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**ORIGINAL INVESTIGATION**

# Biomarkers for attention-deficit/hyperactivity disorder (ADHD). A consensus report of the WFSBP task force on biological markers and the World Federation of ADHD

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**Abstract**

*Objective.* Psychiatric "nosology" is largely based on clinical phenomenology using convention-based diagnostic systems not necessarily reflecting neurobiological pathomechanisms. While progress has been made regarding its molecular biology and neuropathology, the phenotypic characterization of ADHD has not improved. Thus, validated biomarkers, more directly linked to the underlying pathology, could constitute an objective measure for the condition. *Method.* The task force on biological markers of the World Federation of Societies of Biological Psychiatry (WFSBP) and the World Federation of ADHD commissioned this paper to develop a consensus report on potential biomarkers of ADHD. The criteria for biomarker-candidate evaluation were: (1) sensitivity $>80\%$, (2) specificity $>80\%$, (3) the candidate is reliable, reproducible, inexpensive, non-invasive, easy to use, and (4) confirmed by at least two independent studies in peer-reviewed journals conducted by qualified investigators. *Results.* No reliable ADHD biomarker has been described to date, but some promising candidates (e.g., olfactory sensitivity, substantial echogenicity) exist. A problem in the development of ADHD markers is sample heterogeneity due to aetiological and phenotypic complexity and age-dependent co-morbidities. *Conclusions.* Most likely, no single ADHD biomarker can be identified. However, the use of a combination of markers may help to reduce heterogeneity and to identify homogeneous subtypes of ADHD.

**Key words:** *Biomarker, attentention-deficit/hyperactivity disorder, olfaction, transcranial echosonography, neuroimaging, proteomics*

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders in children and adolescents and characterized by the core symptoms of age-inappropriate levels of inattention, hyperactivity and impulsivity (Taylor et al. 2004; Biederman and Faraone 2005). The condition affects approximately 5% of children worldwide (Polanczyk et al. 2007). Epidemiological studies have shown that ADHD can persist into adulthood (reviewed by Biederman and Faraone 2005). There tends to be an age-dependent decline in symptoms, but even if symptoms are not sufficiently prominent to prompt a diagnosis, they are frequently associated with significant clinical problems (ibid.). Thus, although most individuals with childhood ADHD

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will no longer meet the full threshold criteria for the disorder by the age of 30–40 years, approximately half of them will exhibit ongoing psychosocial impairment consistent with the DSM-IV diagnosis of "ADHD in partial remission", suggesting that many still will require treatment.

Despite widespread public scepticism regarding the legitimacy of ADHD as a valid psychiatric disorder (Buitelaar and Rothenberger 2004; Faraone 2005), several recent findings demonstrate the validity of the diagnosis with biological underpinnings such as multiple genetic factors, ADHD-related differences in brain structure and function, and changes in neurotransmission especially in the basal ganglia thalamocortical neurocircuitries (see Biederman and Faraone 2005; Konrad et al. 2006; Mehler-Wex et al. 2006; Volkow et al. 2007; Albayrak et al. 2008; Gerlach et al. 2008a; Thome and Reddy 2009).

The diagnosis of ADHD requires the identification of specific behaviours that meet international diagnostic criteria as delineated in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-R; American Psychiatric Association 1992). Other criteria include those of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10; World Health Organization 1992) which allows the diagnosis of "hyperkinetic disorder", basically a more severe and "refined" subset of DSM-IV ADHD.

Evidence from both clinical and epidemiological studies demonstrates that children with ADHD are at higher risk for other psychiatric and substance use disorders (Biederman and Faraone 2005). Common co-morbidities in children and adolescents include oppositional defiant disorder and conduct disorder, anxiety disorders, mood disorders, tic disorders, motor coordination disorder, learning disabilities and problems in reciprocal social interaction and communication that overlap with those described in autism spectrum disorders (Gillberg et al. 2004; Biederman and Faraone 2005; Taurines et al. 2011a). Some studies suggest that ADHD increases the risk of personality disorders and, if untreated, is associated with functional impairments such as dysfunction within the school environment, peer problems, family conflict, poor occupational performance, injuries, antisocial behaviour, traffic violations, and traffic accidents (Biederman and Faraone 2005; Jacob et al. 2007; Miller et al. 2008).

The aetiology and pathogenesis of ADHD is not yet fully understood. Hypotheses about the cause of ADHD have evolved from simple monocausal theories to the view that it is a complex, multi-factorial disorder caused by the interaction of many different types of risk factors (i.e. genetic, biological, environmental, psychosocial), with every single factor having a small individual effect on the increasing vulnerability to the disorder and leading to different pathophysiological pathways (Biederman and Faraone 2005; Thome and Reddy 2009). This multi-factorial and multi-pathway view of ADHD is consistent with the observed heterogeneity from genetics to behaviour.

