compared to other strategies to estimate SSRT.

Methods

Subjects

Fifty-eight boys aged 8–14 years participated in the study on the basis of informed consent by child and parent with approval of the local ethics committee; all had normal or corrected to normal vision, a full scale IQ above 80 and understood the Stop-task-instructions. Some datasets were deleted a priori because of more than 20% omissions of go-trials (for 2 controls, 1 AD/HD, 1 AD/HD+ODD/CD and 2 ODD/CD), and some were lost due to artifacts in the EEG (1 control, 1 AD/HD, 3 AD/HD+ODD/CD and 1 ODD/CD) or due to age-matching the groups.

Datasets of a total of forty participants were thus analysed. They belonged to one of three clinical subgroups with the ICD-10 diagnoses hyperkinetic disorder (F90.0, N = 11), oppositional defiant/conduct disorder (F91, F92, N = 8), hyperkinetic conduct disorder (F90.1 N = 11) or to a group of 11 healthy controls (Table 4).

Children of the clinical groups were sequential referrals to the Department of Child and Adolescent Psychiatry of the University of Göttingen who met no other psychiatric diagnoses except reading and/or spelling disorders (N = 15), enuresis (N = 1) or encopresis (N = 1). The diagnosis of a hyperkinetic disorder was concordant with the DSM-IV diagnosis of ADHD-combined type. Control children met no other psychiatric diagnoses than reading and/or spelling disorders (N = 4). Diagnoses were verified by senior board-certified child psychiatrists. All children underwent standardized IQ-testing with the German versions of the WISC-R [45] or Culture Fair Intelligence Test (CFT [46]). The CFT was used only in 5 cases (for 3 controls, 1 ADHD and 1 ADHD+ODD/CD).

Groups were matched by age but not by IQ, with lower IQs for the psychopathological groups compared to normal controls ($F(3/36) = 5.9$, $p = 0.01$).

One-way analyses of variance (ANOVAs) were carried out to explore group-differences concerning the scales of the parent-rated Child Behaviour Checklist (CBCL [47]). There were group differences for all CBCL-scales except somatic complaints ($F(3/36>4.5$, $p < 0.01$), results of post-hoc Scheffé-Test are shown in Table 4.

Stimuli and task

The Stop-task consisted of eight blocks with 40 trials each and was identical to that used by Brandeis et al. [27] and Rubia et al [8]. Stimuli were presented in the central 2*2 cm square of a VGA monitor at 120 cm viewing distance with fixation marks above and below the scene. Each trial started with the presentation of an aeroplane in side view, suggesting that is was 'flying to' the left or to the right, and the children had to press a button corresponding to the planes flying direction with the index finger of their left or right hand. They were also told that sometimes a "little man" with his hands raised would follow, indicating that they should withhold their response. This should be easy when the "little man" occurred early, but they should no longer be able to stop their prepared response when the man was late.

Altogether, the "little man" Stop-signal occurred in 50% of the trials. The three fixed Stop-signal-delays (SSD) were 100 ms (10% of all trials), 250 ms (30%) or 700 ms (10%). The summed duration of the two signals was in

Table 4: Sample description

	Group						
	Controls (N) N = 11	**AD/HD (A) N = 10**	**AD/ HD+ODD/CD (AO) N = 11**	**ODD/CD (O) N = 8**	**ANOVA**		
Measure	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	$F_{3;36}$	p <	**Scheffé-Tests** [a]
Full-scale-IQ	110,7 (15,1)	94,4 (6,9)	93,0 (9,4)	96,9 (10,5)	5,9	0,01	N > A, AO
Age (in months)	130,8 (18,9)	130,1 (18,0)	123,7 (18,5)	131,5 (27,4)	0,3	0,81	
CBCL[b]							
Social withdrawal[b]	52,0 (4,6)	59,8 (6,5)	58,7 (7,7)	63,9 (9,9)	4,5	0,01	N < O
Somatic complaints[b]	56,3 (5,0)	56,2 (7,9)	57,2 (9,6)	57,4 (6,1)	0,1	0,98	
Anxiety/Depression[b]	50,3 (0,9)	57,2 (7,1)	64,3 (12,0)	67,3 (8,8)	8,4	0,01	N < O, AO
Social problems[b]	50.0 (0.0)	62.0 (8,7)	58,2 (8,2)	62,3 (11,5)	5,3	0,01	N < A, O
Thought problems[b]	50,6 (2,1)	54,2 (4,9)	61,4 (9,4)	61,8 (10,1)	5,9	0,01	N < O, AO
Attention problems[b]	50,3 (0,5)	67,4 (6,6)	67,3 (6,9)	69,1 (6,5)	25,5	0,01	N < A, AO, O
Delinquent behaviour[b]	50,8 (2,7)	59,7 (8,7)	71,6 (10,2)	69,9 (10,0)	14,1	0,01	N < AO, O/A < AO
Aggressive behaviour[b]	50,3 (0,9)	63,7 (8,7)	78,6 (12,0)	75,8 (14,6)	17,4	0,01	N < A, AO, O/A < AO
Internalizing symptoms[b]	44,3 (7,6)	57,4 (10,0)	62,3 (11,2)	65,8 (8,7)	10,0	0,01	N < A, AO, O
Externalizing symptoms[b]	38,3 (7,7)	63,1 (7,6)	75,3 (9,1)	73,3 (9,8)	41,9	0,01	N < A, AO, O /A < AO

[a] $\alpha < 0,1$
[b] Child Behaviour Checklist, T-scores

every case 800 ms (800+0 ms, 100+700 ms, 250+550 ms, 700+100 ms) and a trial was presented every 1650 ms.

Identical instructions were given to all groups before the practice-block, and were repeated after a block in case the child made more than 25% Stop-failures in the short SSD or less than 75% Stop-failures in the long SSD condition. Thus the short and long SSDs aiming at 0% and 100% stop failures provided a time frame within which the child's response should occur, therefore only the medium SSD was analysed. If there were less than 33% or more than 66% correct Stops at the medium SSD in a given block, additional instructions were given to slow down or speed up responses, respectively. These adaptive instructions prevent undesired strategies in performing the task, such as extreme speed-accuracy-tradeoffs yielding very frequent or very rare Stops at the fixed medium SSD [27]. The inhibitory deficits detected in ADHD children are comparable when using this Stop task with fixed SSDs, or the standard version with adaptive SSDs [8].

ERP recording and processing

An ERP was recorded using a Neuroscan recording system with calibrated technical zero baselines and Nihon Kohden Ag/AgCl electrodes attached to the skin with Grass EC-2 electrode-cream. Sampling-rate was 250 Hz and cut-off frequencies were 0.1 and 50 Hz on all 10–20 electrode positions using FCz as recording reference and a ground electrode placed on the forehead. Vertical and horizontal electro-occulograms (EOGs) were recorded simultaneously from electrodes above and below the left eye and at the outer canthi. Impedances were kept below 5 kΩ, further analyses were computed with the Vision Analyzer 1.05 software.

The EEG was transformed to the average reference of the 10–20 electrodes plus Fpz and Oz. Data were filtered offline (Butterworth, 0.1 to 30 Hz, 24 dB/oct.). For eye movement correction the method of Gratton & Coles [48] without raw average subtraction was used. Trials with performance errors (side-errors, failed Stops and Go-reaction-times faster than 200 ms), amplifier saturation or artefacts exceeding +-200 μV amplitude or more than 200 μV amplitude difference in a segment -100 ms to 1500 ms around go-signal-onset were rejected; remaining segments were subsequently checked visually. A 100 ms pre-stimulus baseline (referred to the go-signal-onset) was taken as zero. Averages for successful Stops in the medium SSD contain at least 25 sweeps, correct Go-Averages contain at least 90 sweeps. Groups did not differ in both numbers of accepted sweeps.

Analyses

SSRT

Reaction-times shorter than 200 ms and Go-Trials with side-errors were excluded from all analyses. SSRT was estimated only for the medium SSD because there were too few Stop-failures in Stop-trials with short and too many in long SSD. The classic approach to calculate SSRT for a specific SSD is to rank-order reaction-times of the go-trials,

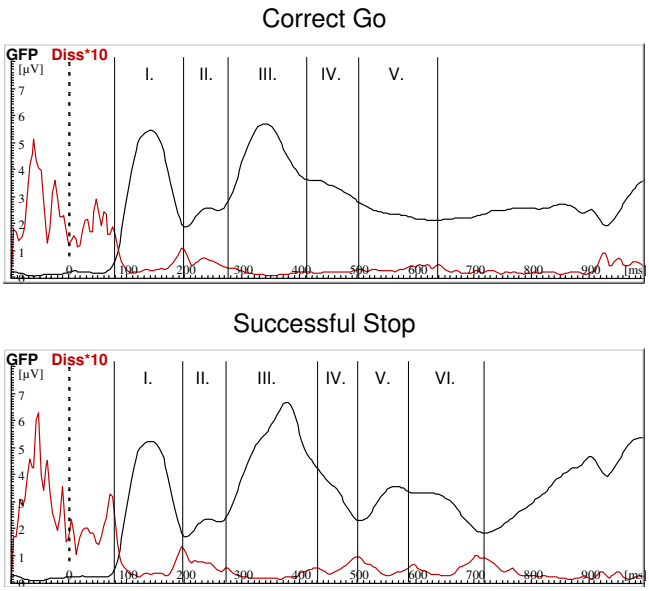

Figure 5
Microstate estimation according to GFP and Diss. Adaptive segmentation of the total groups grand mean from correct Go (top) and successful Stop (bottom). Microstate boarders were determined by relative minima of GFP (black) together with relative maxima in Diss (red, for better scaling multiplicated with 10) Correct Go-trials revealed five microstates (76–196 ms, 200–272 ms, 276–412 ms, 416–504 ms, 508–640 ms), successful Stops six microstates (76–196 ms, 200–272 ms, 276–428 ms, 432–504 ms, 508–592 ms, 596–724 ms).

multiply the probability for a Stop-failure with the number of go reaction-times which yields n, take the go reaction-time of the n*th* rank and subtract the SSD [9,49]. This leads to certain difficulties: for instance, if a participant makes no Stop-failure in the questioned SSD; the probability for a Stop-failure will be zero and there is no zero-rank of go reaction-times. But this participant has initiated a quite well-working Stop-process with which our applied theory can not cope. On the other hand, if a participant was not able to Stop even once, the algorithm would yield a wrong estimate of SSRT. Taken together, the algorithm stated above could lead to an undefined state and to wrong results which makes it susceptible of formal refutation.

Hence, we used a slightly different strategy: We took the probability for a Stop-failure, multiplied it with the total number of correct go-reactions and truncated the result. There we got the rank n (if there is any) of the Go-reaction-time which was just too fast to be stopped, the (n+1)-rank (again, if there is any) denotes the fastest Go-reaction-time slow enough not to yield a Stop-failure, and the mean of the two minus their Stop-signal-delay would yield a good estimate for SSRT. This brings into account, that the distribution of Go-reaction-times is discrete rather than continous.

Applied to a dataset without Stop-failures, we can only determine one border of the area of reaction times in which correct Stops and Stop-failures occur; we only know reaction-times which are slow enough not to evoke a Stop-failure. The best we can say therefore is that the SSRT shall be faster than the fastest Go-reaction-time with Stop-signal-delay subtracted. If a dataset contains no correct Stops, we only know that every Go reaction-time was too fast to be stopped, but we do not know anything more; simply taking the fastest Go-reaction-time with SSD subtracted as SSRT would be wrong. Because of this indeterminacy of Stop-signal-reaction-time, participants with no Stop-failures as well as participants with no correct Stops need to be excluded from analyses. This was not necessary for the dataset presented.

Brain-mapping

Microstates were determined on the total group's grand mean. Borders were set at times with minimal global-field-power (GFP) indicating low map-strength, plus maximal dissimilarity (Diss, the GFP of the difference between successive normalized maps) reflecting high topographic instability [27,50]. In contras, components extracted by principal component analysis (PCA) were only statistically defined as sources of variance and may not necessarily be grounded by physiological components [51,52].

For correct Go, five microstates were found (76–196 ms, 200–272 ms, 276–412 ms, 416–504 ms, 508–640 ms), correct Stops revealed six (76–196 ms, 200–272 ms, 276–428 ms, 432–504 ms, 508–592 ms, 596–724 ms, see Figure 5). For each microstate a mean map with its GFP and summary measures of topography (centroids) [50] were computed (Figure 6).

Stop-N200

In this version of the Stop-task, processing of the Stop-signal is fully time-locked with the preceding go-stimulus and thus highly confounded with go-signal processing. Because of this, differences between features of Stop- vs. Go-trials were analysed in a repeated measure-design; it is likely that such differences were caused by processing the additional Stop-signal on Stop- trials. Separate analyses of the conditions and inspection of the segment *t*-maps of the group differences in the raw conditions were used to exclude alternative interpretations. The term "Stop-N200" as used here thus refers to this difference between mean negativity in the ROI of successful Stop and correct go-trials.

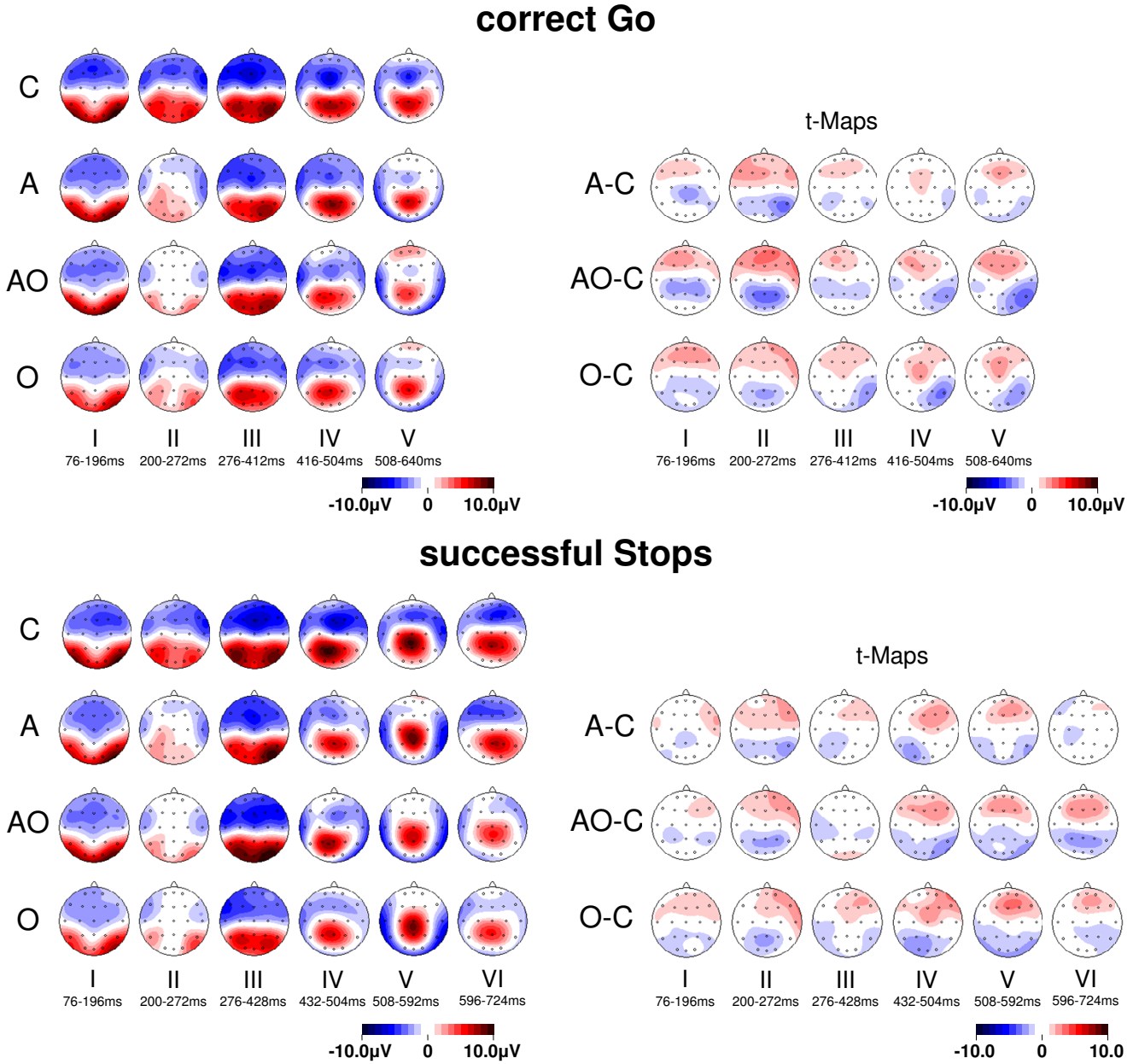

Figure 6

Microstate-maps and t-maps for correct Go and successful Stop-trials. Spline-interpolated microstate-maps for normal controls (C), children with AD/HD (A), ODD/CD (O) and AD/HD+ODD/CD (AO) and additional exploratory t-maps with comparisons of clinical groups vs. controls. Unadjusted two-tailed significance-level is reached at $t_{(17\ to\ 21)} > 1.7$ $p < .05$.

Visual inspection of the normal controls' grand mean of correct Stops revealed a negativity peaking at about 460 ms after go-signal-onset (or 210 ms after Stop-signal-onset) at right-frontal electrodes which was absent in go-trials. For further analyses, the mean amplitude in a time-window 420–500 ms after onset of the Go-signal was computed separately for correct go- and successful Stop-trials. The time-window used to study this local effect is almost identical with microstate IV found with the Brain-mapping-approach.

In order to localize the region of interest in this time-window for the sub-sample of normal controls a repeated-measure-ANCOVA with within-subject-factors "condition" (successful Stop vs. correct Go) and electrode-sites "anterior-posterior" (3 levels) and "left-right" (5 levels)

Table 5: Effect size (Cohen's d) for the main dependent variables

		Controls (N)	AD/HD (A)	AD/HD+ODD/CD (AO)	ODD/CD (O)
Measure		**effect-size d_{sc} [a]**	**effect-size d_{sc} [a]**	**effect-size d_{sc} [a]**	**effect-size d_{sc} [a]**
Stop-failure reaction-time (ms)	**A**	-1.26*			
	AO	-1.22*	.03		
	O	-.87*	.39	.36	
SSRT at 250 ms SSD (ms)	**A**	-.91*			
	AO	.06	.96*		
	O	-1.08*	-.18	-1.13*	
Go-Trial ROI[b] mean amplitude (μV)	**A**	-.29			
	AO	-.57	-.28		
	O	-.60	-.31	-.02	
Stop-Trial ROI[b] mean amplitude (μV)	**A**	-1.16*			
	AO	-.93*	.22		
	O	-1.15*	.01	-.20	
Stop-N200 ROI[b] mean amplitude (μV)	**A**	-1.15*			
	AO	-.66	.49		
	O	-.89+	.26	-.22	

[a] d_{sc} is the standardized mean difference for the sample, based on the ANCOVA model with age as covariate. This is done in order to account for developmental effects.
[b] Region of interest, mean of electrodes F4 and F8 at 420-500 ms post Go-signal onset
* one-tailed, P < 0.05
+ one-tailed, P < 0.10

was computed for the vector-length-normalized dataset. Vector-normalization is necessary, because "condition*location" interactions can result from multiplicative changes in source strength between conditions without specific differences concerning locations [53]. The ANOVA revealed a significant interaction-effect "condition*left-right" ($F_{(4,80)}$ = 5.93, ε = .542, p = .01) and an interaction "condition*left-right*anterior-posterior" ($F_{(8,80)}$ = 3.00, ε = .424, p = .04). Exploratory analyses of repeated measure "condition" for each electrode separately (without vector normalization) revealed significant differences between conditions only at electrodes F4 ($F_{(1,10)}$ = 15.1, p = .003) and F8 ($F_{(1,10)}$ = 15.2, p = .003) with increased negativity in trials with successful Stops as well as increased positivity at P3 ($F_{(1,10)}$ = 20.9, p = .001). Therefore the mean-amplitude of the adjacent right-anterior electrodes F4 and F8 in this time-window were used as region of interest (ROI) in order to analyse Stop-signal-N200, similar to Pliszka et al. [7].