ADHD is a highly heritable disease, with estimated heritability rates of up to 80% (e.g., Levy et al. 1997; Freitag et al. 2010). Results from molecular genetic studies indicate a complex genetic architecture of ADHD, i.e. genetic vulnerability is mediated by a multitude of risk genes with small individual effects (Faraone et al. 2005). In order to gain more insight into the mechanisms leading from a genetic/biological basis of the disease to the full clinical phenotype, intermediate phenotypes (so-called "endophenotypes") have proven to be useful mediators. Endophenotypes are assumed to be more closely linked to the relevant underlying psycho- or neuropathology, i.e. aetiological factors, than categorical clinical diagnoses. They are also usually less complex, and therefore more readily assessable, than diverse clinical phenotypes. Different neuropsychological variables have been considered as putative endophenotypes of ADHD, and more recently, functional imaging methods and neurophysiological techniques have been used to establish corresponding markers grounded in neuroscience (Castellanos and Tannock 2002; Gould and Manji 2004).

A biomarker (or biological marker) is defined as a characteristic that can be "objectively" measured and evaluated as an indicator of normal biological processes, pathogenetic processes or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group 2001). According to the type of information that they provide, biomarkers for CNS disorders can be classified as clinical, neuroimaging, biochemical, genetic or proteomic markers. Expectations towards the development of biomarkers are high since they could lead to a significant improvement in diagnosing and possibly preventing neurological and psychiatric diseases. Biomarkers are particularly relevant in the context of ADHD given its CNS pathology and clinical phenotypes which can change from childhood to adulthood. In addition, the current diagnostic procedures are based on the identification of a cluster of symptoms and the use of specific scales. Therefore, it is at present difficult to identify individuals at risk, to quickly and easily make an accurate diagnosis, to distinct different forms of ADHD for optimal differentiated treatment and management, and to stage reliably the severity of ADHD symptoms. Finally, it is also expected that the use of biomarkers will lead to a better classification of the disorder: based on current knowledge, it must be assumed that a group of disorders with

ADHD-like symptomatology but differing pathogeneses and course are subsumed under the term ADHD.

The task force on biological markers of the World Federation of Societies of Biological Psychiatry (WFSBP) and the World Federation of ADHD therefore commissioned the authors of this paper to develop a consensus report on potential diagnostic biomarkers in ADHD. In June 2010, a general call for contributing to this paper was sent to scientists and clinicians who had published in the field and to the members of the WFSBP task force on biological markers. In September 2010, the manuscript was prepared in accordance with the received submissions and consensus reached in writing via email.

## Criteria for evaluating biomarkers of ADHD

Driven in part by Alzheimer´s disease (AD) drug discovery research, AD is at the forefront of biomarker development for CNS diseases, and many current concepts about ideal biomarkers for these disorders have come from AD research (The Ronald and Nancy Reagan Research Institute of the Alzheimer´s Association and the National Institute on Aging Working Group 1998; Frank et al. 2003; Shaw L et al. 2007; Gerlach et al. 2008b). As initially proposed by the Working Group on Biological Markers of Alzheimer's Disease (The Ronald and Nancy Reagan Research Institute of the Alzheimer´s Association and the National Institute on Aging Working Group 1998), an ideal biomarker for AD should be:

- linked to fundamental features of AD neuropathology,
- validated in neuropathologically confirmed AD cases,
- able to detect AD early in its course and to distinguish it from other dementias,
- non-invasive,
- simple to use and
- inexpensive.

All AD biomarkers require evaluation of their sensitivity, specificity, prior probability, positive predictive value and negative predictive value. For a biomarker to be useful in the diagnosis of AD, it should have a sensitivity and specificity of $>85\%$ and a positive predictive value of $>80\%$. Recommended steps to establish a biomarker include confirmation by at least two independent studies conducted by qualified investigators with the results published in peer-reviewed journals.

However, the quest to find an ideal ADHD biomarker is hampered by the fact that the fundamental feature of ADHD neuropathology is elusive and a post-mortem validation is hardly to achieve. Therefore, we propose the following criteria for an ideal ADHD marker:

1. a diagnostic sensitivity $>80\%$ for detecting ADHD,
2. specificity $>80\%$ for distinguishing ADHD from other disorders with ADHD-like symptoms,
3. reliable, reproducible, and inexpensive to meausure, non-invasive, and simple to perform,
4. confirmed by at least two independent studies conducted by qualified investigators with the results published in peer-reviewed journals.

## Biomarker candidates

### *Putative clinical biomarkers*

*Neurophysiological markers.* ADHD is characterized by a wide range of neurophysiological aberrations, both under resting conditions and during neuropsychological stimulation. Over the last decade, neurophysiological markers have been extensively used to study putative endophenotypes of the disease, often with the aim to establish a link between genetic risk markers and the overt ADHD phenotype (approach of "genomic imaging" or "imaging genetics", firstly described in Fallgatter et al. 1999). Moreover, neurophysiological markers have been discussed as possible predictors of the treatment response to different pharmacological interventions and might eventually become useful diagnostic tools in establishing optimized treatment strategies based on individual aetiopathogeneses.

Here, we will mainly focus on EEG-based event-related potentials (ERPs) and the non-invasive, optical imaging method of functional near-infrared spectroscopy (fNIRS). The wide field of quantitative EEG measures has been comprehensively described elsewhere (Barry et al. 2003).