To test whether dependent measures were confounded with developmental effects (the higher age, the higher performance and the lower ERP-amplitudes), simple correlations with "age" were computed across all groups. For Go-reaction-time (r = -.40*), Stop-failure reaction-time (r = -.72*), SSRT (r = -.76*) and mean amplitude in the ROI for correct Go (r = .27*) and successful Stop (r = .27*) developmental effects occurred, whereas the N200 of the difference-wave in the ROI between correct Go and successful Stop was not affected by age (r = .13; all one-tailed tested, * p < .05).

Therefore, age was taken as a covariate for all comparisons to reduce error-variance due to developmental effects and thus increase statistical power.

Statistical tests

Go-reaction-time, Stop-failure reaction-time and SSRT were analysed with one-way analyses of covariance (ANCOVAs) with between-subject-factor "group" and covariate "age". In case of overall-differences between groups, planned contrasts were computed in order to test the hypothesis that clinical groups display decreased performance (slower SSRT, Go- and Stop-failure-reaction-time) compared to normal controls. The inhibition-function of probabilities of Stop-failures for each SSD was analysed with a two-way repeated measure ANCOVA with within-subject-factor "SSD", between-subject-factor "group" and covariate "age".

All microstates of correct Go and successful Stop were analysed exploratory concerning GFP with one-way ANCOVAs with between-subject-factor "group" and covariate "age". Differences in topography as reflected by locations of centroids were analyzed with MANCOVAs of dependent variables "location of positive and negative centroids" (left to right and anterior to posterior for each), covariate "age" and between-subject-factor "group" [54].

Group-comparisons of Stop-signal-N200 were analysed with a two-way repeated-measure ANCOVA with within-subject-factor "condition" (correct Go vs. successful Stop), between-subject-factor "group" and covariate "age". In case of significant differences, further one-way ANCOVAs and additional planned contrasts were computed. In order to correct results of repeated-measure ANCOVAs from violations from sphericity, Greenhouse-Geisser ε and p-values for corrected degrees of freedom were reported.

To test an additive model of effects on response inhibition, separate 2*2 ANCOVAS with between-subject factors "AD/HD" and "ODD/CD" and covariate "age" were computed for the main dependent variables SSRT and Stop-N200.

Because of small sample size, even trends with $p < .10$ will be reported for hypothesized group and condition differences. Cohen's standardized mean difference for the sample with age taken as covariate d_{sc} were computed (Table 5).

Since groups were not IQ-matched, influences of IQ on dependent measures were analysed using partial correlation coefficients with covariate "age" and will be reported in case of significance.

Procedure

The psychophysiological experiment took place in a video-controlled, noise-protected and slightly dimmed room at the Department of Child and Adolescent Psychiatry at the University of Göttingen. Participants sat in a dentist-chair during electrode-attachment and task performance. Throughout the tasks, they could communicate with the experimenter via intercom. At first, a CPT lasting at about 11 minutes was performed [21,42], followed by this Stop-Task of approximately 10 minutes duration.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

BA performed analyses and drafted the manuscript, TB, DB, HH and AR conceived the study and helped to draft the manuscript.

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2.2. Interference Control in Attention-Deficit / Hyperactivity Disorder: Differential Stroop Effects for Colour-Naming versus Counting

The second manuscript (Albrecht *et al.*, 2008b) follows two lines. In one, interference liability is assessed in children with ADHD; the other on the interpretation of conflicting results takes us half-way through the vast land of methodological pitfalls.

Starting from Barkley's theory of executive functions and ADHD, the ability to inhibit actions in general and interference control in particular may be a core deficit in ADHD. A classical approach to evoke interference was reported by J.R. Stroop in 1935 (see also section 1.1 for a demonstration): it takes longer to name the colour of a patch than to read the colour-word, and combining this into one incongruent item leads to grossly enhanced response times (and error rates) when the (incongruent) colour of a colour word should be named (Stroop, 1935). Consequently, the Stroop task was regarded as an excellent instrument in ADHD diagnostics, tapping frontal-lobe functioning.

However, it seems plausible that patients with ADHD exhibit a colour processing deficit, which was confirmed in an earlier study by our group (Banaschewski *et al.*, 2006). Thus, higher interference liability in ADHD as measured by the colour Stroop test may be due to suboptimal processing of the target information; that is the colour!

In the study described below, the interference effect was elicited in a single trial four-choice reaction time task using colour material following Stroop, and in a parallel form that requires subitizing quantities similar to a procedure described by Flowers et al. (Flowers *et al.*, 1979). Both versions revealed interference effects as indexed by reaction-time or error rates. But impairments in ADHD were detected only for the colour Stroop, although that was the easier one of the two versions.

Taken together, our conclusions are two-fold: It seems plausible that children with ADHD may not display a general interference control deficit; in the case of the Stroop-test this enhanced interference liability in ADHD may be a consequence of sub-optimal processing of relevant information. And second, since no task is process-pure, caution is required whether the findings are indeed due to the desired underlying effects or alternatively due to some confounds.

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Interference control in attention-deficit/hyperactivity disorder: differential Stroop effects for colour-naming versus counting

B. Albrecht[1,2], **A. Rothenberger**[1], **J. Sergeant**[3], **R. Tannock**[4], **H. Uebel**[1], **T. Banaschewski**[2]

[1] Child and Adolescent Psychiatry, University of Goettingen, Goettingen, Germany
[2] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health Mannheim, Germany
[3] Department of Clinical Neuropsychology, Faculteit der Psychologie, Vrije University, Amsterdam, The Netherlands
[4] The Hospital for Sick Children, Toronto, Canada

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Summary. Deficits in interference control are ascribed to patients suffering from ADHD by a number of cognitive theories. However, previous research using the Stroop Colour Word Interference Task has demonstrated mixed results that may be explained by methodological issues (e.g., possible impact of colour perception abilities on interference liability, different approaches to calculate interference scores, conflation of speed and accuracy factors). Hence, this study included two computerized versions of the Stroop (Colour-Stroop, Counting Stroop) which allowed to calculate separate measures of speed and accuracy, provided a more rigorous approach to calculate interference, and permitted to investigate the effects of stimulus properties on interference. Participants were 14 children with a DSM-IV diagnosis of ADHD combined type and 15 matched controls. Children completed a traditional Stroop as well as both a computerized Colour- and Counting-Stroop. Results indicated that the ADHD group showed higher interference scores than controls in the Colour-Stroop, but not in the Counting-Stroop. Thus, interference control may be not generally impaired in ADHD, and examinations with the Colour Stroop should be interpreted with care.

Keywords: ADHD; attention deficit hyperactivity disorder; Stroop; colour perception; interference control

Introduction

More than half a century of research on the Stroop-effect enlightened the relevance of this phenomenon on several topics (MacLeod 1991). In Stroop's original experiment using what is now regarded as the classical Stroop Colour-Word Task, cards with an evenly spaced $10 * 10$ matrix of either colour bars (red, blue, green, brown, purple) or colour words printed in incongruent coloured ink (e.g., the word 'red' printed in blue ink) were presented, and subjects were asked to read out loud the colour of the items (Stroop 1935). It was consistently found, that naming the colour of the bars was faster and evoked fewer errors than naming the colour of incongruent colour words (Stroop 1935; Jensen and Rohwer 1966; MacLeod 1991). Including the examination of black-printed colour-word reading, a number of different scores can be calculated, but in a factor analysis approximative 99% of the variance could be explained by only three orthogonal factors, namely ''colour difficulty'', ''speed'' and ''interference'' as best be scored by the simple difference score of times taken to name the colour of incongruent colour words minus that of colour bars (Jensen 1965).

Several cognitive theories advocate impairments in executive functions (EF) as the core deficit in ADHD, and interference control is thought to be one of EFs key processes (Pennington and Ozonoff 1996; Barkley 1997; van Mourik et al. 2005). Thus, the Stroop-Task is widely used in ADHD research, and some authors recommend it as part of a test battery in clinical settings (Doyle et al. 2000). However, recent meta-analyses showed heterogeneous effect sizes on the interference score when comparing normal control subjects with ADHD patients. Moreover, disagreement continues as to whether interference control is compromised in individuals with ADHD (Frazier et al. 2004; Homack and Riccio 2004; van Mourik et al. 2005; Lansbergen et al. 2007).

Correspondence: Björn Albrecht, Child and Adolescent Psychiatry, University of Goettingen, von Siebold-Str. 5, 37075 Goettingen, Germany
e-mail: balbrec@gwdg.de

In part, this discrepancy may reflect heterogeneity of the methods used; for example how performance errors were accounted for and how the interference scores were computed (Lansbergen et al. 2007). Furthermore, the classical Stroop-Task using item-cards does not allow to monitor performance on a single trial level. A possible solution of these shortcomings is to use a computerized version of the Stroop-Task where a trial consists of a single item to which the subjects have to respond via a multiple-choice response pad. Thus, speed and accuracy do not have to be aggregated in a single score, and other important dimensions of task performance such as response variability and post-error processes can be analysed, which are important parameters in relation to ADHD problems.

Another difficulty is that usually interference is evoked by coloured stimuli, although several studies reported specific processing deficits of ADHD-patients in rapid colour naming but not so in naming uncoloured letters, words or digits (Carte et al. 1996; Semrud-Clikeman et al. 2000; Tannock et al. 2000; Rucklidge and Tannock 2002; Banaschewski et al. 2006). Furthermore, a recent study highlights the importance of visual encoding for Stroop-Interference (Laeng et al. 2005). Hence, it remains to be clarified whether enhanced interference liability in ADHD is based on certain stimuli only. However, Stroop-like interference effects can also be evoked by other materials such as non-coloured quantities (as used by Flowers et al. 1979). In this approach, quantities of digits are counted, and research indicates that it takes longer to respond to incongruent compared to control items (Flowers et al. 1979). Since even young healthy children achieve high accuracy and response-speed in subitizing small quantities (Chi and Klahr 1975), a Counting-Stroop may be an ideal parallel form of the Colour-Stroop to test for a more general problem of interference control.

Thus, aim of this study was to measure performance trial by trial using two computerized Stroop-Tasks (Counting-Stroop, Colour-Stroop), which allowed to compare processing of classical colour-stimuli with processing of subitized of non-coloured stimuli. If ADHD interference control is impaired in ADHD, then we would predict that youngsters with ADHD will show interference problems on both computerized Stroop tasks, regardless of stimulus characteristics.

Materials and methods

Subjects

A total of 29 subjects aged 9.3–12.4 years participated in the study on the basis of informed consent from child and parent. The local ethics committee approved the study. All subjects were free of ophthalmologic disorders or congenital colour blindness and had a full-scale IQ above 85, normal or corrected to normal vision and understood task instructions as verified by practice trials as required. Participants included a group of 14 ($N = 1$ ♀) children suffering from attention deficit/hyperactivity disorder combined type (ADHD) according to DSM-IV (American-Psychiatric-Association 1994) and 15 ($N = 2$ ♀) normal controls.

Children with ADHD were recruited from sequential referrals of the outpatient clinic of the Department of Child and Adolescent Psychiatry at the University of Goettingen. Diagnostics of ADHD based on information obtained from clinical assessment by a board certified child psychiatrist including interviews with the parents and the child as well as teacher reports, and behaviour rating scales such as parent-rated Child Behaviour Checklist (CBCL, (Achenbach 1991; Achenbach et al. 2007)), Strengths and Difficulties Questionnaire (SDQ, (Goodman 1997; Rothenberger and Woerner 2004)) and the German version of the ADHD symptom list (FBB-HKS, (Bruehl et al. 2000)). Those children using methylphenidate were free of medication for at least 48 h before testing. Control children never met a child psychiatric disorder except dyslexia, and T-scores of the CBCL scales for attention problems as well as delinquent and aggressive behaviour were required to be below 55 and 60, respectively.

Groups were matched for age ($F(1,27) = 0.2$, $p = 0.62$), gender-ratio ($\chi^2_{(1)} = 0.30$, $p = 0.58$) and proportion of dyslexia diagnosis (2/15 for controls and 3/14 for ADHD, $\chi^2_{(1)} = 0.33$, $p = 0.56$). IQ was higher for controls compared to ADHD patients ($F(1,27) = 5.9$, $p = 0.02$). Also, as expected the parent-rated SDQ scores were higher on every scale for patients with a diagnosis of ADHD compared to controls (all $F(1,27) > 7.1$, $p < 0.02$).

Tasks and procedure

All children underwent standardized IQ-testing, tests of Spelling Abilities and Word Fluency (Horn 1983) as well as examinations with a classical Stroop-Task using cards with 72 items each (Baeumler 1985). Total time taken to name all 72 items was recorded separately for all three cards (Word, Colour, Colour-Word) of the classical Stroop-Task and interference was calculated as the difference between naming time on the Colour-Word and Colour Card.

The computerized version of the Stroop-Task consisted of two conditions with either colours or non-coloured quantities used as targets presented in neutral or incongruent stimuli (Fig. 1). Each configuration was presented in a randomized block-wise design in order to rule out sequence effects. Each block started with written instructions and practice trials as required for understanding the task, followed by 72 experimental trials. The targets were presented in the centre of a 17″ CRT monitor against a light grey background at a viewing-angle of apprx. 3° horizontally and 1° vertically. Every trial started with the presentation of a fixation mark for 250 msec, a blank screen for another 250 msec followed by the presentation of the stimulus for

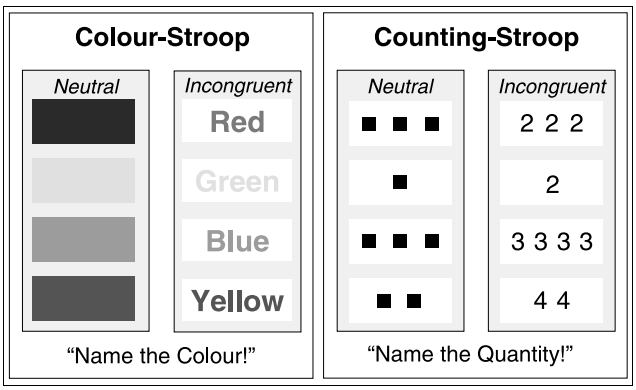

Fig. 1. Task description. Items of Colour- and Counting-Stroop. Correct responses are "*blue*", "*yellow*", "*green*" and "*red*" for the Colour-Stroop and "3", "1", "4" and "2" for the Counting-Stroop

750 msec and a blank screen for 1000 msec. The subjects had to press with the index finger or thumb of their left or right hand the required button of a four choice response box assigned to colours (button layout was an isosceles trapezium; from left to right, upper and lower row: green, red, blue and yellow) or quantities (1, 2, 3 and 4). Total task duration with three supplementary conditions not analysed here was 30 min. Reaction time (RT), intra-individual reaction-time variability (RT-SD), response accuracy (percentage of correct responses) and reaction-times of correct responses following correct or erroneously answered trials were recorded for each component of the task. Also performance adjustments after making an error was examined by comparing RTs of correct responses following an error with RTs of correct responses following a correct response.

The test session was carried out under standard light conditions (325 lux, measured with a LT Lutron LX-101 Lux-meter) in a noise-shielded room. All children earned small prizes; parents did not receive any financial reward for participation, but their travel expenses were reimbursed.

Analyses

Reactions of the four response buttons were collapsed into a grand mean, and trials with reaction-times faster than 150 msec were excluded from analyses. Dependent variables from the two computerized Stroop tasks were analysed with repeated measure analysis of variance (ANOVA), in which "Condition" (colour-naming vs. counting) and "Congruency" (neutral vs. incongruent stimuli) were within subject factors, and "Group" (ADHD vs. control subjects) was the between subject factor. In case of interaction effects, additional ANOVAs and confidence intervals of marginal means with $\alpha = 0.05$ were computed. Significance level was set to $\alpha < 0.05$, but since sample size was small even trends with $p < 0.1$ were reported. Effect sizes were computed, using partial η^2 statistic.

Inter-individual speed-accuracy tradeoffs as reflected by positive correlations between reaction-times of correct responses and percentage of correct responses were computed for neutral and incongruent conditions of the Colour- and Counting-Stroop separately for each group. Homogeneity of correlations across groups were tested using the method described by Rosenthal (Rosenthal 1991). In case of homogeneity, correlations in the total group were analysed.

Results

Classical Stroop-Task, spelling and word fluency

Groups did not differ in Spelling Abilities and Word Fluency (both $F(1,27) < 1.2$, $p > 0.28$). On the classical Stroop-Task, patients suffering from ADHD did not differ from control subjects in their word reading speed ($F(1,27) = 2.4$, $p = 0.13$), but displayed a trend for diminished speed in naming the colour of a bar ($F(1,27) = 3.4$, $p = 0.08$) and showed significantly slower speed in naming the colour of incongruent coloured words ($F(1,27) = 8.7$, $p < 0.01$, see Table 1). Interference liability as measured by the difference between the latter two variables was eminent for both groups, but was higher in ADHD compared to controls ($F(1,27) = 5.5$, $p = 0.03$).

Reaction-times

Reaction-times of incongruent items were slower than those of neutral ($F(1,27) = 74.5$, $p < 0.01$). There were no differences of reaction-times between conditions ($F(1,27) < 2.6$, $p > 0.12$), groups ($F(1,27) = 0.27$, $p = 0.61$) nor any interaction effects (all $F(1,27) < 1.2$, $p > 0.28$) eminent (see Table 2 and Fig. 2).

Table 1. *Sample description*

Measure	Controls (C) $N = 15$ Mean (SD)	ADHD (A) $N = 14$ Mean (SD)	ANOVA $F(1,27)$	ANOVA part. η^2
Age (in months)	129 (10.0)	128 (11.3)	0.2	<0.01
Prorated-IQ	113 (13.6)	103 (7.9)	5.9*	0.18
Spelling abilities (T score)	50.6 (12.3)	46.1 (9.2)	1.2	0.04
Word fluency (n/3 min)	25.7 (7.2)	27.2 (11.4)	0.2	<0.01
Classical Stroop-Task (sec/72 items)				
Word	43.4 (10.1)	54.5 (25.8)	2.4	0.08
Colour (C)	65.5 (12.6)	79.5 (26.2)	3.4+	0.11
Colour/word (CW)	119.9 (33.3)	166.1 (50.0)	8.7**	0.24
Difference (CW-C)	54.3 (24.1)	86.6 (47.0)	5.5*	0.17
SDQ Parents[a]				
Hyperactivity	1.3 (1.4)	8.2 (2.0)	115.3**	0.82
Prosocial behaviour	8.3 (1.7)	6.4 (2.1)	7.2**	0.22
Emotional symptoms	0.9 (1.3)	3.2 (1.7)	16.5**	0.39
Conduct problems	0.7 (0.7)	4.9 (2.1)	53.1**	0.67
Peer problems	0.7 (1.1)	3.3 (2.6)	12.6**	0.33
Total	3.6 (3.0)	19.6 (6.6)	72.0**	0.74

+ $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.
[a] Missing for one subject, df = 1, 26.