Electrophysiological methods such as ERPs have the advantage of an excellent temporal resolution, while spatial resolution is severely limited – even with modern source localization methods – due to the so-called "inverse problem". Neuroimaging methods such as functional magnetic resonance imaging (fMRI), on the other hand, have a very good spatial resolution allowing for a precise localization of activity patterns into the neuroanatomical space. However, temporal resolution is very low, not only due to technical limitations, but due to the natural "lag" of the bold-response relative to the underlying cognitive

or emotional neuronal processes. NIRS is an optical imaging method that allows for an assessment of cortical activation with a spatial resolution of a few centimetres and a temporal resolution of up to 10 Hz. It is especially suited for the examination of ADHD patients, since it is relatively insensitive to movement artefacts and measurements can be conducted in a relaxed sitting position without head fixation or other significant movement restrictions (i.e. it is very well suited for the examination of motorically restless patients or patients with low compliance). Finally, transcranial magnetic stimulation (TMS) allows for a targeted modulation of cortical brain activity both in a facilitating and an inhibitory direction.

*Markers of response inhibition and prefrontal response control.* One of the neuropsychological deficits that have repeatedly been reported in studies on ADHD and have therefore been proposed as putative endophenotypes of the disease concerns the process of response inhibition, a frontal lobe function closely linked to the ADHD symptom of (motor) impulsivity (Slaats-Willemse 2003; Crosbie et al. 2008). Several ERP indices have been discussed to reflect response inhibition and associated functions of cognitive response control (NoGo-P3, NGA, N200). Moreover, intracortical inhibition (a prominent motor cortex function related to a more basic form of neural inhibition) can be neurophysiologically assessed using double-pulse TMS.

Response inhibition and associated neurophysiological parameters can be easily assessed using standard Go-NoGo paradigms, during which subjects are instructed to press a response button under specific (Go) conditions and withhold the response following other (NoGo) stimuli. Under NoGo conditions, a prepared motor response has to be actively suppressed, constituting the process of response inhibition. Over the past decade, a topographical ERP marker has been developed and validated as a neurophysiological index of response inhibition and cognitive response control (Fallgatter et al. 1997). This topographical ERP parameter, termed NoGo-Anteriorization (NGA), has been shown to be closely linked to a NoGo-related hyperactivation of the ACC, a prominent medial prefrontal control structure (Fallgatter et al. 2002). Based on ERPs elicited by Go and NoGo trials, the NGA quantifies the frontalization of the P300 topography (the distribution of the brain-electrical field of the surface ERP in a P300 time-frame) that is associated with the inhibition (NoGo) relative to the execution (Go) of a primed motor response. In healthy subjects, the NGA was found to have a very high interindividual stability, excellent test–retest reliability, and it appears to be unaffected by age and gender (Fallgatter 2001). Moreover, in healthy controls, source localization methods (Low Resolution Electromagnetic Tomography, LORETA) indicate a neural source of the statistical contrast "NoGo vs. Go ERP" (i.e. the NGA) within the anterior cingulate cortex (ACC) (Fallgatter et al. 2002). In line with the hypothesis that response inhibition is impaired in ADHD, both children (Fallgatter et al. 2004) and adults (Fallgatter et al. 2005) with ADHD were found to exhibit significantly reduced activation within the medial prefrontal cortex during NoGo trials. Moreover, altered surface ERPs were found. Specifically, children suffering from ADHD showed significantly reduced NoGo-P3 amplitudes over centrally located electrode positions due to a lack of frontalization of the brain electrical field during NoGo trials (Fallgatter et al. 2004). In line with these findings, adult patients with a suspected childhood ADHD diagnosis and comorbid personality disorders showed significantly reduced mean NGA values and fronto-central P300 amplitudes (NoGo) when compared to healthy controls or personality disorder patients without a childhood ADHD diagnosis (Fallgatter et al. 2005). However, variance of individual NGA values was high, suggesting the existence of possible subgroups of the disease characterized by more or less pronounced prefrontal inhibitory dysfunction. Future studies are needed to more closely examine the relationship between baseline prefrontal control function and prognostic factors.

From an imaging genetics perspective, both serotonergic and dopaminergic single nucleotide polymorphisms (SNPs) were found to significantly affect the measure of the NGA. Specifically, the tryptophan hydroxylase (TPH2) gene significantly impacted NGA values in adult ADHD patients as well as healthy control participants (Baehne et al. 2009). Moreover, a common variable number of tandem repeats (VNTR) polymorphism of the dopamine transporter (DAT) gene (SLC6A3) was found to have a significant effect in adult ADHD patients, but not in healthy controls (Dresler et al. 2010). In this study, the 9-repeat allele of *DAT* led to significantly reduced NGA values; interestingly, this allele has recently been associated with an increased risk for adult ADHD (Franke et al. 2008, 2010).

Regarding other ERP indices of response inhibition and prefrontal response control, findings are partly inconsistent. While some abnormalities of the N200 were observed (e.g., Pliszka et al. 2000), other studies report aberrations only under very specific task conditions (Yong-Liang et al. 2000). Further studies are needed to more closely investigate these early inhibitory components.

The method of double-pulse TMS allows for an experimental assessment of intracortical inhibition

in the motor cortex of healthy controls and ADHD patients. For this procedure, an above-threshold stimulation of the motor cortex is conducted by a single TMS pulse, which can be measured via the resulting motor evoked potential (MEP) of the contralateral musculus abductor pollicis brevis. If, instead of a single pulse, a double pulse is applied with a very brief inter-stimulus interval of 2 ms between both pulses, the resulting MEP is physiologically reduced by about 70%. This phenomenon has been assumed to reflect an intracortical inhibition, already within the primary motor cortex, a mechanism possibly meant to prevent the system from overstimulation. In adult ADHD patients, this intracortical inhibition is significantly reduced as compared to matched healthy control subjects (Richter et al. 2007), replicating previous findings in children (e.g., Moll et al. 2000). Moreover, large variability was observed within the group of ten adult ADHD patients, again indicating the existence of different (diagnostic or prognostic) subgroups. Right now, we are interested in whether this reduced intracortical inhibition might also show a good response to treatment with MPH or atomoxetine, and respective studies are on the way.

Another function closely related to prefrontal response control is the complex process of action monitoring and error processing. Two prominent ERP components have been described that seem to reflect different aspects of such an action monitoring process. The error-related negativity (Ne, ERN) usually peaks early after an incorrect motor response and is closely followed by a positive deflection, the so-called error-positivity (Pe). Similar to the NGA, both components have been shown to be located within the medial prefrontal cortex (ACC) and both have been found to be altered in adult patients with ADHD (Herrmann et al. 2010). Interestingly, an age effect was found, indicating a "recovery" of function with increasing age, possibly reflecting compensatory mechanisms through continuous learning experience. One of the two potentials (the Pe) was also found to be affected by the inattention subscale of an ADHD screening questionnaire within a non-clinical population (Herrmann et al. 2009), suggesting a continuum of ADHD symptoms with an impact on error-processing/action-monitoring even in categorically non-diseased subjects. For a comprehensive review on further studies conducted on the subject, the interested reader is referred to a recent publication by Shiels and Hawk (2010).

*Other markers of executive function.* Looking beyond the process of response inhibition and action control, further executive dysfunctions have been considered as possible endophenotypes of ADHD (Doyle et al. 2005; Slaats-Willemse et al. 2007; Gau and Shang 2010). Since NIRS is relatively insensitive to movement artefacts, it allows for an assessment of paradigms involving overt verbal responses. The method is therefore well suited to study the executive function of word fluency in ADHD patients using standard verbal fluency tasks. We could previously show that NIRS allows for an assessment of cortical activation (as indicated by an increase in the concentration of oxygenated haemoglobin with a corresponding decrease in the concentration of deoxygenated haemoglobin) in lateral prefrontal areas during performance of a verbal fluency test (VFT) with a high test–retest reliability (Schecklmann et al. 2008a). Adult ADHD patients were found to show reduced activation during such a task in inferior areas of the lateral PFC, as compared to a healthy control sample. This neurophysiological finding reached statistical significance despite non-significant behavioural differences, i.e. neurophysiological abnormalities were detectable despite comparable overt performance. This finding indicates that subtle changes in brain function in ADHD patients are detectable with NIRS, even when overt neuropsychological performance can still be compensated, possibly via additional activation of regions outside the measurement area. This additional recruitment of supplementary brain areas might not be sufficient anymore to completely compensate for existing deficits when the task becomes more difficult (Schecklmann et al. 2008b). Similar prefrontal cortical deficits could also be observed during working memory (n-back) tasks (Ehlis et al. 2008): For this executive function, adult ADHD patients showed a reduced task-related increase in the concentration of oxygenated hemoglobin in NIRS channels located over the ventrolateral prefrontal cortex, especially in conditions containing high working memory load. Moreover, a tendency towards an increased number of omission errors was observed, confirming a working memory dysfunction in ADHD patients. Taken together, NIRS is well suited to assess and quantify altered activation of the lateral PFC during tasks of executive function in patients with ADHD. Moreover, this technique allows for an assessment of individual brain activation patterns, thereby again facilitating the approach of identifying subgroups of patients with specific functional deficits, possibly profiting from specific therapeutic interventions.

Another potential endophenotype that has been discussed to be independent of other executive dysfunctions concerns the symptom of "delay aversion" (Sonuga-Barke 2003), which is often operationalized via delay discounting paradigms and which has also been examined using NIRS. Delay discounting refers to the preference of small, immediate over later but

larger rewards. In delay discounting paradigms, subjects have to decide, for example, whether they would potentially like to gain €19.21 today or €21.13 in 4 weeks. In behavioural experiments, the "switch" from one strategy or preference to the other can be relatively exactly determined for every individual by systematically varying both the amount of money offered and the different delay periods. As a result, an individual impulsivity index *K* can be calculated, which reflects the individual preference or choice behaviour. For highly impulsive subjects, the subjective value of a particular amount of money decreases relatively steeply with relatively little delay. On the other hand, for subjects with low impulsivity on this measure, the subjective value of the money decreases more slowly with increasing time delay. Simon McClure and colleagues could show that – in healthy controls – delay discounting paradigms activate two different neuronal systems within the frontal cortex (McClure et al. 2004). While the dorsolateral prefrontal cortex (DLPFC) shows activation for different delay conditions (immediate reward, delay by 2 weeks, delay by 4 weeks), the orbitofrontal cortex (OFC) is activated specifically by immediate rewards. We replicated this finding using NIRS and a similar delay discounting paradigm in 49 healthy controls (unpublished data). We were furthermore able to show that his effect is mainly caused by a more pronounced activation (increase of oxygenated haemoglobin) specifically in the OFC when comparing immediate vs. delayed reward conditions in subjects showing an increased impulsivity as indexed by the impulsivity index *K*. Moreover, we found evidence that these findings were additionally modulated by individual prefrontal dopamine levels, as indicated by different genotypes of the COMT gene.