Percentage of correct responses

Percentage of correct responses yielded main effects of "Group" ($F(1,27) = 7.3$, $p = 0.01$), "Condition" ($F(1,27) = 6.7$, $p = 0.02$) and "Congruency" ($F(1,27) = 32.6$, $p < 0.01$) as well as interaction effects "Condition*Group" ($F(1,27) = 23.7$, $p < 0.01$), "Condition*Congruency*Group" ($F(1,27) = 4.2$, $p = 0.05$) and a trend for "Congruency*Group" ($F(1,27) = 3.5$, $p = 0.07$). Separate ANOVAs on each level of factor "Condition" revealed main effects "Interference" for both conditions (both $F(1,27) > 11.0$, $p < 0.01$), but a main effect "Group" and an interference effect "Congruency*Group" was present for Colour-($F(1,27) = 12.9$, $p < 0.01$ and $F(1,27) = 8.6$, $p < 0.01$, respectively), but not for Counting-Stroop ($F(1,27) = 1.7$, $p = 0.21$ and $F(1,27) < 0.1$, $p = 0.88$, respectively). Examining confidence intervals revealed congruency effects in both groups for the Counting-Stroop, while for the Colour-Stroop ADHD patients but not controls showed lower percentage of correct responses in incongruent compared to neutral trials.

Table 2. *Computer-Stroop-task performance*

Measure	Controls (C)		ADHD (A)		ANOVA[a]
	Colour Mean (SD)	Counting Mean (SD)	Colour Mean (SD)	Counting Mean (SD)	
RT of correct responses (msec)					
Neutral	648 (104)	654 (99)	655 (93)	675 (66)	"Condition": $F(1,27) = 2.6$, $p = .12$, part. $\eta^2 = 0.09$
Incongruent	709 (143)	733 (138)	727 (116)	764 (80)	"Congruency": $F(1,27) = 74.5$, $p < 0.01$, part. $\eta^2 = 0.73$
Difference	61 (47)	78 (78)	72 (48)	88 (69)	
Proportion of correct responses (%)					"Group": $F(1,27) = 7.3$, $p = 0.01$ "Condition": $F(1,27) = 6.7$, $p = 0.02$, part. $\eta^2 = 0.20$
Neutral	90 (9.7)	91 (7.8)	81 (10.7)	87 (10.0)	"Cond.*Group": $F(1,27) = 23.7$, $p < 0.01$, part. $\eta^2 = 0.47$
Incongruent	89 (6.9)	83 (9.6)	71 (15.3)	79 (8.4)	"Congruency": $F(1,27) = 32.6$, $p < 0.01$, part. $\eta^2 = 0.55$ "Cong.*Group": $F(1,27) = 3.5$, $p = 0.07$, part. $\eta^2 = 0.11$
Difference	1 (4.5)	9 (9.2)	10 (11.8)	8 (10.4)	"Cond.*Cong.*Group": $F(1,27) = 4.2$, $p = 0.05$, part. $\eta^2 = 0.13$
RT-variability (msec)					
Neutral	160 (54)	160 (53)	185 (43)	173 (37)	"Group": $F(1,27) = 3.7$, $p = 0.07$, part. $\eta^2 = 0.12$
Incongruent	162 (57)	169 (52)	216 (61)	197 (31)	"Congruency": $F(1,27) = 14.5$, $p < 0.01$, part. $\eta^2 = 0.35$
Difference	2 (19)	9 (33)	31 (48)	24 (33)	"Cong.*Group": $F(1,27) = 6.6$, $p = .02$, part. $\eta^2 = 0.20$
RT of incongruent trials (msec)[b]					
Post-correct, correct	693 (148)	699 (145)	700 (129)	733 (91)	"Condition": $F(1,26) = 4.5$, $p = 0.04$, part. $\eta^2 = 0.15$
Post-error, correct	745 (138)	785 (166)	750 (126)	829 (121)	"Post-error": $F(1,26) = 29.3$, $p < 0.01$, part. $\eta^2 = 0.53$
Difference	52 (156)	86 (63)	50 (58)	96 (122)	

[a] For ease of reading, only $F(1,27) > 1.73$, $p < 0.20$ were reported in the table.
[b] One subject omitted no error in one of the Interference blocks, thus df = 1, 26.

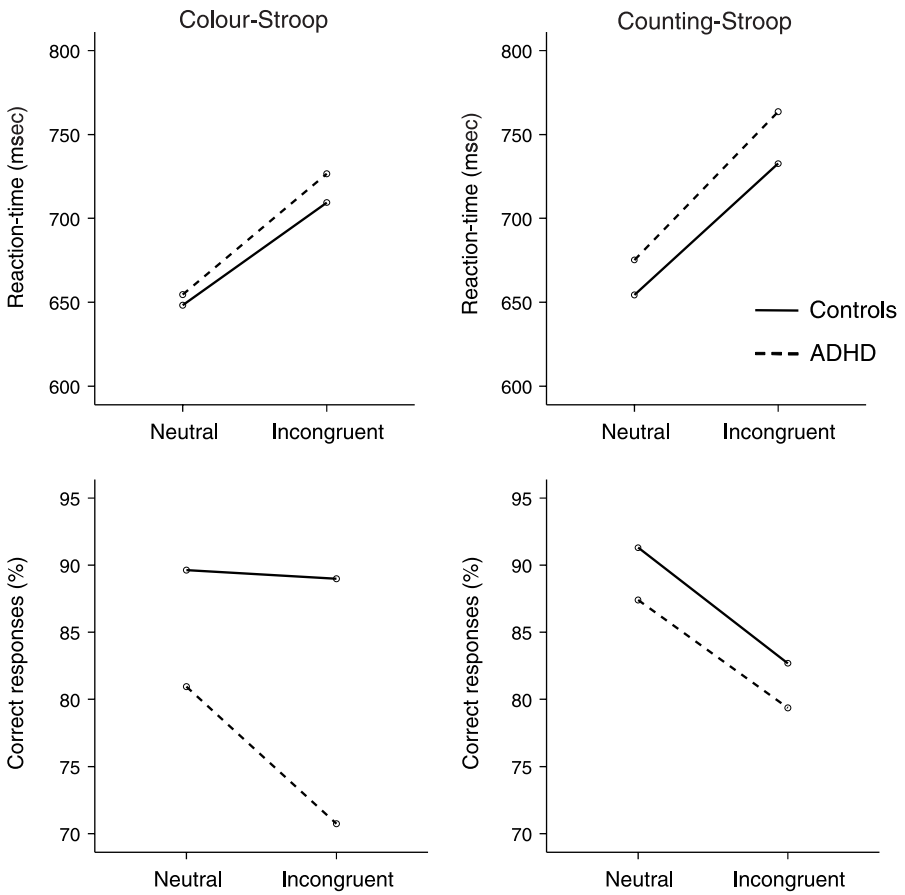

Fig. 2. Performance data. Main dependent variables reaction-time and percentage of correct responses for neutral and incongruent stimuli of both versions of the Stroop-test. Controls' data were indexed by solid, data from patients suffering from ADHD were indexed with dashed lines

Intra-individual reaction-time variability

Intra-individual reaction-time variability (RT-SD) showed a main effect of "Congruency" ($F(1,27) = 14.5$, $p < 0.01$) and a trend for a main effect "Group" ($F(1,27) = 3.7$, $p = 0.07$) paralleled by an interaction "Congruency*Group" ($F(1,27) = 6.6$, $p = 0.02$). Additional analysis of the differences in RT-SD between neutral and incongruent trials for both conditions revealed a congruency effect for children suffering from ADHD, but not for controls. Moreover, a higher congruency effect in children suffering from ADHD compared to normal controls was eminent ($F(1,27) = 6.6$, $p = 0.02$). The meaning of the trend for a main effect "Group" in presence of an interaction "Congruency*Group" was disentangled by separate ANOVAs on each factor level of "Congruency". It revealed no significant group differences of RT-SD on neutral trials ($F(1,27) = 1.6$, $p = 0.22$), but higher RT-SD in ADHD compared to controls on incongruent trials ($F(1,27) = 5.7$, $p = 0.02$).

Reaction-times of post-error trials

Reaction-times after errors were analysed for incongruent trials only since error rates were low for neutral trials. Reaction-times of correct answered trials were slower if the preceding trial was erroneously-answered as if it was correctly answered ($F(1,27) = 29.3$, $p < 0.01$). Separation concerning the preceding trials revealed faster reaction times in the Colour- compared to the Counting-Stroop ($F(1,27) = 4.5$, $p = .04$) in absence of any interaction effects (all $F(1,27) < 1.6$, $p > 0.21$).

Inter-individual speed-accuracy-tradeoff

Partial correlations taking age as covariate between reaction-times and the corresponding accuracy were not found to be heterogeneous across groups for neutral and incongruent blocks of both Colour- and Counting-Stroop (all $\chi^2_{(1)} < 0.89$, $p > 0.30$). Analyses of the total sample's data revealed trends for correlations in neutral and incongruent blocks of the Counting-Stroop ($r = 0.262$ and $r = 0.254$, respectively, $p < 0.10$ one-tailed), but not in the Colour-Stroop ($r = 0.035$ and $r = 0.122$, respectively, $p > 0.26$ one-tailed).

Discussion

In this study, carefully matched samples of patients suffering from ADHD and normal control children were compared on interference control as measured by three variants of the Stroop-Task in order to investigate if interference control deficits in ADHD can be found beyond the classical Colour-Stroop.

Generally speaking, both groups displayed interference liability as indexed by slower response speed or diminished accuracy in incongruent compared to neutral stimuli on all three Stroop-Tasks indicating that they were viable methods for ascertaining Stroop interference. As hypothesized, children with ADHD showed higher liability to interference than controls in the classical Stroop-Task as measured by the simple difference score between neutral and incongruent colour items. These findings are in line with several studies using the same procedure (Spalletta et al. 2001; Scheres et al. 2004), although others have not not found impairments for the ADHD group (Perugini et al. 2000; Willcutt et al. 2001).

In contrast to the classical Stroop-Task, the use of a computerized version allows to measure performance trial by trial and could disentangle speed and accuracy as important features of task performance. Trends for inter-individual speed accuracy tradeoffs were eminent for the Counting-, but not for the Colour-Stroop. No group-differences on speed-accuracy were found on any comparison.

Both computerized versions replicated the Stroop-Task specific features of interference in incongruent compared to neutral material: Reaction-times or accuracy were compromised in incongruent compared to neutral stimuli for both groups. In the reaction-time domain both the Colour- and Counting-Stroop as well as ADHD vs. control groups did not differ in general reaction-times and magnitude of interference-effects. However, differences between groups were found for accuracy, but depended on the material used. It turned out, that for the Colour-Stroop, ADHD children showed higher interference liability on accuracy than controls did. In fact, control children showed no interference effect for accuracy (but they did for reaction times!), whereas children suffering from ADHD showed interference effects in both reaction-times and accuracy. However, the Counting-Stroop revealed interference effects on both reaction-times and accuracy in absence of any group-differences. Taken together, children with ADHD showed higher interference liability than controls only for the Colour-, but not for the Counting-Stroop. This pattern of findings indicates that there is no evidence of general impairment in interference control as measured with the Colour-Stroop, because this neuropsychological effect is highly influenced by stimulus characteristics. A potential explanation of the diverging findings of Counting- compared to Colour-Stroop may bring into account that children suffering from ADHD display impairments in colour

perception and colour naming (Banaschewski et al. 2006): If processing of target information is impaired, interference induced by incompatible colour words would be enhanced. Furthermore, children suffering from ADHD sometimes benefit from distracting information as these increase orienting responses and may thus enhance activation (van Mourik et al. 2007). One might speculate that difficulties in colour naming would induce a sub-optimal activation status and may thus lead to higher interference liability. Finally, the contribution of this study with the use of computerized Stroop-Tasks to measure trial-by-trial performance locates the ADHD problems in Stroop-Tasks merely in the realm of accuracy and not speed.

Higher intra-individual reaction-time variability in children with ADHD as found in different tasks and interpreted as a basic deficit of these patients (Castellanos and Tannock 2002; Doyle et al. 2005; Nigg et al. 2005; Albrecht et al. 2007) was replicated for incongruent items only. This may be partly explained by our implementation of the Computer-Stroop using a four-choice response pad which yielded higher RT-variability per se that may mask probable group-differences when demands were relatively low. Also, we found clear post-error slowing that was more pronounced for the Counting-Stroop in absence of any group-differences. Thus, post-error processing as reflected by adaptations in response speed did not differ at the level of overt performance. However, our group recently could show differences in error processing at the covert electrophysiological level, i.e. diminished conflict monitoring due to performance errors as reflected by lower error negativity for ADHD, but no group-differences on later error positivity that may reflect affective error assessment (Albrecht et al. 2007).

In conclusion, computerized versions of the Stroop-Task were shown as fruitful tools to improve the classical procedure using cards with item-matrices. The Counting-Stroop was found to be at least as effective as the Colour-Stroop in evoking interference effects in children, but avoids some of its limitations and would thus be a feasible parallel-form of the Colour-Stroop. However, higher interference liability for children suffering from ADHD as detected by the Colour-Stroop was not found with the Counting-Stroop. Thus, findings on interference liability based on the Colour-Stroop should not be generalized.

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2.3. Action Monitoring in Boys with Attention-Deficit / Hyperactivity Disorder, their Nonaffected Siblings, and Normal Control Subjects: Evidence for an Endophenotype

Heritability estimates larger than 70% explained variance favour a model of strong genetical impact on the expression of ADHD (Faraone *et al.*, 2005), but developmental pathways from environmental factors and genetics to the disorder are not well understood (Banaschewski *et al.*, 2005; Castellanos & Tannock, 2002). Endophenotypes, which are quantitative and heritable vulnerability traits may help to clarify the effects of genetic and environmental factors on ADHD (Gottesman & Gould, 2003). Theoretically, genetic effects should be larger for endophenotypes than for diagnostic phenotypes, making them better targets for molecular genetic studies (Doyle *et al.*, 2005). Moreover, endophenotypes may serve as useful intermediate constructs that explain the heterogeneity of the ADHD phenotype (Buitelaar, 2005). As a first step on this venue, the manuscript below (Albrecht *et al.*, 2008a) addresses whether action monitoring does show familiality and may thus represent an endophenotype for ADHD.

The applied two-choice Flanker-Task requires responding to the direction indicated by a target arrowhead in the centre of the screen. Conflict in task demands was manipulated using two vertically adjacent flanker arrowheads pointing either into the same congruent or into the opposite incongruent direction as the target. As a novel approach, standardized feedback was used to control for speed-accuracy tradeoff by adjusting error-rates.

The study confirmed that responses to incongruent items were prolonged and more error-prone. Event-related potentials showed the expected N2-enhancement following incongruent items and also Ne and Pe following errors. Compared to controls without family history of ADHD, Children with ADHD showed slower and more variable responses, as well as both reduced N2-enhancement and Ne. Since nonaffected siblings of ADHD-patients were located intermediate, these parameters may reflect endophenotypes for ADHD.

In a supplementary analysis we showed that the proposed endophenotype parameters do show familiality independent of gender effects (Albrecht *et al.* 2010). A recent study using the same task with adults confirmed this pattern of results: ADHD-patients were impaired as compared to controls, whilst unaffected parents of children with ADHD were also located intermediate (McLoughlin *et al.*, 2009). A recent publication based on time-

frequency decompositions of the Controls' ERP signal using Morlet wavelets confirmed that error processing in children may likewise in adults comprise multiple processes that work in parallel at different frequencies and may represent limitations of processing capacity (Albrecht *et al.*, 2009; Yordanova *et al.*, 2004). An ongoing analysis of risk-allele polymorphisms addresses the genetic impact on these parameters (Albrecht et al., in preparation).

Action Monitoring in Boys With Attention-Deficit/Hyperactivity Disorder, Their Nonaffected Siblings, and Normal Control Subjects: Evidence for an Endophenotype

Bjoern Albrecht, Daniel Brandeis, Henrik Uebel, Hartmut Heinrich, Ueli C. Mueller, Marcus Hasselhorn, Hans-Christoph Steinhausen, Aribert Rothenberger, and Tobias Banaschewski

Background: Attention-deficit/hyperactivity disorder (ADHD) is a very common and highly heritable child psychiatric disorder associated with dysfunctions in fronto-striatal networks that control attention and response organization. The aim of this study was to investigate whether features of action monitoring related to dopaminergic functions represent endophenotypes that are brain functions on the pathway from genes and environmental risk factors to behavior.

Methods: Action monitoring and error processing as indicated by behavioral and electrophysiological parameters during a flanker task were examined in boys with ADHD combined type according to DSM-IV ($n = 68$), their nonaffected siblings ($n = 18$), and healthy control subjects with no known family history of ADHD ($n = 22$).

Results: Boys with ADHD displayed slower and more variable reaction-times. Error negativity (Ne) was smaller in boys with ADHD compared with healthy control subjects, whereas nonaffected siblings displayed intermediate amplitudes following a linear model predicted by genetic concordance. The three groups did not differ on error positivity (Pe). The N2 amplitude enhancement due to conflict (incongruent flankers) was reduced in the ADHD group. Nonaffected siblings also displayed intermediate N2 enhancement.

Conclusions: Converging evidence from behavioral and event-related potential findings suggests that action monitoring and initial error processing, both related to dopaminergically modulated functions of anterior cingulate cortex, might be an endophenotype related to ADHD.

Key Words: Action monitoring, ADHD, endophenotype, error negativity, error positivity, N2

Attention-deficit/hyperactivity disorder (ADHD) is a very common child psychiatric disorder. The core symptoms of severe age-inappropriate levels of hyperactivity, impulsivity, and inattention affect at least 3%–5% of school-age children (1) independent of cultural background (2) and with an overrepresentation of boys (3). Heritability estimates are high (4), but developmental pathways to the phenotype ADHD are not well understood (5). This potential gap might be filled by the concept of quantitative trait loci (QTL) and endophenotypes. Following this, multiple susceptibility genes might constitute a rather continuous dimension of ADHD symptoms in which an endophenotype is a simple function more proximal to biological foundations in between, on the one hand, genetic and environmental risk factors and, on the other hand, the phenotype (6–8). Theoretically, associations between genes and endophenotype should be larger than those between genes and phenotype, qualifying the endophenotype as a better ground for molecular genetic studies (9).

Several cognitive theories ascribe impairments in executive functions or self-regulation associated with dysfunctions in fronto-striatal dopaminergic networks that control attention and response organization to patients suffering from ADHD (3,10–14). Children with ADHD perform poorly in a wide range of tasks involving executive control. In general, their responses tend to be slower, more variable, and more error prone (11,12,15,16). Specific deficits in adaptation to task demands and error monitoring such as diminished post-error slowing have been reported early on (17,18), but little is known about neural mechanisms in ADHD. With event-related potentials (ERP), covert neurophysiological correlates of task performance can be tracked with high temporal resolution (19,20).