In summary, neurophysiological measures obtained by EEG, NIRS or TMS allow for an "objective" measurement of altered neural processes in ADHD, thereby complying with the general definition of a biomarker as cited in the introductory chapter. However, regarding the specific criteria we proposed for an ideal marker for ADHD – even though some of them are already met by the techniques and measures outlined above (e.g., good reliability and reproducibility of NIRS or ERP measurements, non-invasive examinations which are simple and relatively inexpensive to perform) – further studies are needed to determine the diagnostic sensitivity and specificity of the procedures. The described neurophysiological markers, therefore, must be viewed as promising candidates for biomarkers of ADHD, but further studies by independent groups are needed.

*Neuropsychological markers.* While neuropsychological measures are no biological markers stricto sensu, they nevertheless fulfil some of the criteria of classical biological markers such as the objective measurement of processes that have the potential to indicate the presence of a pathology, physiological alteration, deficit or psychological condition. Furthermore, neuropsychological measures are the most frequently considered behavioural correlates of classical biological markers. For example, neuropsychological measures are often used in genetic research of psychiatric disorders such as ADHD in order to find candidate endophenotypes. They are also useful in neurophysiological or functional neuroimaging studies.

Neuropsychological measures are designed to provide an objective, reliable and valid description of the association between behaviour and brain activity, i.e. neuropsychological assessment assumes that behaviour is directly affected by brain activity. Neuropsychological assessment comprises the measurement of cognitive, emotional and motor consequences of brain alterations. However, it focuses primarily on the assessment of cognitive dysfunctions. In neuropsychological assessments, various functional domains, such as attention, memory, executive functions, language skills and spatial abilities are examined. These domains have also been investigated in studies on the neuropsychology of children and adults diagnosed with ADHD.

*Attention.* Attention is a critical ability that is important in a variety of everyday life functions including perceptual, motor, emotional and cognitive functioning. Current models and theories of attention define attention as a multidimensional concept with several distinct functions (Cohen 1993). A prominent multidimensional model of attention differentiates between alertness, vigilance/sustained attention, selective attention, divided attention and shifting (van Zomeren and Brouwer 1994). While tonic alertness refers to a relatively stable level of attention which changes slowly according to diurnal physiological variations of the organism, phasic alertness is the ability to enhance the activation level following a stimulus of high priority. The ability to sustain attention enables a subject to direct attention to one or more sources of information over a relatively long and uninterrupted period of time. Vigilance is a special type of sustained attention and describes the ability to maintain attention over a prolonged period during which infrequent response-demanding events occur. Selective attention is defined as the ability to focus attention in the presence of distracting or competing stimuli. Divided attention is required when responding simultaneously to multiple tasks or demands. Shifting refers to the ability to flexibly shift the focus of attention in order to control which information from competing sources will be selectively

processed. By definition, an inappropriate level of attention is of particular importance in ADHD. Numerous well-controlled studies have therefore examined various aspects of attention in patients with ADHD. This research has revealed that both children and adults with ADHD may suffer from deficits of alertness (Cao et al. 2008), vigilance/shifting (Corkum and Siegel 1993; Losier et al. 1996; Weyandt et al. 1998; Manly et al. 2001; Tucha et al. 2009), selective attention (Seidman et al. 1998; Jonkman et al. 1999; Lovejoy et al. 1999; Tucha et al. 2008), divided attention (Jenkins et al. 1998; Tucha et al. 2006a; Lange et al. 2007) and shifting (Hollingsworth et al. 2001; Tucha et al. 2006b). However, a closer inspection of the scientific literature indicates that the entire spectrum of attention deficits appears not to be consistently affected in patients with ADHD. Furthermore, some of the attention functions (e.g., divided attention) have not yet been examined in detail. The most robust findings indicated that both children and adults with ADHD displayed difficulties in measures of selective attention and vigilance/sustained attention. Impairments of vigilance/sustained attention are the most replicated neuropsychological finding in ADHD.

*Executive functions.* Executive functions are an umbrella term encompassing various functions of higher cognitive functioning including planning, problem solving, concept formation, fluency, cognitive flexibility, working memory as well as goal-directed initiation, monitoring and inhibition of actions (Lezak et al. 2004). Neuropsychological assessment of children and adults with ADHD has demonstrated that the behavioural problems displayed by these patients are similar to the problems of patients with acquired lesions of the frontal lobes (Boucugnani and Jones 1989; Benson 1991). Therefore, the concept of executive dysfunctioning as the underlying deficit of the cognitive and behavioural disturbances associated with ADHD has received particular attention in recent years (Williams et al. 1999). The assumption of an executive function deficit in ADHD is supported by the findings of neuroimaging studies showing anomalies of prefrontal cortical regions and the basal ganglia in patients with ADHD (Hynd et al. 1993; Castellanos et al. 1996; Casey et al. 1997; Filipek et al. 1997; Vaidya et al. 1998). Furthermore, the findings of genetic research (Cook et al. 1995; LaHoste et al. 1996) and neurochemical studies (Barkley 2006) indicate alterations of dopaminergic, noradrenergic and fronto-striatal systems and are in accord with the assumption of an executive function deficit in ADHD. Psychometric assessments have demonstrated that both children and adults with ADHD display deficiencies of various functions which have been associated with the frontal lobes. These functions include working memory (Schweitzer et al. 2000; Westerberg et al. 2004; Klingberg et al. 2005), problem solving (Tucha et al. 2011), planning (Sergeant et al. 2002; Willcutt et al. 2005), concept formation (Lawrence et al. 2004; Antshel et al. 2010), impulsivity (Willcutt et al. 2005), verbal fluency (Tucha et al. 2011) and cognitive flexibility (Shue and Douglas 1992). Although neuropsychological studies have repeatedly demonstrated various deficits of executive functions in patients with ADHD, these research findings remain inconsistent. While some studies found clear differences in measures of executive functioning, others failed to find evidence of a reduced performance of patients with ADHD in these measures (Sergeant et al. 2002; Homack and Riccio 2004; van Mourik et al. 2005). The most consistent finding in the domain of executive functions is that patients with ADHD display impairments in working memory, i.e. the ability to simultaneously store and manipulate information. Working memory measures appear therefore to be the most sensitive indicator of executive dysfunctioning in ADHD.