Action monitoring comes into play when actual requirements interfere with automatisms or after errors. For instance, in Go/No-Go tasks, which require responding to frequent stimuli but withholding the response to rare ones, the stimulus-locked ERP usually shows a fronto-central negativity peaking approximately 200–400 msec after onset of the stimulus (N2), which is larger for the No-Go than for the Go condition. The same effect can be observed for a target primed with incongruent compared with congruent distractors. This N2-enhancement was originally attributed to response inhibition (21–23), but recent studies suggest that it might reflect a more general monitoring process, which is also present without need for response inhibition (24,25). Sources of the N2 as evoked by Go/No-Go and Stroop tasks have been localized in the anterior cingulate cortex (ACC) (24,26,27).

Although most studies using continuous performance task (CPT) or Go/No-Go tasks in children did not find specific

From Child and Adolescent Psychiatry (BA, HU, AR, TB), University of Göttingen; Department of Child and Adolescent Psychiatry and Psychotherapy (BA, TB), Central Institute of Mental Health Mannheim; Child and Adolescent Psychiatry (HH), University of Erlangen; Heckscher-Klinik (HH), München; German Institute for International Educational Research (MH), Frankfurt/Main, Germany; Child and Adolescent Psychiatry (DB, UCM, H-CS); and the Center for Integrative Human Physiology (DB), University of Zürich, Switzerland.

Address reprint requests to Björn Albrecht, Dipl.Psych., University of Göttingen, Child and Adolescent Psychiatry, von Siebold-Str. 5, 37075 Göttingen, Germany; E-mail: balbrec@gwdg.de.

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differences in N2 between ADHD and control subjects (16,28,29), some studies did, but effects were explained by comorbidity (30,31) or appeared only within time-on-task effects (32). However, in more demanding tasks such as the Stop-Task, diminished N2 amplitudes or topographic N2 alteration have been reported (33–36).

Error processing is generally accompanied by a negative component (error negativity [Ne]) peaking approximately 40–120 msec after the erroneous response at fronto-central sites. It is frequently followed by a more parietal positive deflection (error positivity [Pe]) within 200–500 msec after the response (37–39). The Ne is described in a variety of tasks (38,40,41), error types (42), and response modalities (43,44). Thus, several hypotheses ascribe to Ne a crucial role in error detection and action monitoring such that it might reflect mismatch (37,39) or conflict (45) between error and required response. The Ne is susceptible to dopaminergic manipulations (46), i.e., dopamine agonists enhance [47] and antagonists reduce [48,49] its amplitude. Dipole modelling showed a generator of Ne located in the ACC (43,50–53). A number of studies suggest that Ne and N2 might reflect the same process, which relies on different aspects of task performance (54,55). Far less research has addressed the subsequent Pe. It is elicited, unlike Ne, only after full errors of which the subject is aware (44) and seems to mature earlier (56). The rostral ACC generators of Pe suggest that it rather reflects affective error assessment (53).

Clinical studies found Ne to be enhanced in patients with obsessive-compulsive disorder (57) or in subjects with obsessive-compulsive or anxiety characteristics (58,59) or negative affect (60). Higher sensitivity for punishment also goes along with enhanced Ne, whereas Pe was enhanced in subjects with higher reward sensitivity (61). A reduction of Ne but not Pe was found for patients with schizophrenia (62,63) and borderline personality disorder (64). Parkinson's disease associated with dysfunctions in the dopaminergic system of basal ganglia was also accompanied with reduced Ne (65,66) but unimpaired Pe (67). Moreover, Ne was found to be reduced in patients suffering from Huntington's Disease, which goes along with neural cell death in the striatum (68). Thus, there is converging evidence, that Ne is related to striatal dopaminergic modulations, which leads to the hypothesis that it might also be impaired in ADHD (14,69). However, the few studies on ADHD or ADHD-related behaviors yielded mixed results. Although Ne was found to be reduced in adult subjects with higher impulsiveness (70) and in children suffering from ADHD (71), other studies with younger ADHD children found no error-specific Ne and similar amplitude reductions for errors and correct responses (72), failed to find a reduction of Ne but found a reduction of Pe (73), or even observed an enhanced Ne in ADHD children (74), which might again be explained in part by heterogeneity of the methods used.

In search of ADHD endophenotypes, this study was focused on action-monitoring and error-processing, using a simple, nonverbal flanker-task that is highly demanding (75–77). It was hypothesized that control children would exhibit higher task performance (i.e., fewer errors, shorter reaction times, and less intra-individual reaction-time variability) than children of the ADHD-group. Furthermore, we predicted that the effect of congruency on N2 amplitude as well as Ne and Pe amplitudes were higher in control subjects compared with those of ADHD subjects.

To differentiate effects from partial overlap of phenotypes, nonaffected siblings of ADHD patients were included in analyses regarding the endophenotype concept. If the parameter in question reflects the phenotype, nonaffected siblings should display the same difference as unrelated control subjects, compared with ADHD patients. In contrast, because nonaffected siblings share one-half of their genes with ADHD patients, according to the QTL model susceptibility genes and therefore impairments should also be shared to that extent. Hence, the respective parameter should decrease as a linear function of genetic concordance with ADHD across groups (control subjects 0%, nonaffected siblings 50%, children with ADHD 100%) without a residual component (78–80) and might thus constitute an endophenotype.

Methods and Materials

Subjects

Recruitment of ADHD sib pairs was conducted as part of the IMAGE (International Multi-center ADHD Gene) study (81,82). For this analysis, European Caucasian subjects, all age 8–15 years with an estimated full-scale IQ above 80 (83,84) and no known child psychiatric disorder that might mimic ADHD were included. They belonged to one of three subgroups:

Children with DSM-IV diagnosis of ADHD combined type having at least one biological sibling
Nonaffected siblings of children with DSM-IV diagnosis of ADHD combined type, without any clinical diagnosis of ADHD
Unrelated healthy control subjects without a clinical diagnosis or a known family history of ADHD

Children of groups 1 and 2 were recruited by child psychiatry clinics from Goettingen, Germany and Zurich, Switzerland. The control group was recruited from regular schools in Goettingen only. Ethical approval was obtained from local ethical review boards. Detailed information sheets were provided, and informed consent from children and parents were obtained. Children taking stimulant treatment were off medication for at least 48 hours before testing. All children earned small prizes; parents did not receive any financial reward except travel expense reimbursements.

The diagnostic assessment was performed with long versions of Conners' rating scales (85,86) and Strengths and Difficulties Questionnaires (SDQ) for parents and teacher (87,88). If T scores on Conners ADHD scales (L, M, N) exceeded 62 and scores on SDQ Hyperactivity scale exceeded the 90th percentile, a semi-structured clinical interview (PACS) (89–92; also H. Uebel, unpublished data, 2007) was applied by trained investigators to verify ADHD diagnosis according to DSM-IV and to confine symptoms from other child psychiatric disorders (93,94). To ensure that control subjects were free of susceptibility for ADHD, children with T scores exceeding 60 on both parent and teacher scales of the Conners' total symptoms scale were excluded from that group.

Because female subjects in our ADHD sample were outnumbered and considerably younger, only datasets from 125 male subjects (14 from Zürich and 111 from Göttingen) were analyzed here. All had normal or corrected-to-normal vision and understood task instructions as verified during practice blocks. Seventeen subjects had to be excluded [3 control subjects, 2 nonaffected siblings, and 12 subjects with ADHD; reflecting comparable exclusion-ratio across groups, $\chi^2(2) = .41$, $p = .82$], owing to excessive artefacts in the electroencephalogram (EEG) or too few errors or correct responses.

Groups were matched for age [$F(2,105) = .1$, $p = .90$], and there

Table 1. Sample Description

Measure	C (n = 22) Mean (SD)	S (n = 18) Mean (SD)	A (n = 68) Mean (SD)	ANOVA F(2,105)	ANOVA Post Hoc Tests
Age (months)	134.1 (20.6)	137.0 (26.5)	135.9 (19.0)	.1	—
Prorated-IQ	110.3 (11.5)	109.3 (12.7)	104.4 (10.8)	2.9[a]	—
SDQ					
Parents[b]					
Hyperactivity	2.3 (1.8)	2.9 (2.4)	8.3 (1.5)	135.1[c]	C < A[c], S < A[c]
Prosocial behavior	7.8 (1.7)	6.7 (2.1)	6.5 (2.2)	3.0[d]	C < A[d]
Emotional symptoms	1.7 (1.7)	2.5 (3.3)	4.4 (2.6)	10.4[c]	C < A[c], S < A[d]
Conduct problems	1.1 (1.3)	2.8 (2.3)	5.1 (2.1)	35.6[c]	C < A[c], S < A[c]
Peer problems	1.0 (1.4)	2.2 (2.3)	4.4 (2.5)	18.8[c]	C < A[c], S < A[c]
Teacher[e]					
Hyperactivity	2.2 (2.8)	4.1 (3.1)	8.3 (1.7)	70.3[c]	C < A[c], S < A[c], C < S[d]
Prosocial behavior	6.8 (1.8)	6.8 (1.7)	5.3 (2.9)	4.1[d]	C < A[a]
Emotional symptoms	1.2 (1.8)	2.3 (2.7)	3.4 (2.6)	6.3[c]	C < A[d]
Conduct problems	.8 (2.1)	2.2 (2.0)	3.5 (2.1)	12.6[c]	C < A[c], S < A[a]
Peer problems	.8 (1.5)	1.8 (2.0)	3.9 (2.6)	15.0[c]	C < A[c], S < A[c]

A, attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; C, control subjects; S, nonaffected siblings; SDQ, Strengths and Difficulties Questionnaires.

[a] $p < .1$.

[b] Not available for one subject, $df = 2, 104$.

[c] $p < .01$.

[d] $p < .05$.

[e] Not available for four subjects, $df = 2, 101$.

was only a trend for different estimated total IQs [$F(2,105) = 2.9$, $p = .06$; see Table 1 for further sample characteristics]. In the ADHD group, PACS interview yielded susceptibility for mood disorder ($n = 7$), Tourette's syndrome ($n = 2$), substance abuse ($n = 1$), obsessive-compulsive disorder ($n = 3$), anxiety disorder ($n = 34$), oppositional defiant disorder (ODD; $n = 46$) and conduct disorder (CD; $n = 14$).

Procedure

Assessments of children were carried out on 2 days. The neurophysiological took place before the neuropsychological testing or vice versa, following a randomization scheme. Neurophysiological test sessions were carried out in video-controlled, noise-shielded, and slightly dimmed rooms. Subjects sat on a comfortable seat during electrode attachment and task-performance. The flanker-task was administered after 6 min of resting EEG followed by a Continous Performance Test lasting 11 min and, if desired, a short break.

Stimuli and Task

The flanker-task consisted of 10 blocks of 40 trials each, modeled after Kopp *et al.* (75) (Figure 1). Columns of black arrowheads (equilateral triangles with 18-mm edge length at three positions with 23-mm distance center to center) were presented in the center of a 17-inch CRT monitor with 800 × 600 points resolution against a light grey background at 120 cm viewing-distance. On every trial, a fixation mark in the center of the screen was replaced by the stimuli. Initially, only flankers (two arrowheads pointing to the same direction above and below the position of the fixation mark) were presented for 100 msec, before the target arrowhead also appeared for 150 msec between the flankers. Subjects had to press response buttons with the index-finger of their hand corresponding to the direction indicated by the target. The standard serial mouse used to record responses caused a response-trigger delay of approximately 35 msec, which was corrected for in the analyses (95). On

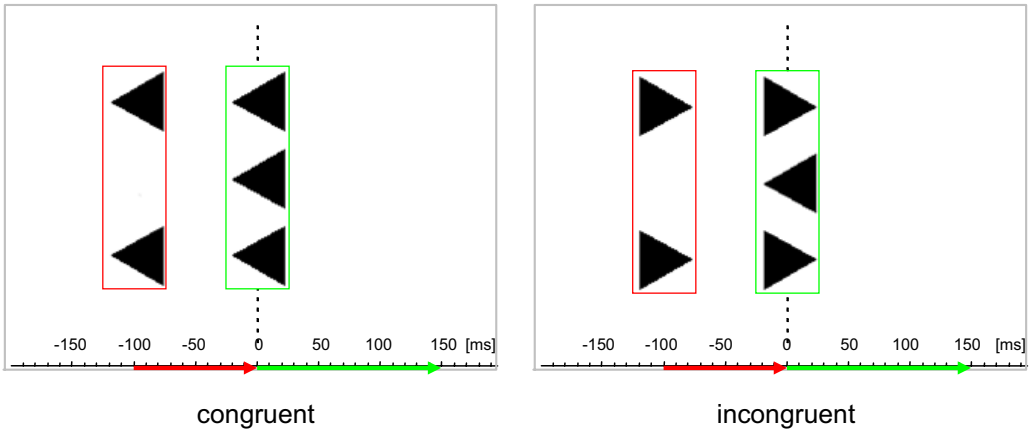

Figure 1. Task description. Flanker arrowheads (red) preceded the presentation of the central target and flanker arrowheads (green) by 100 msec. Conditions were congruent or incongruent, and responses were required either to the left or right.

congruent trials, flanker and target arrowheads pointed in the same direction, and on incongruent trials they pointed in opposite directions. A trial was presented every 1650 msec, and total task duration was approximately 13 min. The features congruent versus incongruent and target pointing to the left versus right were balanced and randomized.

Written feedback was given at the end of each block. If there were more than 10% errors on congruent or more than 40% errors on incongruent trials, the subject was instructed to be more accurate. In case of < 10% errors in the congruent and < 40% errors in incongruent trials, faster response was stressed; otherwise, the subject was told to continue in the same manner. Feedback was introduced to control for accuracy, which might influence error processing (38,39). Two practice blocks with 24 trials each were administered first.

Electrophysiological Recording and Processing

For subjects from Göttingen, the EEG was recorded with silver/silver-chloride (Ag/AgCl) electrodes and Abralyt 2000 electrode cream from 23 sites according to an extended 10–20 system using a BrainAmp amplifier (Brain Products, Munich, Germany). The electrooculogram (EOG) was recorded from two electrodes placed above and below the right eye and at the outer canthi. The EEG and EOG were recorded simultaneously with FCz as recording reference at a sampling rate of 500 Hz with low and high cut-off filters set to .016 Hz and 100 Hz, respectively, and a 50-Hz notch filter. The ground electrode was placed at the forehead. In Zürich, the EEG was recorded from additional channels with a Neuroscan SynAmps (Neuroscan, El Paso, Texas) amplifier with reference at Fpz and a ground electrode placed at the forehead. The EOG was recorded from electrodes below the left and right eyes. Sampling rate was 500 Hz, and filter settings were .1–70 Hz. Impedances were kept below 10 kΩ. Postprocessing ensured full compatibility.

Altogether 24 common sites were analyzed here. After downsampling to 256 Hz, the EEG was re-referenced to the average and filtered offline with .1–15 Hz, 24 dB/oct Butterworth filters. Ocular artifacts were corrected with the method of Gratton and Coles (96). If the amplitude at any EEG electrode exceeded ±100 μV, a section −100 to +800 msec was excluded from further analyses. Response-locked (−500 msec to +1000 msec relative to the button press) and stimulus-locked (−200 to +1825 msec around target-onset) segments were subsequently checked and averaged. To avoid distortion of ERP topography, no baseline subtraction was applied.

Averages of stimulus-locked waveforms to congruent and incongruent correctly responded trials contained at least 40 sweeps, response-locked averages to incongruent trials contained at least 25 sweeps for errors and 40 sweeps for correct responses. Consideration of signal/noise ratios (SNRs) revealed group differences only for waveforms stimulus-locked to congruent correct responded trials at site Cz [$F(2,105) = 3.2$, $p = .04$] and response-locked to errors in incongruent trials at Pz [$F(2,105) = 4.8$, $p = .01$].

Analyses

Effects of "congruency" (congruent vs. incongruent trials) and "group" (control subjects vs. nonaffected siblings vs. ADHD) on number of errors, reaction time of correct responses, and reaction-time variability of correct responses (intra-individual SD of reaction times with sum of squares computed separately for each block to control for potential reaction-time differences between blocks) were assessed with repeated measure analyses of variance (ANOVAs). Additional univariate ANOVAs were conducted to explore interactions and further details. If effects reached significance, additional post hoc tests adjusted for multiple comparisons following Sidak were conducted.

Inspection of the grand average waveforms revealed that both the effect of congruency on N2 components and the error-related negativity (Ne) were maximal at frontocentral electrodes (see Figures 2 and 3). Stimulus-locked N2 peaks scored at FCz 200–400 msec after the stimulus-onset of correctly responded trials were subject to an ANOVA with factors "congruency," "site" (Fz, FCz, Cz), and "group." Violations from sphericity were corrected following Greenhouse-Geisser; ε and adjusted p values are reported along with original degrees-of-freedom. The Ne measured at FCz was defined as the most negative peak 0–150 msec after erroneous response on incongruent trials with respect to the preceding positivity (PNe, −100–20 msec) in order to obtain a more robust measure of this component (44,68,97). Amplitudes and latencies of Ne were analyzed with repeated measure ANOVAs with factors "peak" (Ne vs. PNe) and "group." The plateau-like Pe on incongruent error trials maximal at centro-parietal electrodes was analyzed with the mean amplitude in time window 200–500 msec after an error in an ANOVA with factors "site" (Cz, Pz) and "group." Because Pe might be confounded with stimulus-locked components, the P3 to incongruent error trials was scored 350–650 msec after target onset at site Cz, and its mean amplitude at Cz and Pz was entered subsequently as a covariate. Both Ne and Pe were specific for errors.

For each dependent variable, contrasts over the three groups were computed to clarify which measures directly reflected genetic concordance with ADHD. Additional correlations between electrophysiological and behavioral parameters were tested for the total sample to clarify functional significance of ERP findings.

All analyses remained stable when subjects from Zürich were excluded. To differentiate effects of comorbid ODD/CD, analyses were subsequently conducted with patients possibly suffering from ODD/CD excluded.

Results

Performance Data

More errors were committed in incongruent than congruent trials [$F(1,105) = 495.2$, $p < .01$, Table 2], which was more pronounced in the group of control subjects compared with ADHD [$F(2,105) = 3.8$, $p = .03$]. Furthermore, groups differed only regarding error rates of congruent [$F(2,105) = 5.4$, $p = .01$, control subjects permitted less errors than ADHD] but not incongruent stimuli [$F(1,105) = .6$, $p = .53$]. If subjects with ODD/CD were excluded, the interaction "congruency × group" vanished and only a trend toward group differences on error rate for the congruent condition was found [$F(2,59) = 2.5$, $p = .09$].