*Memory.* Memory refers to the acquisition (encoding), storage, and retrieval of information. Several studies on memory have been performed in children and adults with ADHD. These studies have shown that, in comparison with healthy individuals, patients with ADHD performed worse in standardized tests of short-term memory (Barnett et al. 2005; Lorch et al. 2010) and long-term memory (Muir-Broaddus et al. 2002; Quinlan and Brown 2003). However, these findings were not found to be consistent (Horton 1996; Kovner et al. 1998). In addition, thorough analysis taking into account the amount of originally encoded information, showed no differences between healthy individuals and patients with ADHD (Kaplan et al. 1998). Therefore, reduced memory performances of patients with ADHD have been related to attention deficits and impaired executive functioning (Kaplan et al. 1998; Seidman et al. 1998; Pollak et al. 2008).

*Spatial abilities.* Spatial skills subsume a number of abilities such as spatial orientation, perception of spatial relations (e.g., between objects), spatial imagination, mental spatial manipulation (e.g., mental rotation of a map) and visuo-constructive abilities including handwriting. Both children and adults with ADHD have been found to be impaired in spatial abilities (Biederman et al. 1993; Aman et al. 1998; Schreiber et al. 1999; Sheppard et al. 1999; Tucha et al. 2001; Rolfe et al. 2008). However, other

studies found impairments regarding different aspects of spatial functioning or were unable to present any evidence of impaired spatial abilities. For example, while Biederman and colleagues (1993) observed a difference in visuo-constructive abilities between healthy adults and adults with ADHD, several studies failed to find such an impairment, although the same tests were applied (e.g., Biederman et al. 1994; Gansler et al. 1998; Kovner et al. 1998; Seidman et al. 1998). Patients' performance in spatial ability tasks, in particular in visuo-constructive tasks, has been shown to be adversely influenced by executive dysfunctioning (Schreiber et al. 1999; Sami et al. 2003).

*Language*. Various deficits of language and communication have been reported in patients with ADHD, in particular in children affected by the disorder. These deficits may concern the development of language skills, expressive language, language comprehension, communication and private speech (Hartsough and Lambert 1985; Berk and Landau 1993; Barkley 2006; Bruce et al. 2006; Wassenberg et al. 2010). However, these deficits are not very common (10–30% of patients, Barkley (2006)), and therefore not a prominent feature of ADHD.

*Olfactory function*. Alterations in olfactory function have consistently been reported in neuropsychiatric disorders with putative dopaminergic dysfunction such as Parkinson's disease or schizophrenia (Mesholam et al. 1998; Moberg et al. 2006). In Parkinson's disease, deficits in olfaction are regarded as early differential diagnostic measure and potential biomarker, especially when combined with further methods such as transcranial sonography or single photon emission computed tomography (SPECT) (Sommer et al. 2004; Berendse and Pondsen 2009). Olfaction is mediated by neurotransmitters such as dopamine delivering a potential link to the pathophysiology of ADHD (Halasz and Shepherd, 1983; Hsia et al. 1999). Convergence of the implicated neurotransmitters and involved central regions has additionally strengthened the argument for considering olfaction as possible biomarker for ADHD and neuropsychiatric disorders in general (Atanasova et al. 2008; Romanos et al. 2008).

Primary olfactory neurons in the olfactory epithelium are synaptically linked to secondary neurons in regions of high synaptic density (glomeruli) within the olfactory bulbs (OBs). At this early stage olfactory information from the epithelium is processed via contrast enhancement by inhibitory dopaminergic interneurons. These effects of dopamine in the OBs seem to be mediated via D2 receptors thus modifying odour detection and discrimination (Halasz and Shepherd 1983; Hsia et al. 1998; Cleland and Sethupathy 2006). Further on, olfactory information is processed in secondary regions including the piriform cortex, amygdala and anterior olfactory nucleus largely circumventing the thalamic relay. From here, projections to tertiary regions including the hypothalamus, hippocampus and orbitofrontal cortex facilitate higher olfactory functions such as odour memory or verbal identification of odours (Savic et al. 2000; Savic et al. 2002; Kareken et al. 2003; Albrecht and Wiesmann 2006; Brand 2006; Plailly et al. 2007).

Only few previous studies focused on olfaction in ADHD and they are also solely limited to the investigation of olfactory identification (Gansler et al. 1998; Murphy et al. 2001; Karsz et al. 2008). However, "identification" is a rather complex function implicating widespread fronto-temporal regions, while more basal olfactory domains such as sensitivity or discrimination are largely linked to olfactory bulb functions (Brand 2006). Furthermore, identification seems to be substantially influenced by individual intelligence and verbal capabilities (Murphy et al. 2001). Thus, the finding of diminished identification in ADHD (Karsz et al. 2008) could not be replicated when controlling for IQ (Murphy et al. 2001; Romanos et al. 2008; Schecklmann et al. 2010).

To overcome these shortcomings, we conducted studies in children and adults with ADHD, in which we carefully matched controls for age, gender and IQ (Romanos et al. 2008; Schecklmann et al. 2010). Interestingly, we found no alterations in discrimination and identification. However, we found increased olfactory sensitivity in those children with ADHD, who did not receive chronic pharmacological treatment with dopaminergic stimulant medication (Romanos et al. 2008). In contrast, those children with ADHD who were treated with methylphenidate did not differ from controls suggesting that dopaminergic medication normalizes increased olfactory sensitivity.

To our knowledge, this study constitutes the only finding of improved olfactory function in any neuropsychiatric disorder. Various research groups investigated olfaction in Parkinson's disease, dementia, schizophrenia, depression, obsessive compulsive disorder, autism and eating disorder (Gross-Isseroff et al. 1994; Mesholam et al. 1998, Barnett et al. 1999; Lombion-Pouthier et al. 2006; Moberg et al. 2006, Bennetto et al. 2007; Pollatos et al. 2007; Schreder et al. 2008). All alterations, if present at all, pointed to diminished olfactory performance. Thus, the finding of improved olfaction in children with ADHD may be specific to the disorder. Since in our primary investigation we identified a large effect size (Cohen's $d > 1.2$), high sensitivity (0.7) and specifity (0.85),

increased olfactory function may possibly be apt as biomarker in childhood ADHD according to the criteria proposed in the introduction of this manuscript (Romanos et al. 2008). Our consequent investigations of adult ADHD patients revealed no significant differences between patients and controls suggesting that developmental trajectories in ADHD may as well affect olfactory function. However, cortical oxygenation patterns during olfactory processing indicated alterations in the olfactory system that are still present in adult patients (Schecklmann et al. 2010).

We previously hypothesized that alterations in olfactory function may be explained by effects exerted on dopaminergic neurogenesis in the olfactory bulb (Romanos et al. 2008). Dopaminergic interneurons in the olfactory bulb are constantly renewed by stem cells migrating from the subventricular zone into the olfactory bulb (Whitman and Greer 2009). Since results of post-mortem studies pointed to increased numbers of dopaminergic interneurons in the olfactory bulbs of patients with Parkinson's disease, animal models were used to investigate the effects of striatal dopamine metabolism on dopaminergic neurogenesis (Winner et al. 2006). These investigations indicate that striatal dopaminergic cell loss results in decreased dopaminergic afferentiation in the subventricular zone, thus causing a (possibly compensatory) increase of neurogenesis in the olfactory bulb. Olfactory function may thus be impaired due to an increased dopaminergic inhibitory tone in the olfactory bulb (Huisman et al. 2004; Berendse and Ponsen 2006; Borta and Höglinger 2007). In analogy, we hypothesize that alterations in striatal dopaminergic function in ADHD may result in decreased neurogenesis thus resulting in reduced dopaminergic inhibition in the olfactory bulb. Current preliminary findings corroborate those interpretations, although further explanations such as alterations in gene expression and receptor adaptation processes may as well apply.

### *Putative neuroimaging biomarkers*

*Magnetic resonance imaging (MRI) findings.* Studies employing MRI have consistently shown a reduced volume of the frontal cortex and striatal structures in children with ADHD (Cherkasova and Hechtman 2009). Whereas caudate volume normalizes in adolescence, prefrontal volume reduction is still evident in adult ADHD patients (Castellanos et al. 2002; Schneider at al. 2006). Several studies have demonstrated that children with ADHD show a delay in structural and functional parameters of brain development (Shaw P et al. 2007, 2009; Giedd and Rapoport 2010), e.g., delayed development of cortical thickness especially in the frontal cortex, the cerebellum, and the basal ganglia as well as delayed development of frontal asymmetry (Lenroot et al. 2007; Mackie et al. 2007). Trajectories have been shown to be actually more predictive of functionality than comparison measures at one time point (Shaw et al. 2006; Giedd et al. 2008). In ADHD, remission was associated with convergence to the template of typical development, whereas persistence was accompanied by progressive divergence away from typical trajectories. Worse clinical outcome was found to be associated with a progressive volume decrease in the inferior posterior cerebellar lobes (Mackie et al. 2007).