Reaction times (RTs) of correctly responses were generally slower for incongruent compared with congruent trials [$F(1,105) = 753.9$, $p < .01$]. Groups differed in their reaction times [$F(2,105) = 3.8$, $p = .03$], with control subjects responding faster than individuals with ADHD for both congruent and incongruent correct trials. Nonaffected siblings did not differ in response speed from boys with ADHD or from control subjects. Contrasts revealed a linear trend between reaction times and genetic concordance with ADHD [$F(1,105) = 7.3$, $p < .01$] in absence of a significant residual [$F(1,105) = .3$, $p = .58$]. With subjects suffering from ODD/CD excluded, the main effect of group was

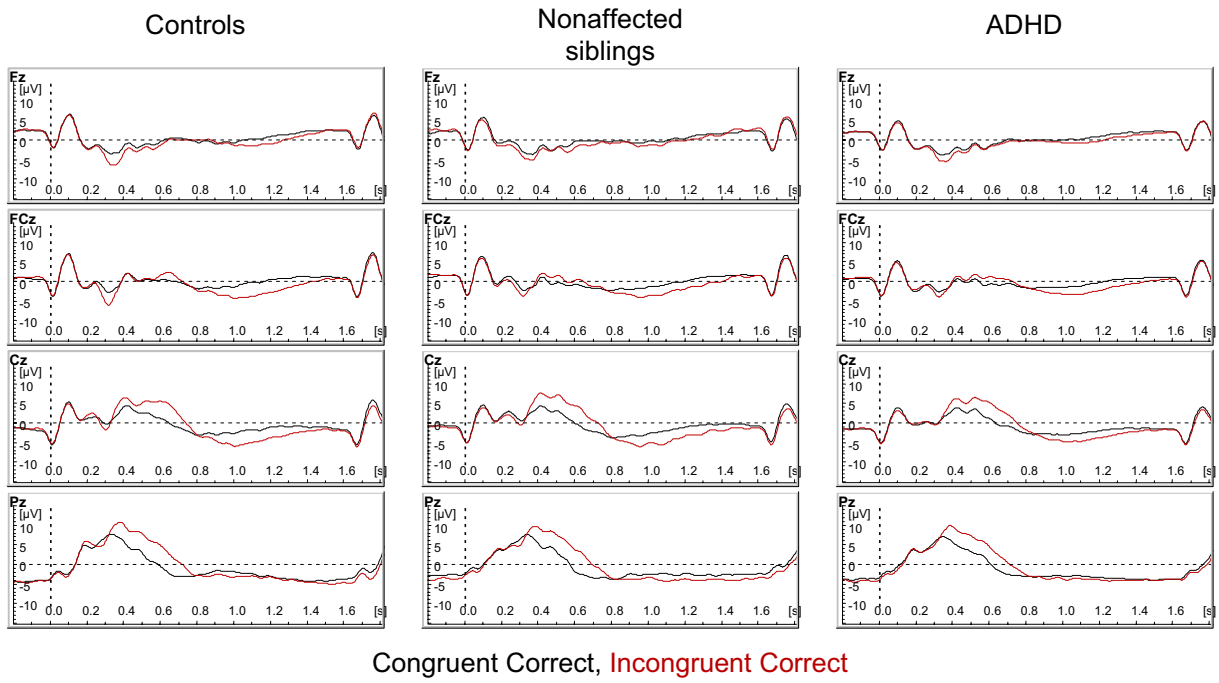

Figure 2. Stimulus-locked curves. For both congruent and incongruent correctly responded trials a N2 is apparent at a latency of 330 msec after the onset of the target. The N2 amplitude is enhanced in incongruent trials. ADHD, attention-deficit/hyperactivity disorder.

diminished to a trend [$F(2,59) = 2.9$, $p = .06$], but results of trend analyses remained stable.

Although congruent and incongruent correct trials yielded similar intra-individual reaction-time variability [$F(1,105) = 1.4$, $p = .23$], group differences were found [$F(2,105) = 10.1$, $p < .01$]: control subjects revealed lower reaction time variability than boys with ADHD in both conditions (Table 2). Nonaffected siblings did not differ from control subjects or ADHD. Contrasts between RT variability and genetic concordance with ADHD again detected a linear trend [$F(1,105) = 19.1$, $p < .01$] without

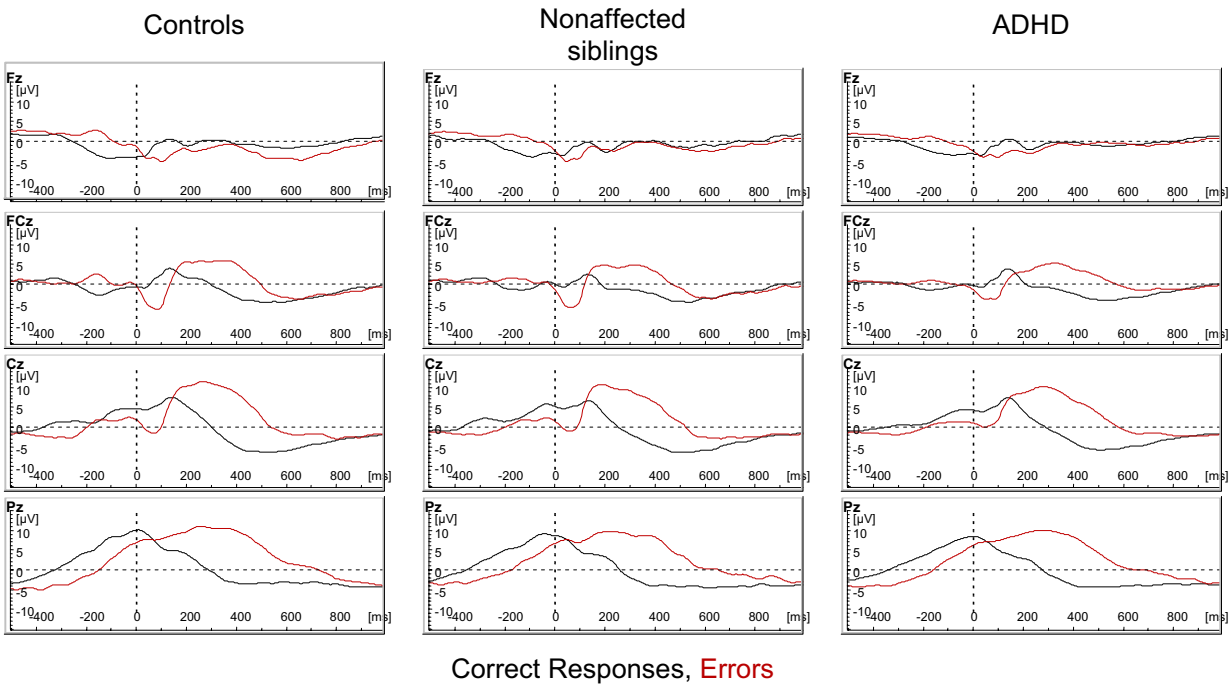

Figure 3. Response-locked curves to correct responses and errors in incongruent trials. Response-locked grand average waves of control subjects (black), nonaffected siblings (red), and boys with attention-deficit/hyperactivity disorder (ADHD) (green). The error negativity peaked for all groups at approximately 60–80 msec after the erroneous response (red curve) and was followed by an adjacent more posteriorly located error positivity. Both deflections were not present in curves evoked by correct responses.

Table 2. Performance Data

Measure	C $n = 22$ Mean (SD)	S $n = 18$ Mean (SD)	A $n = 68$ Mean (SD)	ANOVA $F(2,105)$	ANOVA Sidak-Tests	Repeated Measure ANOVA Congruency	Repeated Measure ANOVA Group	Repeated Measure ANOVA Conflict × Group
Error-Rate (%)						$F(1,105) = 495.2^a$ part. $\eta^2 = .83$ con. < incon.^{a}	$F(2,105) = .6$ part. $\eta^2 < .01$ —	$F(2,105) = 3.8^b$ part. $\eta^2 = .07$ C > A^b
Congruent trials	4.5 (5.7)	5.4 (4.6)	8.5 (5.6)	5.4^a	C < A^b			
Incongruent trials	31.5 (11.6)	29.0 (9.4)	29.2 (7.7)	.6	—			
Difference	27.0 (11.8)	23.6 (9.4)	20.7 (8.6)	3.8^b	C > A^b			
Reaction-Times of Correct Responses (msec)						$F(1,105) = 753.9^a$ part. $\eta^2 = .88$ con. < incon.^{a}	$F(2,105) = 3.8^b$ part. $\eta^2 = .07$ C < A^b	$F(2,105) = .2$ part. $\eta^2 < .01$ —
Congruent trials	335 (56.7)	358 (70.0)	386 (79.4)	4.3^b	C < A^b			
Incongruent trials	433 (71.7)	459 (79.9)	482 (86.8)	3.1^b	C < A^b			
Difference	98 (33.2)	101 (34.2)	96 (30.2)	.2	—			
Reaction-Time Variability of Correct Responses (msec)						$F(1,105) = 1.4$ part. $\eta^2 = .01$ —	$F(2,105) = 10.1^a$ part. $\eta^2 = .16$ C < A^a	$F(2,105) = .4$ part. $\eta^2 < .01$ —
Congruent trials	91 (39.6)	129 (75.9)	161 (68.7)	9.9^a	C < A^a			
Incongruent trials	94 (42.1)	132 (81.0)	170 (81.7)	9.0^a	C < A^a			
Difference	3 (19.1)	3 (25.4)	9 (42.4)	.4	—			

Con., congruent trials; incon., incongruent trials; part., partial; other abbreviations as in Table 1.
$^a p < .01$.
$^b p < .05$.

a residual [$F(1,105) = 1.1$, $p = .31$]. These effects persisted if subjects with ODD/CD were excluded.

ERP Data

The N2 peaked at about 330 msec relative to target-onset (Table 3 and Figure 4). No effects of any independent variable were found on N2 latency [all $F < 1.1$, $p > .35$].

The N2 amplitude was enhanced by incongruent compared with congruent items [$F(1,105) = 50.8$, $p < .01$] and was generally higher at Fz and FCz compared with Cz [$F(2,210) = 102.2$, $p < .01$]. The N2 enhancement was also highest at Fz and FCz ["congruency × site," $F(2,210) = 17.5$, $p < .01$]. Furthermore, the N2 congruency effect (i.e., the mean difference of N2 amplitude across sites Fz, FCz, Cz) differed between groups ["congruency × group," $F(2,105) = 4.1$, $p = .02$], being more pronounced in control subjects compared with ADHD, whereas nonaffected siblings displayed no differences from both other groups. Contrasts between the N2 congruency effect and genetic concordance with subjects suffering from ADHD showed a linear trend [$F(1,105) = 7.7$, $p < .01$] and no significant residual

Table 3. Stimulus-Locked Effects of Congruency on Electrophysiological Parameters

Measure	C $n = 22$ Mean (SD)	S $n = 18$ Mean (SD)	A $n = 68$ Mean (SD)	ANOVA
Stimulus-Locked N200 Latency at FCz (msec)				
Incongruent correct	329 (34)	335 (30)	338 (27)	congruency: $F(1,105) = .5$, part. $\eta^2 < .01$
Congruent correct	328 (29)	331 (23)	337 (33)	congr. × group: $F(2,105) = .1$, part. $\eta^2 < .01$
Difference	1 (26)	5 (25)	1 (29)	group: $F(2,105) = 1.0$, part. $\eta^2 = .02$
Stimulus-Locked N200 Amplitude (μV)				
Congruent correct				congruency: $F(1,105) = 50.8^a$ part. $\eta^2 = .33$ (incon. < con.^{a})
Fz	−4.5 (3.5)	−4.1 (3.8)	−4.5 (2.9)	congr. × group: $F(2,105) = 4.1^b$, part. $\eta^2 = .07$ (C < A^b)
FCz	−3.8 (2.5)	−3.3 (3.2)	−3.7 (3.4)	site: $F(2,210) = 102.2^a$, $\varepsilon = .60$, part. $\eta^2 = .49$ (Fz < Cz^a, FCz < CZ^a)
Cz	−.3 (3.3)	.5 (2.9)	−.3 (3.8)	
Incongruent correct				site × group: $F(4,210) = .3$, part. $\eta^2 < .01$
Fz	−7.0 (3.7)	−6.4 (3.1)	−6.1 (3.7)	congr. × site: $F(2,210) = 17.5^a$, $\varepsilon = .66$, part. $\eta^2 = .14$ (Fz < Cz^a, FCz < CZ^a)
FCz	−7.5 (4.2)	−5.6 (3.4)	−5.2 (3.8)	
Cz	−2.0 (3.7)	−.3 (4.1)	−.4 (3.9)	congr. × site × group: $F(4,210) = 1.2$, part. $\eta^2 = .02$
				group: $F(2,105) = .9$, part. $\eta^2 = .02$

Congr., congruency; con., congruent trials; incon., incongruent trials; part., partial; other abbreviations as in Table 1.
$^a p < .01$.
$^b p < .05$.

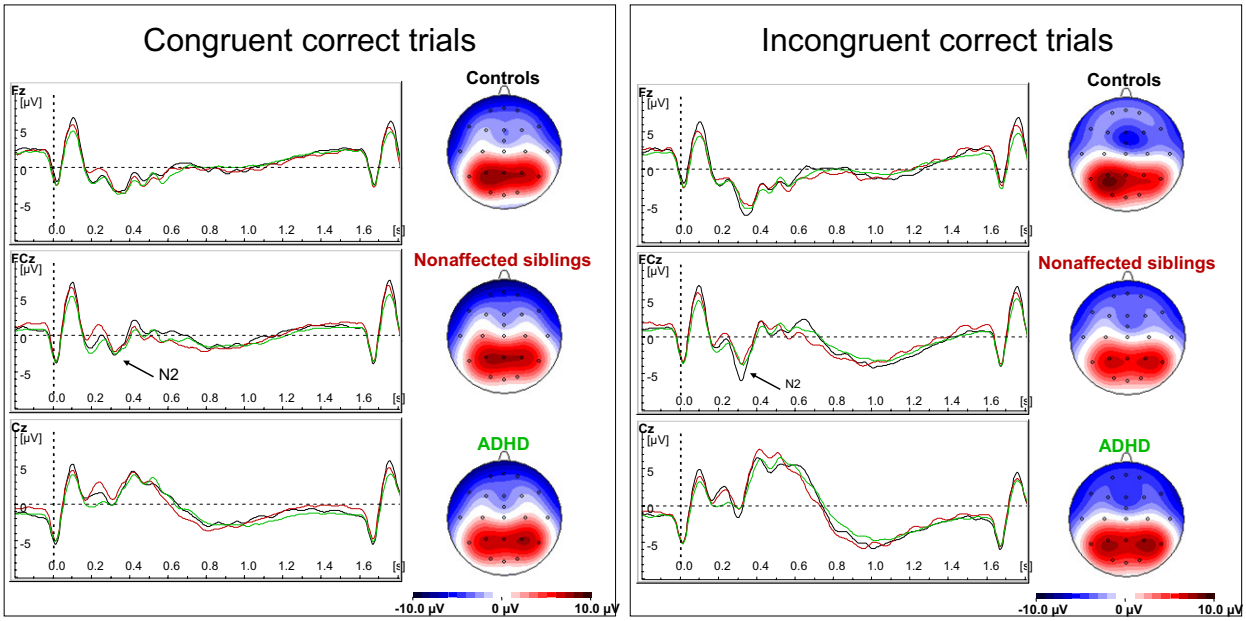

Figure 4. Stimulus-locked N2 to congruent and incongruent correctly responded trials. Response-locked grand average waves of control subjects (black), nonaffected siblings (red), and attention-deficit/hyperactivity disorder (ADHD) boys (green) with spline-interpolated maps of N2 evoked by correct congruent (left) and incongruent (right) trials at the respective group mean latency.

[$F(1,105) = .5$, $p = .47$]. The effects persisted when subjects suffering from ODD/CD were excluded.

Mean N2 enhancement across electrodes Fz, FCz, and Cz was correlated with faster and less variable reaction times in both congruent and incongruent trials (all $r \geq .25$, $p < .01$) and lower error rate in the congruent condition ($r = .34$, $p < .01$) but also with higher congruency effect on error rate (increased error rate in incongruent compared with congruent trials, $r = -.31$, $p < .01$).

The whole complex of PNe and Ne had a similar mean latency for all groups [$F(2,105) = .7$, $p = .51$] but was more widespread for control subjects compared with ADHD ["peak × group," $F(2,105) = 4.7$, $p = .01$] (Table 4 and Figure 5).

The Ne amplitude measured peak-to-peak was higher in control subjects compared with ADHD ["peak × group," $F(2,105) = 5.7$, $p < .01$]. There was a linear trend [$F(1,105) = 10.9$, $p < .01$] but no significant residual [$F(1,105) = .5$, $p = .50$] between genetic concordance with ADHD and Ne amplitude peak-to-peak. Higher peak-to-peak Ne amplitude was correlated similarly to N2 enhancement with faster and less variable reaction times as well as with lower error rate in the congruent condition (all $r \geq .32$, $p < .01$) but also with higher increase in error rate in incongruent compared with congruent trials ($r = -.26$, $p < .01$). Peak-to-peak Ne ($r = .33$, $p < .01$) but not Pe were correlated with N2 enhancement. When subjects with ODD/CD were excluded, effects on the peak-to-peak Ne amplitude remained stable.

A strong effect of stimulus-locked P3 amplitude to incongruent error trials on Pe was found [$F(1,104) = 315.0$, $p < .01$, partial $\eta^2 = .75$] but no group differences were detected, irrespective of whether P3 amplitude was taken as covariate or not. Higher Pe amplitude was correlated with lower error rate in both congruent and incongruent conditions and lower RT variability in both congruent and incongruent conditions [all $r < -.22$, $p < .03$].

Discussion

In this study, we examined neuropsychological and neurophysiological aspects of action monitoring and error processing as candidates for endophenotypes of ADHD. Because nonaffected siblings were contrasted with children suffering from ADHD and unrelated control subjects, effects that go beyond differences in the phenotype as reflected by increased ADHD prevalence among family members of patients (98–100) can be detected. The adaptive feedback procedure used in this version of the flanker-task prompted subjects to respond with similar accuracy; thus confounds with speed-accuracy tradeoff and possible task-induced differences in motivation could be avoided. Therefore, groups differed mainly in reaction time and intra-individual reaction-time variability. As expected (3,11,12,15), boys with ADHD performed worse than unrelated healthy control subjects. However, the performance deficit of the boys with ADHD did not increase under conflict. Nonaffected siblings of subjects suffering from ADHD—despite sharing the same phenotype with unrelated healthy control subjects—differed neither from ADHD subjects as control subjects did nor from control subjects. There was a reliable linear trend between genetic concordance with children suffering from ADHD and reaction time as well as RT variability without significant residuals. This finding agrees with recent articles concluding that state regulation as indexed by RT variability is probably an endophenotype for ADHD (9; also H. Uebel, unpublished data, 2007).

Incongruent compared with congruent stimuli yielded the typical N2 amplitude enhancement (24,25), which is correlated with faster and less variable reaction times in both congruent and incongruent conditions. This is in line with the notion that N2 is an index for a more general monitoring process, triggered in this case by incongruent stimuli features. Because the magnitude of diminished accuracy due to incongruent trials is additionally correlated with higher magnitude of N2 enhancement, modulations in N2 amplitude do not reflect activity of response-inhibitory processes, which should control for conflicting impact and should thus lead to an inverse correlation.

N2 enhancement was found to be higher in unrelated control subjects but not in nonaffected siblings compared to boys with

Table 4. Response-Locked Electrophysiological Data of Error Processing

	C	S	A					
	$n = 22$	$n = 18$	$n = 68$	ANOVA		Repeated Measure ANOVA		
Measure	Mean (SD)	Mean (SD)	Mean (SD)	$F(2,105)$	Sidak-Tests	Peak	Group	Peak × Group
Error Negativity Latency at FCz (ms)						$F(1,105) = 912.0^b$ part. $\eta^2 = .90$ Ne < PNe^b	$F(2,105) = .7$ part. $\eta^2 = .01$ —	$F(2,105) = 4.7^c$ part. $\eta^2 < .08$ C > A^b
PNe	−31 (29)	−30 (27)	−27.0 (29)	.2	—			
Ne	78 (29)	62 (25)	61 (32)	2.8^d	C > A^d			
Peak-to-Peak	109 (21)	92 (22)	88 (31)	4.7^b	C > A^b			
Error Negativity Amplitude at FCz (μV)						$F(1,105) = 305.3^b$ part. $\eta^2 = .74$ Ne < PNe^b	$F(2,105) = .4$ part. $\eta^2 < .01$ —	$F(2,105) = 5.7^b$ part. $\eta^2 = .10$ C < A^b
PNe	1.8 (3.6)	1.4 (3.6)	.8 (3.3)	.7	—			
Ne	−8.1 (3.4)	−6.9 (4.8)	−5.7 (4.3)	2.8^d	C < A^d			
Peak-to-Peak Ne	−9.9 (4.2)	−8.3 (4.0)	−6.6 (4.2)	5.7^b	C < A^b			
Error Positivity Mean Amplitude (μV)						site	group	site × group
Cz	9.1 (4.1)	7.2 (3.8)	8.0 (4.4)	1.0	—	$F(1,105) = 3.2^d$ part. $\eta^2 = .03$	$F(2,105) = 1.3$ part. $\eta^2 = .03$	$F(2,105) = .1$ part. $\eta^2 < .01$
Pz	9.8 (4.0)	8.2 (2.8)	8.6 (4.0)	1.1	—			
mean	9.5 (3.8)	7.7 (3.0)	8.3 (3.7)	1.3	—	—	—	—

Ne, error negativity; PNe, positive peak preceeding NE; other abbreviations as in Table 1.
[a] $p < .01$.
[b] $p < .05$.
[c] $p < .1$.

ADHD. It followed a purely linear trend for genetic concordance with ADHD over groups, which indicates that conflict-monitoring as indexed by N2 enhancement might be a specific biological basis for behavioral endophenotypes like RT SD as described earlier.

Furthermore, this flanker-task evoked clear fronto-central Ne in children. We found reduced Ne amplitude in ADHD compared to unrelated control subjects, which might reflect impairments in fronto-striatal networks as advocated by several cognitive theories of ADHD (11–13). This finding is also in agreement with other clinical studies (70,71) but not with selective Pe reduction in a Go/No-Go task (73) or with unexpected Ne enhancement in a simple discrimination task, presumably reflecting compensatory processes (74). There was also a linear relation between genetic concordance and Ne amplitude, and nonaffected siblings did not differ from both other groups but had intermediate scores, which again points out that Ne might index an endophenotype (6). Because both N2 and Ne are highly correlated and

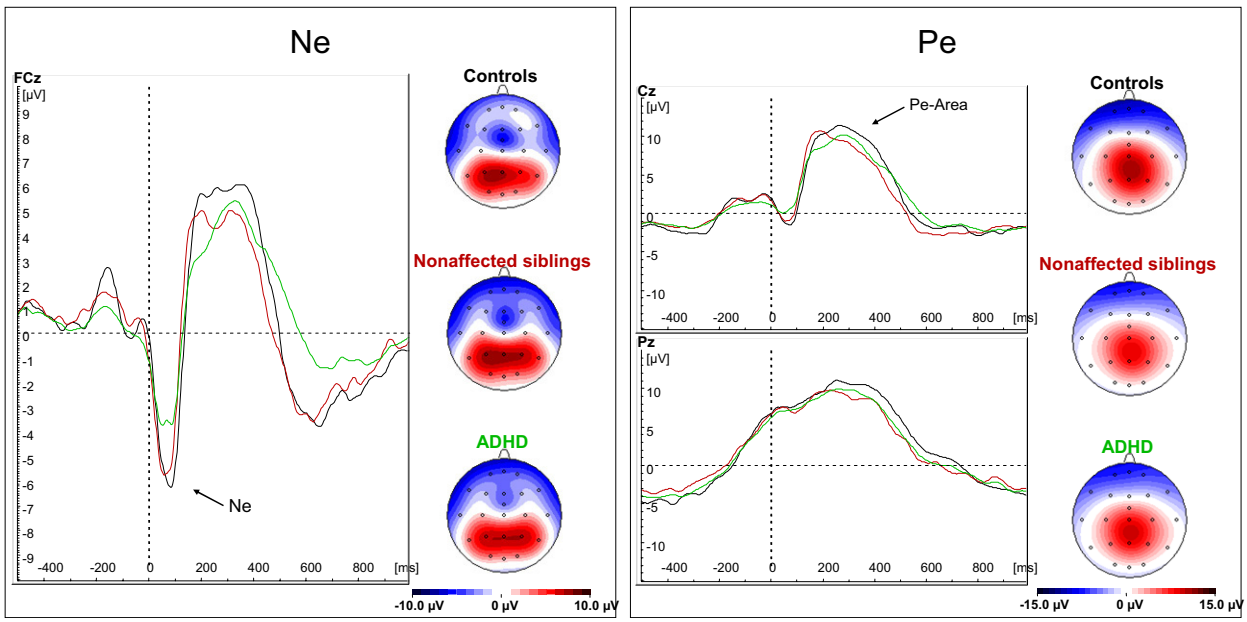

Figure 5. Response-locked error-related components. Response-locked grand average waves of control subjects (black), nonaffected siblings (red), and attention-deficit/hyperactivity disorder (ADHD) boys (green) with spline-interpolated maps of error negativity (Ne) at the respective group mean latency (left side) and error positivity (Pe) mean activity 200–500 msec after error response (right side). The response-locked Ne has its maximum at FCz (even more prominent when measured peak-to-peak), whereas Pe was maximal at centro-parietal electrodes.

share sources in ACC, a common dopaminergic dysfunction might underlie these findings. Thus, it might be fruitful to search for associations between the reported endophenotypes and risk alleles related to dopaminergic pathways (101).

No such relations were found for Pe, which did not differ between groups irrespective of whether amplitude of potentially confounded stimulus-locked P3 was controlled for or not. This is similar to what was reported in a study with patients suffering from Parkinson's disease (67), which supports the notion that Pe, unlike Ne, does not depend on the dopaminergic system.

The findings reported might be compromised by confounding comorbid disorders. Concerning mood disorders, anxiety, and obsessive-compulsive disorder, an effect of Ne enhancement is widely reported (57–59), which would have diminished the effect of ADHD. However, comorbid oppositional defiant or conduct disorder might have led to reduced Ne (31), but effects remain stable even when subjects possibly suffering from those disorders were excluded. Another limitation of this study is that we administered the clinical interview only if susceptibility for ADHD was given; thus cases of potentially comorbid ODD/CD might not have been detected in control subjects and nonaffected siblings. However, SDQ scores of Conduct Problems did not differentiate these groups. Thus, we think that results reported are not compromised by comorbidities.

Group differences in ERP parameters might originally be due to differences in data quality. Thus we analyzed SNRs for each examined waveform. It turned out that differences in SNR emerged only for waveforms in which no significant group-differences were found, and therefore rejections of the null hypotheses are not compromised by data quality.

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2.4. Performance Variability, Impulsivity Errors and the Impact of Incentives as Gender-Independent Endophenotypes for ADHD

As described in chapter 1.2.2, ADHD as a heterogeneous disorder is characterized by cognitive, motivational or state regulation deficits that may lead to reduced performance in tasks tapping executive functions. However, there were very few attempts to test these explanations directly within one study, and there was so far to the best of my knowledge no evidence concerning the familiality of these factors.

The fourth manuscript by Uebel et al. (2009) covers the impact of incentives, event-rate and ADHD familiality on a number of performance parameters in a Go/Nogo Task which requires executive functioning like sustained attention and response control. The children showed enhanced performance if incentives were given and when the event-rate was higher and closer to the expected optimal frequency, indicating that both manipulations were effective. It was further confirmed that the performance of children with ADHD was lower than in healthy controls without a family history of ADHD, whilst nonaffected siblings showed intermediate performance. However, the performance enhancement due to incentives also showed a pattern of familiality, which could not be confirmed for the proposed state-regulatory impact of event-rate. Thus, we concluded that performance, particularly response speed and response variability, as well as a motivational dysfunction may be suitable endophenotypes for ADHD. It was further confirmed that these effects were independent of differences between genders, which is of importance for further studies on gene and environmental factors associated with ADHD.

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Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD

Henrik Uebel,[1] Björn Albrecht,[1] Philip Asherson,[2] Norbert A. Börger,[3] Louise Butler,[7] Wai Chen,[2] Hanna Christiansen,[5] Alexander Heise,[1] Jonna Kuntsi,[2] Ulrike Schäfer,[6] Penny Andreou,[2] Iris Manor,[4] Rafaela Marco,[8] Ana Miranda,[8] Aisling Mulligan,[7] Robert D. Oades,[9] Jaap van der Meere,[3] Stephen V. Faraone,[10] Aribert Rothenberger,[1] and Tobias Banaschewski,[1,11]

[1]Child & Adolescent Psychiatry, University of Göttingen, Germany; [2]MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, UK; [3]Laboratory of Clinical and Developmental Psychology, Groningen, Netherlands; [4]ADHD Unit, Geha Mental Health Centre, Petach-Tikva, Israel; [5]Department of Clinical Psychology, Philipps University of Marburg, Germany; [6]Child and Adolescent Psychiatrist in Private Practice, Göttingen, Germany; [7]Department of Psychiatry, Trinity Centre for Health Sciences, St. James's Hospital, Dublin, Ireland; [8]Department of Developmental and Educational Psychology, University of Valencia, Spain; [9]Clinic for Child and Adolescent Psychiatry and Psychotherapy, University of Duisburg-Essen, Germany; [10]Departments of Psychiatry and Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA; [11]Central Institute of Mental Health, Department of Child and Adolescent Psychiatry and Psychotherapy, Mannheim, Germany

Background: Attention-deficit hyperactivity disorder (ADHD) is one of the most common and highly heritable child psychiatric disorders. There is strong evidence that children with ADHD show slower and more variable responses in tasks such as Go/Nogo tapping aspects of executive functions like sustained attention and response control which may be modulated by motivational factors and/or state-regulation processes. The aim of this study was (1) to determine if these executive functions may constitute an endophenotype for ADHD; (2) to investigate for the first time whether known modulators of these executive functions may also be familial; and (3) to explore whether gender has an impact on these measures. **Methods:** Two hundred and five children with ADHD combined type, 173 nonaffected biological siblings and 53 controls with no known family history of ADHD were examined using a Go/Nogo task in the framework of a multi-centre study. Performance-measures and modulating effects of event-rate and incentives were examined. Shared familial effects on these measures were assessed, and the influence of gender was tested. **Results:** Children with ADHD responded more slowly and variably than nonaffected siblings or controls. Nonaffected siblings showed intermediate scores for reaction-time variability, false alarms and omission errors under fast and slow event-rates. A slower event-rate did not lead to reduced performance specific to ADHD. In the incentive condition, mean reaction-times speeded up and became less variable only in children with ADHD and their nonaffected siblings, while accuracy was improved in all groups. Males responded faster, but also committed more false alarms. There were no interactions of group by gender. **Conclusions:** Reaction-time variability and accuracy parameters could be useful neuropsychological endophenotypes for ADHD. Performance-modulating effects of incentives suggested a familially driven motivational dysfunction which may play an important role on etiologic pathways and treatment approaches for ADHD. The effects of gender were independent of familial effects or ADHD-status, which in turn suggests that the proposed endophenotypes are independent of gender. **Keywords:** Attention-deficit hyperactivity disorder, ADHD, endophenotype, executive function, reaction-time variability, false alarms, state regulation, incentives.

The core symptoms of attention-deficit/hyperactivity disorder (ADHD) – age-inappropriate levels of hyperactivity, impulsivity and inattention – are present in at least 3–5% of school-aged children (American Psychiatric Association, 1994). They occur independently of cultural background, but are overrepresented in boys (Rohde et al., 2005). Twin and adoption studies yielded heritability rates of 76% (Faraone et al., 2005), but single risk-alleles contribute only slightly to the overall risk for ADHD (Castellanos & Tannock, 2002; Faraone et al., 2005).

Endophenotypes are intermediate phenotypes representing quantitative and heritable vulnerability traits. To clarify the etiologic pathways from genes over gene–environment interactions to the symptoms of ADHD, endophenotypes should be assessed at different levels of investigation (e.g., neuropsychology, EEG, MRI) (Buitelaar, 2005; Gottesman & Gould, 2003). Theoretically, genetic effects should be larger for endophenotypes than for the phenotypes used in

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diagnosis, making them better targets for molecular genetic studies (Doyle et al., 2005). Moreover, endophenotypes may serve as useful intermediate constructs to explain the heterogeneity of the ADHD phenotype (Banaschewski et al., 2007; Buitelaar, 2005; Rommelse et al., 2007).

At the level of neuropsychology, numerous studies suggest that ADHD symptoms may be closely related to impairments of executive functions (EF) such as behavioural inhibition or sustained attention (Barkley, 1997; Pennington & Ozonoff, 1996; Sergeant, 2005; Sonuga-Barke, 2005). Children suffering from ADHD perform poorly in a wide range of tasks that require response control (Drechsler et al., 2005; Mason et al., 2005). In general, their responses tend to be slower, more variable and more error-prone (Barkley, 1997; Tannock, 1998). These findings may indicate a suboptimal state of activation (Castellanos et al., 2005; Kuntsi et al., 2001; Sergeant, 2005). They may also, in part, be explained by delay aversion (Scheres et al., 2001; Sonuga-Barke, 2005) or alterations in a delay-of-reinforcement gradient (Luman et al., 2005; Sagvolden et al., 2005). Slow event-rates should lead to underactivation and thus to slow and inaccurate responding; fast event-rates might induce a fast but inaccurate response style (Sanders, 1983), particularly in ADHD (Sergeant, 2005). Thus, various studies reported that slow event-rates can impair performance in ADHD compared to normal control children (Sergeant, 2005; van der Meere et al., 1995a). Further, children with ADHD seem to be highly sensitive to reward (Douglas & Parry, 1994), and some studies found improved performance if incentives were given within due time (Sagvolden et al., 2005; Slusarek et al., 2001). Recently, it was reported that certain performance parameters of a four-choice reaction-time task (e.g., reaction-time variability) seemed to reflect an endophenotype, although it remained unclear whether the modulators of performance, event-rate and incentives, were familial (Andreou et al., 2007).

Hence, several models of ADHD impairment can explain poorer performance, slower reaction-times (RT) and higher reaction-time variability (RT-SD) and their modulation by event-rates and incentives. The Go/Nogo task has been found to be adequate to assess sustained attention and response control and for investigation of the influence of the above-mentioned conditions (Borger & van der Meere, 2000).

The aim of this study was to examine whether general aspects of task performance such as speed, accuracy or performance homogeneity represent endophenotypes. Further, the influence of modulating factors like event-rate and incentives on these parameters was investigated. Finally, we tested whether there were effects of age and gender independent of performance differences between groups.

Methods and materials

Sample

Recruitment of participants was conducted as part of the International Multi-Center ADHD Gene study (Asherson, 2004; Kuntsi et al., 2006). Families with more than three biological members including at least one child with ADHD symptoms were recruited from ADHD outpatient clinics or specialized private practices in Germany, Ireland, Israel, Spain and the United Kingdom. The control group was recruited from primary and secondary schools in London, UK, and in Göttingen, Germany. Participants had to be 6–18 years of age at the time of entry into the study. Exclusion criteria included autism, epilepsy, IQ below 70, brain disorders and any genetic or medical disorder that may mimic ADHD. Ethical approval for this study was obtained from local ethical review boards.

Overall, datasets from 445 children aged 6–18 years, either diagnosed with a research diagnosis of ADHD combined type, or nonaffected siblings of ADHD children or unrelated controls without a clinical diagnosis or known family history of ADHD as described below, were available. Due to technical problems, datasets of 14 ADHD participants had to be excluded. Therefore, the sample analysed consisted of 53 (38 boys) controls, 173 (75 boys) nonaffected siblings of ADHD-participants and 205 (186 boys) participants with a diagnosis of ADHD combined-type (see also Table 1 of the supplementary online material). Outlying task performance was defined as two standard deviations over the mean target RT and with the false alarm rate below the grand mean or vice versa. No outliers with such extreme speed–accuracy trade-offs were found. As females were outnumbered in the ADHD-group ($\chi^2_{(2)} = 99.3$, $p < .01$), analyses controlled for gender effects. There were no group or gender differences in age (both $F_{(1/2,\ 425)} < .1$, $p > .9$); but control children showed higher estimated IQs than nonaffected siblings and participants with ADHD ($F_{(2,\ 425)} = 4.7^{**}$, $p < .01$). In addition, the males' estimated IQs were higher than females' ($F_{(2,\ 425)} = 5.2^{**}$, $p = .02$). The proportion of children with an estimated IQ lower than 80 was small (6%) and did not differ among groups ($\chi^2_{(2)} = 2.4$, $p = .31$). As indicated by the Strengths and Difficulties Questionnaire (SDQ), participants with ADHD displayed more behaviour problems than both controls and nonaffected siblings (all $F_{(2,\ 423/411)} > 8.3$, $p < .01$; see Figure 1). Nonaffected siblings were rated as slightly more hyperactive than control children by teachers, but the mean ratings lay in the normal range (Woerner et al., 2004). Parents and teachers reported girls as less hyperactive (both $F_{(1,\ 423/411)} > 7.9$, $p < .01$) and more prosocial (both $F_{(2,\ 423/411)} > 5.3$, $p < .05$).

Procedure

Families that came into consideration were contacted. In case of interest, detailed information material and clinical questionnaires as screening instruments for ADHD and global psychological background (Long versions of Conners rating scales for parents, CPRS-R:L and teachers CTRS-R:L (Conners et al., 1998a, 1998b), parent and teacher version of the Strengths and Difficulties Ques-

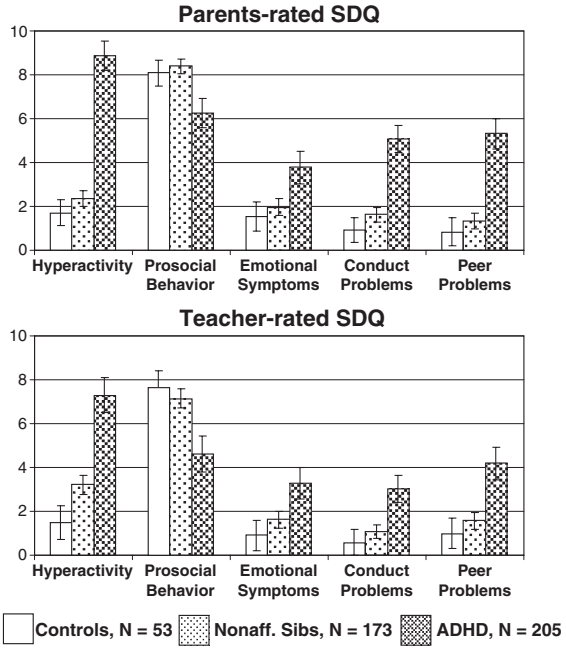

Figure 1 Sample description. Estimated marginal means as well as confidence intervals at $p = .05$ for parent- and teacher-rated SDQ

tionnaire (SDQ; Goodman, 1997; Woerner et al., 2004), Social Communication Questionnaire (SCQ; Berument et al., 1999) were provided for all children. If T-scores on the Conners ADHD scale (N) exceeded 63 and scores on the SDQ Hyperactivity scale exceeded the 90th percentile, a semi-structured clinical interview (PACS; Chen & Taylor, 2006) was conducted with one or both parents by trained investigators in order to verify ADHD diagnosis and to confirm the presence or absence of symptoms from other child psychiatric disorders. To ensure that unrelated control children recruited from primary and secondary schools were free of a susceptibility for ADHD, children with T-scores exceeding 63 on both parent- and teacher-rated Conners DSM-IV ADHD total symptoms scales or with a family history of ADHD as obtained by non-structured clinical interviews were excluded.

The Go/Nogo task reported here was part of a neuropsychological test-battery that also contained two other neuropsychological tests described elsewhere (Andreou et al., 2007; Marco et al., in press) and several subtests from the WISC/WAIS (vocabulary, similarities, picture completion, and block design) in order to obtain an estimate of the child's IQ (Sattler, 1992). Prior to cognitive testing children were free of medication for at least 48 hours. Blood samples were also taken for subsequent DNA extraction. The neuropsychological testing took place in noise-shielded rooms in the respective departments. At the end of the session, all children earned small prizes; parents did not receive any financial reward for participation except reimbursement.

Stimuli and task

On each trial of the Go/No-Go Task (Borger et al., 1999; Kuntsi et al., 2005; van der Meere et al., 1995b), one of two possible stimuli (letters X or O) appeared for 300 ms in the middle of the computer screen. The children were instructed to respond only to the 'go' stimuli (letter X) and to react as quickly as possible, but to maintain a high level of accuracy. The proportion of 'go' to 'no-go' stimuli was 4:1.

The children performed the task under three different conditions. The fast condition consisted of 462 trials with an inter-stimulus interval (ISI) of 1 s. The ISI increased to 8 s in the slow presentation condition, which consisted of 72 trials. The order of the slow and fast conditions varied randomly across children. During practice sessions (with 18 trials for fast and 6 trials for the slow condition), the tester ensured that the child had understood the instructions and gave feedback. The incentive condition was always administered last at the centres in Göttingen and London. This condition is a modification of the incentive condition used in the study of the stop task by Slusarek (Slusarek et al., 2001). Each correct response to the letter X and each correct non-response to the letter O earned one point, but for each omission error (failure to respond to X) and for each failure to respond within 2 s one point was lost. Each false alarm (incorrect response to O) led to the loss of five points. The points were shown in a box, immediately right of the screen centre, that was updated continuously throughout. The task started with a deposit of 40 points to avoid the possibility of a negative tally. The children were asked to earn as many points as possible, as the points would be exchanged for a real prize after the game ended. This condition was intended to be comparable to the slow condition and thus consisted of 72 trials and had an ISI of 8 s.

Altogether, fast, slow and incentive condition lasted approximately 11 minutes each. A preliminary reliability study revealed moderate-to-good retest reliability (Kuntsi et al., 2005).

Analyses

All analyses were conducted using SPSS 12.0.2. Since the dependant variables RT, intraindividual variability of RT (RT-SD), percentage of false-alarms and percentage of omission-errors for both fast and slow condition show developmental trends, age was taken as a covariate in every comparison.

Repeated-measure ANCOVAs with the within-subject factor 'condition' (slow vs. fast) and between-subject factors 'group' (controls, nonaffected siblings, participants with ADHD) and 'gender' together with Sidak-adjusted post-hoc tests were conducted for all dependant variables. For significant interaction effects 'condition*group', a post-hoc ANCOVA with dependant variable 'difference between conditions' was performed. Effects of the incentive condition were analysed for the Göttingen and London subsample separately, with repeated measure ANCOVAs for all dependant variables with within-subject factor 'condition' (slow vs. incentive) and between-subject factor 'group' and 'gender'.

As four performance parameters were tested in each analysis, following the Sidak procedure a significance level of $p < .013$ retains the overall significance level of $p < .05$. Moreover, additional nonparametric statistics (overall Kruskal–Wallis tests, followed by post-hoc Mann–Whitney U-tests) for the boys-only subsample were performed in order to provide a statistic free of assumptions about the distribution of the data.

To address effects of familiality, trend analyses across groups were performed to test whether nonaffected siblings were located intermediately between ADHD and control children. This would be indexed by a linear trend in the absence of a residual quadratic trend. A residual quadratic component would indicate that the nonaffected siblings were either more similar to the control or more similar to the ADHD group (Albrecht et al., 2008; Hager, 1996; Slaats-Willemse et al., 2003).

Results

Impact of event-rate

Go mean reaction-time. Reaction-times were generally slower for the slow compared to the fast event-rate condition ('Condition', $F_{(1,\ 424)} = 135.9$, $p > .01$, see Figure 2 and Table 2 of the supplementary material) and are subject to developmental effects ('Age', $F_{(1,\ 424)} = 225.3$, $p < .01$). The difference between conditions was smaller with increasing age ('Condition*Age', $F_{(1,\ 424)} = 43.1$, $p < .01$). Groups differed in mean RT ($F_{(2,\ 424)} = 9.9$, $p < .01$), with controls and nonaffected siblings responding generally faster than individuals with ADHD, which was confirmed by nonparametric analyses of the boys-only subsample ($\chi^2_{(2)} = 14.9$, $p < .01$). Generally, boys responded faster than girls ($F_{(1,\ 424)} = 6.2$, $p = .01$), and this effect of gender was additive in both groups and conditions (interaction-effects revealed in any case $F_{(1/2,\ 424)} < 1$, $p > .38$).

Total mean RT showed a linear ($p < .01$) but also a quadratic trend ($p = .02$) whilst the total RT-difference between fast and slow condition showed no linear trend ($p = .20$) but a tendency towards a quadratic trend ($p = .09$) across groups, which indicates that nonaffected siblings' performance was distributed near that of controls.

Reaction-time variability. Analyses of RT-SD showed a similar pattern of results to the analyses of RT, with the exception that no gender-differences were found. RT-SD decreased with age ($F_{(1,\ 424)} = 155.9$, $p < .01$) and was higher in the slow compared to the fast condition ($F_{(1,\ 424)} = 68.9$, $p < .01$); however, with increasing age this effect was less pronounced ('Condition*Age', $F_{(1,\ 424)} = 42.5$, $p < .01$). Furthermore, controls showed the lowest and participants with ADHD showed the highest RT-SD, with nonaffected siblings located intermediate ('Group', $F_{(2,\ 424)} = 17.4$, $p < .01$, confirmed by the nonparametric analyses of the boy-only subsample, $\chi^2_{(2)} = 38.6$, $p < .01$).

Trend analyses across groups revealed for total mean RT-SD a linear ($p < .01$) and not a quadratic trend ($p = .47$), which indicates that nonaffected siblings did show a degree of RT-SD intermediate between the controls and participants with ADHD. For the RT-SD difference between conditions no clear trends across groups were found.

Percentage of false alarms. The percentage of false alarms decreased with increasing age ($F_{(1,\ 424)} = 54.4$, $p < .01$). Both event-rates yielded the same proportion of false alarms ($F_{(1,\ 424)} = 1.1$, $p = .30$) and no interaction with group ($F_{(2,\ 424)} = .3$, $p = .77$). Participants with ADHD and nonaffected siblings committed more false alarms than controls ($F_{(2,\ 424)} = 11.9$, $p < .01$; confirmed nonparametrically for boys-only, $\chi^2_{(2)} = 13.3$, $p < .01$). Girls generally committed fewer false alarms than boys ($F_{(1,\ 424)} = 19.9$, $p < .01$), which again was additive, i.e., did not show any interactions with group or condition ($F_{(1/2,\ 424)} < 1.1$, $p > .29$).

Analyses of the total mean false alarms rate revealed a linear ($p < .01$) without a quadratic trend across groups ($p > .47$).

Percentage of omission errors. Omission errors also decreased with age ($F_{(1,\ 424)} = 117.0$, $p < .01$). There was an interaction effect between condition and group

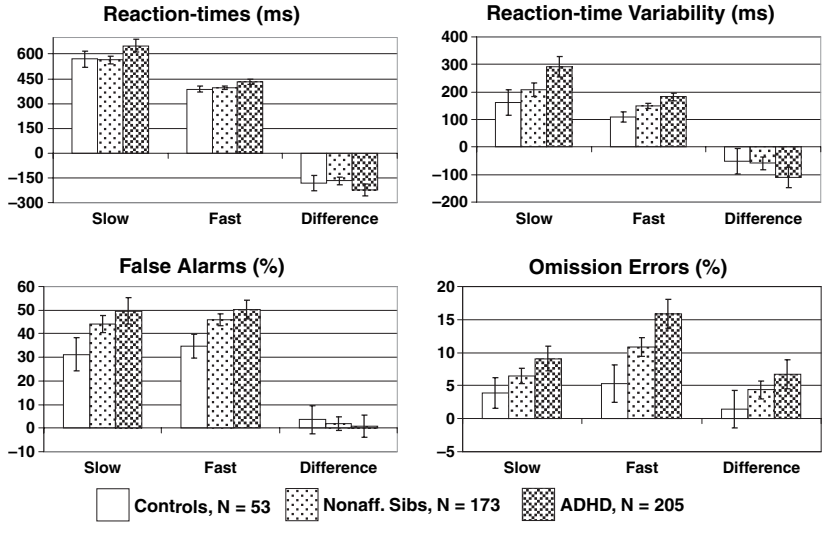

Figure 2 Behavioural data of slow vs. fast event-rate. Estimated marginal means with age taken as covariate as well as confidence intervals at $p = .05$ for slow and fast conditions

which indicated that omission-error rate was particularly reduced rather than enhanced by the slow event-rate in participants with ADHD compared to controls ($F_{(1, 424)} = 4.3$, $p = .01$). Subsequent univariate ANOVAs revealed for both conditions that participants with ADHD made more omission errors than their nonaffected siblings and controls, but for the fast condition even nonaffected siblings omitted more trials than controls (both $F_{(2, 424)} > 6.3$, $p < .01$). This was confirmed by nonparametric analyses of the boys-only subsample (both $\chi^2_{(2)} > 9.4$, $p < .01$). No influences of gender were found.

Both total mean as well as the impact of event-rate showed linear (both $p < .01$) and no quadratic trends ($p > .82$) across groups, thus nonaffected siblings showed intermediate effects.

Impact of incentives

Data from 2 nonaffected siblings and 3 participants with ADHD were not available, so a total of 308 participants from London or Göttingen entered this comparison (Figure 3 and Table 3 of the supplementary material). Neither groups nor genders differed in age (both $F_{(2, 302)} < 1$, $p > .7$), but lower IQs were found in participants with ADHD compared to controls ($F_{(2, 302)} = 4.4$, $p = .01$) and in females compared to males ($F_{(1, 302)} = 4.4$, $p = .04$).

Go mean reaction-time. Reaction-times were faster in older children ($F_{(1, 301)} = 75.3$, $p < .01$) and for boys compared to girls ($F_{(1, 301)} = 4.9$, $p = .03$). Furthermore, mean RT differed for both, conditions ($F_{(1, 301)} = 55.9$, $p < .01$) and groups ($F_{(2, 301)} = 6.2$, $p < .01$) with significant interactions Condition* Group ($F_{(2, 301)} = 6.1$, $p < .01$) as well as Condition* Age ($F_{(1, 301)} = 44.7$, $p < .01$, the main effect of faster mean RT in the incentive compared to the slow condition diminished with increasing age). Additional Sidak-adjusted post-hoc tests revealed that only participants with ADHD improved their mean RT if incentives were given. Subsequent nonparametric analyses for boys-only confirmed the findings on mean RT ($\chi^2_{(2)} > 7.6$, $p = .02$), but the impact of incentives revealed a trend only ($\chi^2_{(2)} = 4.4$, $p = .10$).

Similar to the outcome of the fast vs. slow event-rate comparison, mean RTs showed linear and quadratic trends across groups (both $p < .05$). However, the impact of incentives showed solely a linear trend ($p < .01$ and $p = .27$, respectively).

Reaction-time variability. Generally, intra-individual RT-SD decreased with increasing age ($F_{(1, 301)} = 99.8$, $p < .01$), and was larger in the slow compared to the incentive condition, particularly in younger children ('Condition' $F_{(1, 301)} = 38.5$, $p < .01$ and 'Condition*Age' $F_{(1, 301)} = 22.9$, $p < .01$). The ADHD-group showed the highest RT-SD ($F_{(2, 301)} = 13.0$, $p < .01$).

Total mean RT-SD revealed linear and quadratic trends across groups (both $p < .04$).

Percentage of false alarms. False alarm rates ($F_{(1, 301)} = 58.4$, $p < .01$) and the impact of incentives decreased with increasing age ('Condition*Age' ($F_{(1, 301)} = 6.3$, $p = .01$)). Controls committed fewer false alarms than both nonaffected siblings and participants with ADHD, which did not differ ($F_{(1, 301)} = 8.2$, $p < .01$). In a nonparametric analysis of boys-only this overall group-effect on mean false alarms was diminished towards a trend ($\chi^2_{(2)} = 4.6$, $p < .10$), although nonparametric post-hoc Mann–Whitney-U-tests confirmed higher error-rates for the participants with ADHD alone with respect to the controls ($p = .03$). Additionally, boys committed more false alarms than girls ($F_{(1, 301)} = 8.3$, $p < .01$).

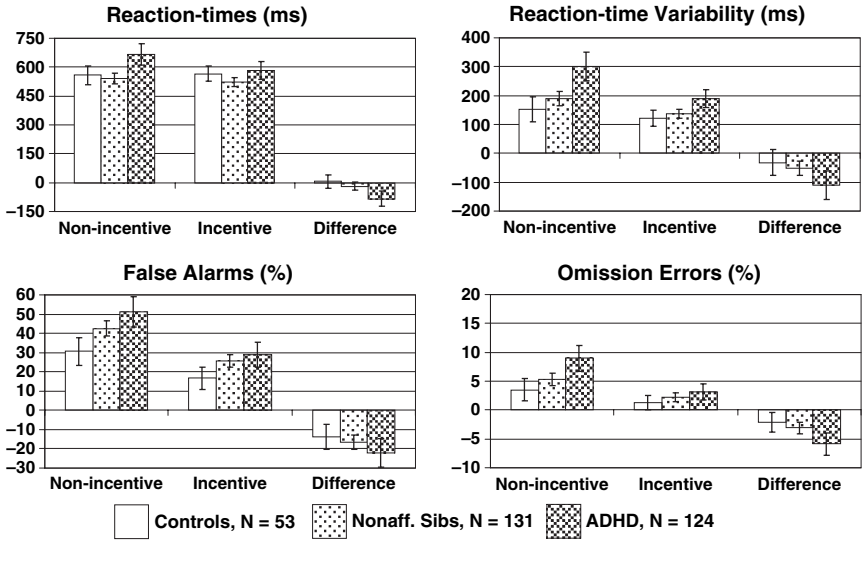

Figure 3 Behavioural data of non-incentive vs. incentive condition, both with slow event-rate. Estimated marginal means with age taken as covariate as well as confidence intervals at $p = .05$ for the non-incentive and incentive slow conditions

Total false-alarm rates revealed a clear linear trend across groups only ($p > .01$), and the impact of incentives on it revealed neither a linear nor quadratic trend across groups ($p > .1$).

Percentage of omission errors. Fewer omission errors were made in the incentive compared to the slow condition ($F_{(1,\ 301)} = 74.0$, $p < .01$), but this effect diminished with increasing age ($F_{(1,\ 301)} = 41.6$, $p < .01$). Generally groups differed ($F_{(2,\ 301)} = 5.5$, $p < .01$), but there was also an interaction 'Condition*Group' ($F_{(2,\ 301)} = 4.3$, $p = .01$). Additional analyses revealed that all groups showed reduced omission error rates in the incentive compared to the slow condition, but improvement was larger for participants with ADHD compared to both their nonaffected siblings and unrelated controls (see Table 3 of the supplementary material). Additional nonparametric analyses of the boys-only subsample confirmed group-differences ($\chi^2_{(2)} = 14.6$, $p < .01$), but revealed larger improvement for the ADHD group as compared to Controls only ($p = .02$). There were no significant gender differences or interactions (all $F_{(1/2,\ 301)} < 1.3$, $p > .27$).

Both total mean omission-error rate as well as the impact of incentives on it revealed linear (both $p < .01$) but no quadratic ($p > .26$) trends across groups.

Discussion

In this multi-centre study we examined aspects of executive functioning, in particular neuropsychological parameters of sustained attention and response control in a Go/Nogo task and their modulation by event-rate or incentives as candidates for endophenotypes in children with ADHD. It was hypothesised that task performance operationalised by reaction-times of correct responses, intra-individual reaction-time variability and error rates was diminished in children with ADHD, and that their nonaffected siblings show intermediate impairments as compared to controls without a family history of ADHD.

Performance without modulators

As expected, children with ADHD displayed poorer performance in terms of slower mean RT as well as higher percentages of false alarms and omission errors compared to unrelated healthy controls, which is in line with many studies (Albrecht et al., 2008; Banaschewski et al., 2003; Oosterlaan et al., 1998).

Further, increased RT-SD was demonstrated in ADHD subjects. Although a good theoretical account for RT-SD is still lacking (Castellanos et al., 2005), it may index temporal processing deficits (Castellanos & Tannock, 2002) or more general problems in maintaining an alert and focused state over time (Russell et al., 2006). In addition, nonaffected siblings were found to respond more variably than controls, but still less variably than children suffering from ADHD, thus being located in an intermediate position. This is convergent with results from recent studies concluding that RT-SD may be a suitable endophenotype (Andreou et al., 2007; Doyle et al., 2005).

Children with ADHD committed more false alarms than controls, with nonaffected siblings in an intermediate position as confirmed by statistical trend analyses across groups. Again, particularly for the fast condition, nonaffected siblings show more false alarms than controls, but less than those with ADHD, which again suggests that an impulsive response style may constitute an endophenotype for ADHD (Oades et al., 2008). It remains questionable whether RT-SD and false alarms are like two sides of the same coin. However, since false alarms but not RT-SD showed gender effects, this seems unlikely, and thus these parameters may indeed reflect separable processes.

Event-rates and performance

Manipulation of event-rate to impact energetic state using event-rates yielded expected task-related effects: given a slow stimulus presentation rate, mean reactions were generally slower but not more accurate. While this may indicate a suboptimal activation state in the slow condition, children with ADHD were not particularly impaired as proposed by the cognitive-energetic model of ADHD (Sergeant, 2005). Instead, participants with ADHD showed under slow event-rates a substantial reduction in omission errors compared to controls. It remains unclear whether this is due to a more basic effect. Since in the fast condition the density of go-responses in time is much higher than in the slow condition, the tendency to respond may become more prepotent, and mean RT decreased accordingly. Thus, the Nogo part of the task becomes more difficult with fast event-rates. Given that the false alarm-rate did not change between conditions, one may speculate that the increase in difficulty has been compensated for by omissions, in order to avoid commission errors. However, our results do not support the view that performance deficits in children with ADHD during the Go/Nogo task may be explained by underactivation as induced by event-rate, and thus question the cognitive-energetic explanation for this experiment.

Incentives and performance

Under low event-rate conditions, incentives led to enhanced performance concerning speed or accuracy, particularly in younger children. Furthermore, false alarms, omission errors, mean RT and RT-SD decreased, particularly in participants with ADHD and to a lesser extent in their nonaffected siblings, while for controls enhancements were only found for accuracy. Since incentives were given predominantly for accuracy, participants optimized their response

strategies accordingly in order to get more payback. Consistently for all four performance parameters, the impact of incentives followed a linear trend across groups. Thus nonaffected siblings displayed intermediate effects, suggesting that sensitivity to reward on the Go/Nogo task may constitute an endophenotype for ADHD. This complements the conclusion drawn by Andreou et al. (2007) from an overlapping sample – incentives generated stronger effects between groups than manipulations of event-rate – and is in line with recent theories that attribute main ADHD symptoms to deficits in a reinforcement system partly due to deficient fronto-striatal dopaminergic circuits (Luman et al., 2005; Sagvolden et al., 2005; Tripp & Wickens, 2008).

Although the incentive condition was always administered last, differential effects of incentives are not explainable by means of training or fatigue: there would have to be a stronger training-effect or less fatigue in ADHD compared to other groups analysed in order to support this alternative explanation – which is generally not supported by the literature (Heinrich et al., 2001; van der Meere et al., 1995a; Willcutt et al., 2005).

Effects of gender and age

In this study based on participants with ADHD who had been referred to an outpatient service, females were outnumbered. However, since the sample size was large, effects of gender could be disentangled from effects of ADHD or familiality. We found generally that females showed a response-style shifted towards accuracy, which was similar in all three groups. However, in this study only additive effects of gender were found, and thus the conclusions drawn remain applicable to both genders. This was supported for the boys-only subsample by additional analyses with nonparametric tests.

As expected, younger childern showed generally poorer performance. Their RTs were slower and the accuracy reduced. Moreover, both effects of poorer performance due to slow event-rate as well as enhanced performance due to incentives were more pronounced in younger children. But no interactions of age by group were found. Thus, for the broad age-range assessed, we can confirm the relevance of cognitive-energetic and motivational factors on performance.

Limitations

Since this was a multi-centre, multi-country project with the benefits of a large sample size, some heterogeneity in samples and procedures cannot be avoided. However, the researchers were well trained on the instruments used and a maximal compatibility of equipment and diagnostic procedure was ensured. Nevertheless, ADHD should be regarded as a disorder with heterogeneous underlying neuropsychological and neurophysiological strengths and difficulties.

Conclusion

It is a well-established finding that children with ADHD exhibit poor performance in tasks involving executive functions. Furthermore, it is even likely that these deficits form endophenotypes. However, there is some evidence that different event-rates and the presence/absence of immediate incentives are performance modulators for children. With this study, we could replicate deficits in some executive functions such as sustained attention, response control and performance variability as endophenotypes for ADHD, reflected particularly by the performance parameters response variability and accuracy. Further, for the first time we could show the moderating effects of incentives, but not of event-rate, as an endophenotypic function for ADHD. Thus, motivationally driven behaviour seems to be familial and may play an important role with regard to etiologic pathways as well as approaches to treatment in ADHD. Moreover, these potential endophenotypes are not confounded by influences of gender and age, which may have additional impact on molecular genetic studies.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table 1 Sample description. (Word document)

Table 2 Behavioral data for the slow vs. fast event-rate comparison. (Word document)

Table 3 Behavioral data for the non-incentive vs. incentive comparison (centers Göttingen and London only) (Word document)

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Correspondence to

Henrik Uebel, University of Göttingen, Child and Adolescent Psychiatry, von Siebold-Str. 5, 37075 Göttingen, Germany; Email: huebel@gwdg.de

Key points

- ADHD is a common and highly heritable child psychiatric disorder, but developmental pathways from genes and environmental factors to behaviour are poorly understood. Searching for neuropsychological intermediate phenotypes (endophenotypes) may be warranted to close the gap.
- In ADHD, good candidates for endophenotypes may be the known parameters of executive functions, which may also reflect deficits in motivation or state regulation.
- In this study using a Go/Nogo task controlled for event-rates and incentives, deficits in sustained attention, response control and performance variability could be confirmed as gender-independent endophenotypes of ADHD. Moreover, a motivational dysfunction in ADHD was found to be familially driven.
- These findings extend the view on ADHD and highlight that familiality and the role of incentives need to be considered in further research on and clinical practice of ADHD.

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3. Summary

This thesis is opened by a brief review of current models of cognitive control and their support mainly from studies with adults and animals. It is demonstrated that several structural predictions of the attention network model by Posner and colleagues can be confirmed also for adolescents using event-related potentials. Recent theories propose dysfunctions in neuronal networks involved in cognitive control as an important developmental pathway to ADHD. The latter is considered as a heterogeneous disorder characterized among others by dysfunctions in fronto-striatal neuronal networks responsible for cognitive control, attention and motivation.

The presented work aims to test whether cognitive control as carried out by activity in certain neuronal networks is a possible biological factor of ADHD. The first experiment used a task that requires stopping of an ongoing response to assess whether an inhibitory control deficit is specifically present in ADHD, or whether children with oppositional defiant or conduct disorder also show such impairments. Contrary to the predictions of a disorder-specific cognitive theory of ADHD, ODD/CD without ADHD was also characterized by inhibitory deficits. Moreover, children fulfilling criteria of both disorders showed considerably lower impairment, which supports the view that this co-existence forms a separate clinical entity. The second experiment with a well established task tapping interference liability showed that impaired performance of children with ADHD may alternatively be a consequence of impairments of some other functions. This surprising finding, unfortunately based on performance data alone from a relatively small sample, is not in line with the results of the other studies and requires further research. However, conclusions drawn from performance data alone have limited validity since differences in covert brain processes may lead to similar overt performance und go undetected (Banaschewski and Brandeis, 2007). Finally, the third and fourth experiments revealed that impaired cognitive control and a slower and more variable response style as well as motivational deficits may be familially driven in ADHD and may thus represent endophenotypes for the disorder.

Diagnosis and Treatment

The presented results give evidence that cognitive control and related brain activity is an important factor in ADHD, but it is not unique for it since similar impairments were also

found in children with other externalising child psychiatric disorders, e.g. ODD/CD. It is possible that current classification systems as DSM-IV and ICD-10, which work reasonably at the level of the behavioural phenotype, may be misleading at the level of physiological dysfunctions. In line with the presented data, several psychiatric disorders may be associated with partly overlapping dysfunctions in neuronal networks.

Along these rather technical considerations, the current results may be relevant for treatment of ADHD. If behavioural and thought problems classified as psychiatric disorders are associated or even regarded as consequences of impaired activity in neuronal networks, a more fundamental therapy would at least consider brain activity parameters to guide the intervention or potentially tackle problematic brain activity parameters directly. The first strategy is already in use for the evaluation of therapies: pharmacological treatment of ADHD with methylphenidate can ameliorate previously impaired task performance (Broyd *et al.*, 2005, Pliszka *et al.*, 2007), and neurofeedback therapy can have specific impacts on electrophysiological brain activity parameters (Gevensleben *et al.*, 2009, Heinrich *et al.*, 2004). The second approach is used in a recent promising treatment study using tomographic neurofeedback: activity in a brain region relevant for cognitive control (the anterior cingulate cortex and the right dorsolateral prefrontal cortex) was used as target parameters to improve behavioural symptoms of ADHD (Liechti *et al.*, 2008).

Moreover, parameters of cognitive control may be used to optimize pharmacological treatment. Previous studies demonstrated that error processing as an important feature of cognitive control may be supported by dopamine-agonists (de Bruijn *et al.*, 2004) whilst antagonists led to impairments (de Bruijn *et al.*, 2006; Zirnheld *et al.*, 2004). It remains an open question whether patients with ADHD behavioural problems but with intact cognitive control processes receive an optimal treatment with stimulants, or instead whether other interventions are more promising. Hence, the strengths and difficulties of these children or adults with ADHD symptoms need to be further investigated, and it remains open whether other neuronal dysfunctions may better or in addition explain their disturbances.

Further research

There is considerable heterogeneity of results in the literature on cognitive control in ADHD. E.g., the reported evidence that ADHD is characterised by diminished N2-enhancement during increased need for cognitive control does probably hold for paradigms

that require a response to each and every stimulus such as the Stop- and Flanker-Tasks (e.g. Albrecht *et al.,* 2008). However, the situation appears to be different for several variants of Go-Nogo-Tasks that require responses to frequent stimuli (which induces a prepotency to respond throughout the task), but to withhold responses to rare Nogo stimuli (e.g. Banaschewski *et al.*, 2004). It may be that the former paradigms are more demanding, but this interpretation would neglect obvious qualitative differences in task demands.

In a recent study of our group, the impact of N2-enhancement in a CPT-Go-Nogo paradigm also with incongruent ("flankered") stimuli was contrasted with N2-enhancement evoked by a Flanker-Task within the same sample (Albrecht *et al.* 2010). Performance data revealed significant congruency effects in RT (slower RT in incongruent trials) in both tasks, and larger congruency effects for children with ADHD only in the CPT. As expected, N2-enhancement was significantly evoked by Nogo compared to Go-trials in the CPT and due to stimulus incongruency in both Flanker-Task and CPT. But the three types of demands for cognitive control revealed divergent ADHD effects on N2-enhancement: no impairments were found for congruency and Nogo effects in the CPT while the Flanker-Task congruency effect revealed clear medium effect-sized impairments in ADHD (see Figure 8).

It appears reasonable that the N2-enhancement reflects in principle some kind of cognitive control process, but there may be also several distinctions in the way it is triggered. N2-enhancement due to incongruent stimuli in the Flanker-Task or due to the additional letters presented in the Flanker-CPT was triggered in each trial, but only the Flanker-Task requires continuous responding, whilst the CPT requires a response only in a fraction of the trials (e.g. in 10% of the trials of the CPT used in this study). Thus, cognitive control is constantly required for Flanker-Task performance, and it remains open whether impairments in ADHD are a consequence of depletion due to permanent task demand and may thus increase with time on task. And if so, it needs to be tested whether this effect occurs within each block of trials or across blocks. Another consequence that may have some significance for the interpretation of the results is that the CPT may be better regarded as a "Nogo-Go-Task", as it is most common not to respond. Additionally, the N2-enhancement in the comparison between Nogo and Go-trials of the CPT is difficult to interpret since it is confounded with motor activity.

Moreover, these three instances of cognitive control may activate different neuronal networks responsible for N2-enhancement, which remains to be tested using tomographic

electrical neuroimaging. Taken together, the heterogeneity reported in the literature on N2-enhancement does probably reflect important functional distinctions which need to be considered in further research.

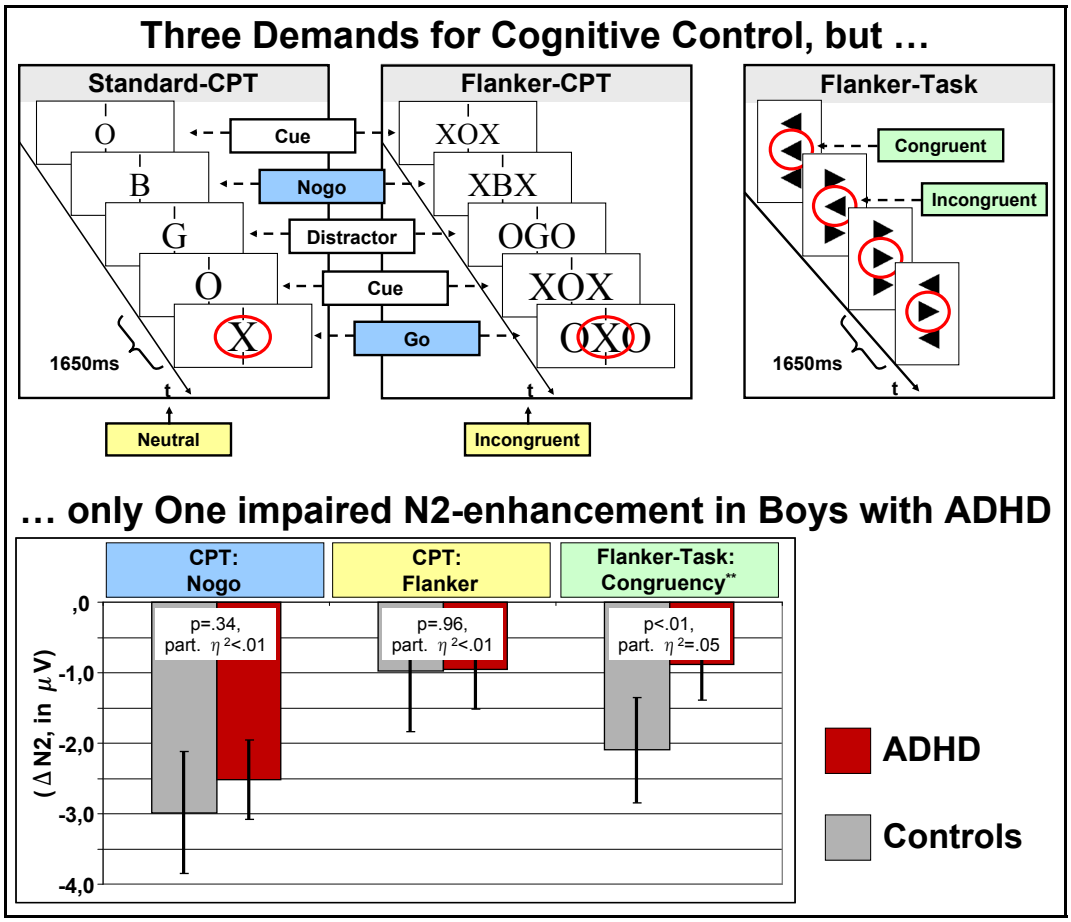

Figure 8: Cognitive Control is required in correct responded trials by the Nogo- (blue: cued Nogo vs. Go items) as well as Flanker-effect (yellow: cued incongruent vs. neutral) in the CPT, and the Congruency-effect (green: incongruent vs. congruent items) in the Flanker-Task (above). Please note that all three demands evoked significant N2-enhancement (since all confidence intervals did not include zero), but only the Flanker-Task Congruency-effect revealed an impairment in boys with ADHD (see below for marginal means of the respective difference N2-amplitudes and confidence intervals with $p<.05$).

Another open research question is the role of genetics and environmental factors in ADHD in general and cognitive control in particular. Although twin studies suggest high

heritability rates of ADHD symptoms only slightly below estimates for body size and autism, and on par with heritability of disorders like schizophrenia, there is still little known about the interplay of genetical and environmental factors in ADHD (Banaschewski et al., 2005, Faraone et al., 2005). As ADHD should be regarded as a disorder with heterogeneous underlying neuronal dysfunctions, it may be more fruitful for further research to disentangle this heterogeneity by focussing on endophenotypical parameters that may reflect neuronal functions more closely related to genetic and environmental factors. Recent studies on healthy adults suggest that COMT, DRD4 and BDNF polymorphisms play an important role in performance monitoring (Beste *et al.*, 2010, Kramer *et al.*, 2007) or cognitive control (Blasi et al., 2005, Diamond *et al.*, 2004, Fossella et al. 2002), and it appears to be worthwhile to assess their association in path models including ADHD symptoms. Moreover, patients with ADHD and difficulties in cognitive control may show larger and functionally more specific genetical or environmental commonalities.

However, it remains difficult to differentiate causes from effects in observational case-control studies, as potential differences between the groups may also be a consequence of treatment history or discontinued medication before testing, or may simply be caused by secondary consequences of a life with ADHD difficulties (e.g. higher level of persistent stress). Some of these confounds can be avoided in studies including also healthy siblings of patients.

Conclusion

Taken together, the studies provided in this thesis show that cognitive control is probably a fundamental impairment in many patients with ADHD. It is not exclusive for ADHD, since patients with other disorders like ODD/CD may also show difficulties in tasks tapping these functions. Impaired cognitive control is familially driven in ADHD, and thus be more proximal to biological factors on the way from genetic and environmental risk factors to the phenotype. Consideration of such endophenotypes may not only have an impact on classification systems and molecular genetic studies on mental disorders, but may further make a contribution to their treatment.

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Abbreviations

ACC	anterior cingulate cortex
ADHD	Attention Deficit / Hyperactivity Disorder
Ag / AgCl	silver / silver chloride
ANOVA	analysis of variance
CD	Conduct Disorder
CPT	Continuous Performance Test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EEG	electroencephalogram
EOG	electrooculogram
EPSP	excitatory postsynaptic potential
ERP	event-related potential
Hz	hertz
ICD-10	International Statistical Classification of Diseases and Health Related Problems, Tenth Revision
IPSP	inhibitory postsynaptic potentials
kΩ	kilo Ohm
λ	decay constant; $\lambda=\ln 2 * T_{1/2}^{-1}$ with $T_{1/2}$ as the half-life
LC	locus coeruleus
N2	second negative peak in the stimulus-locked ERP
Ne	response-locked error negativity
P3	third positive deflection in the stimulus-locked ERP
ODD	Oppositional Defiant Disorder
p	probability
PFC	prefrontal cortex

RT	reaction time
RT-SD	intra-individual reaction time variability
SMA	supplementary motor area
SNR	signal to noise ratio
VTA	ventral tegmental area

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Curriculum Vitae

Name	Björn Albrecht
Date of birth	December 12, 1976
Place of birth	Detmold, Germany

Since 2006	Head of the neurophysiological laboratory at the Department for Child and Adolescent Psychiatry of the University of Göttingen
Since 2005	PhD studies at the University of Göttingen (Prof. M. Hasselhorn & Prof. A. Rothenberger)
Since 2004	Researcher at the Department for Child and Adolescent Psychiatry at University of Göttingen (Prof. Rothenberger, Prof. T. Banaschewski), responsible for the neurophysiological laboratory

2004	Diploma
2002	Lab visit at the Department of Neuroendocrinology at University of Lübeck, Germany (Prof. J. Born)
2001-2002	Lab visit at IGPP in Freiburg, Germany (Prof. D. Vaitl, Dr. W. Plihal)
2001-2004	Research assistant at the Department for Child and Adolescent Psychiatry, University of Göttingen (Prof. A. Rothenberger & Prof. T. Banaschewski)
2001	Tutor for the Experimental Practical and Research assistant at the Department for Cognitive Psychology, University of Göttingen (Prof. G. Lüer, Dr. S. Werner & Dr. T. Schmidt)
2000-2004	Advanced studies of Psychology at University of Göttingen
2000	Intermediate diploma
1999-2001	Participation at a student-initiated project „Client-Centered Therapy for Children and Adolescents“

1999-2000	Research assistant at the Department for Individual Differences and Psychological Assessment, University of Göttingen (Prof. T. Rammsayer & Dr. W. Plihal)
1997-2000	Undergraduate student of Psychology at University of Göttingen, Germany
1996-1997	Civil Service
1992-1996	Secondary school, Städt. Gymnasium Steinheim
1986-1992	Secondary school, Städt. Realschule Steinheim
1982-1986	Elementary school, Grundschule Belle

List of Publications

2010

Albrecht, B., Brandeis, D., Uebel, H., Heinrich, H., Heise, A., Hasselhorn, M., Rothenberger, A., & Banaschewski, T. (2010). Action monitoring in children with or without a family history of ADHD - Effects of gender on an endophenotype parameter. Neuropsychologia, 48, 1171-1177.

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The bear was white.