Recent imaging approaches have revealed differences in the morphology of various brain regions by detailed surface analysis (Plessen et al. 2006; Qiu et al. 2009; Ivanov et al. 2010) refining conventional volume measurements. Qiu et al. (2009) showed that boys but not girls with ADHD (aged 8–13) showed reduced volume of the left caudate, putamen, and globus pallidus in comparison to healthy controls. Surface deformation maps furthermore showed significant shape differences in the left and right caudate and putamen of ADHD boys indicative of structural and functional alterations. Ivanov et al. (2010) showed that despite overall normal thalamic volume there were regional volume reduction especially in the pulvinar in children and adolescents with ADHD. The amount of regional volume decrease was actually associated with previous or on-going stimulant treatment. However, it was not clear whether stimulant medication actually changed pulvinar volume or whether stimulants were more likely prescribed to ADHD patients with large pulvinar volume. ADHD patients who received medication, showed smaller regional volumes in the posterior and anterior thalamic surface. Mediotemporal changes in morphology were assessed in one study, revealing increased anterior hippocampal volume in ADHD (Plessen et al. 2006). The overall amygdala volume was unaffected, but the volume of the basolateral nucleus was reduced. Increased volume of the anterior hippocampus was thought to be compensatory for prefrontal dysfunction. Disturbances in connectivity between amygdala and orbitofrontal cortex (OFC) were discussed to be associated with impaired decision making.

Task related activation is generally measured by fMRI. In ADHD patients, e.g., attentional functions, response inhibition, working and episodic memory, interference control, reward processing were associated in the vast majority of studies with a hypoactivation of prefrontal areas, the anterior cingulate, and the dorsal and ventral striatum. Reduced activity in parietal areas has been consistently reported in tasks tapping visuospatial attentional processing. However, some studies have found increased compensatory parietal activation accompanying frontal

hypofunction (Durston et al. 2006; Konrad et al. 2006; Krauel et al. 2007).

Imaging approaches in ADHD have increasingly focused on structural and functional measures of connectivity (Konrad and Eickhoff 2010) acknowledging that the integration of activation in distributed brain areas is crucial to efficient processing. Diffusion tensor imaging (DTI) is employed to visualize anatomical connections between brain areas. So far, there are only few studies that use DTI in ADHD to investigate long-range connections between brain areas. Compromised white matter integrity has been mostly shown in fronto-striatal and fronto-cerebellar circuits (Valera et al. 2007; Castellanos et al. 2009; Konrad and Eickhoff 2010), with fronto-striatal connectivity being observed both in ADHD parents and their children (Casey et al. 2007).

Functionally, compromised connectivity is for example evident in changed activation pattern with the default mode network (DMN). The DMN comprises the medial frontal cortex, medial, lateral and inferior parietal lobe, and the precuneus/posterior cingulate cortex (Castellanos et al. 2009). During healthy development, the DMN moves from a segregated ensemble of brain structures to an increasingly integrated functional network. Activation of the DMN is associated with daydreaming and mental processes unrelated to task processing and is downregulated/decreased in the presence of a cognitive task (Daselaar et al. 2004). In ADHD patients, some studies have suggested differences in DMN activation at rest. Moreover, patients with ADHD do not succeed to attenuate DMN activity to the same extent as healthy controls (Weissman et al. 2006; Sonuga-Barke and Castellanos 2007). There is evidence from fMRI and positron emission tomography (PET) data that methylphenidate supports downregulation of the DMN and leads to more focused processing in face of a task (Volkow et al. 2008; Peterson et al. 2009). However, it is unclear whether DMN findings are specific or unique to ADHD, since decreased attenuation of the DMN has been also observed in healthy subjects where it might be related to fatigue/sleepiness (Volkow et al. 2008).

During vigilance tasks, ADHD patients show reduced fronto-striato-parieto-cerebellar functional connectivity (Rubia et al. 2009a). MPH improved connectivity, and it is worth noting that the effect on connectivity was larger than on activation strength within respective single brain regions. Beside attentional networks, functional connectivity of brain regions associated with reward processing are also investigated (Rubia et al. 2009b).

*Transcranial sonography (TCS).* In recent years, TCS has been used as a non-invasive method to detect basal ganglia abnormalities with its most frequent use in ultrasound imaging of the substantia nigra (SN) (Walter et al. 2007; Berg et al. 2008). Post mortem studies have suggested that increased echogenicity of the SN could be related to enhanced iron content in the midbrain (Berg et al. 2002; Zecca et al. 2005). Significantly increased echogenicity of the SN is evident in about 90% of patients with Parkinson's disease (Becker et al. 1995; Berg et al. 2001a; Spiegel et al. 2006), but can also be found in approximately 10% of healthy individuals (Berg et al. 1999). Combined TCS and PET studies have revealed that increased SN echogenicity is associated with reduced dopamine synthesis in the caudate nucleus and putamen (Berg et al. 1999; Behnke et al. 2009). In adult psychiatric patients, larger echogenic size of the SN is associated with a higher number of extrapyramidal symptoms during neuroleptic treatment (Berg et al. 2001b). Increased SN echogenicity is considered a risk marker indicating an increased vulnerability of the nigrostriatal dopaminergic system to instances or pathologies that cause further dopamine depletion.

In ADHD, imaging studies using PET have provided evidence that dopamine synthesis is altered in presynaptic neurons of the midbrain nuclei and (Ernst et al. 1999; Jucaite et al. 2005; Forssberg et al. 2006; Ludolph et al. 2008) suggesting that the conspicuities in the substantia nigra could contribute to the pathogenesis of ADHD. In ADHD, PET studies have provided evidence that dopamine synthesis is already altered in presynaptic neurons of the midbrain nuclei (Ernst et al. 1999; Jucaite et al. 2005; Forssberg et al. 2006; Ludolph et al. 2008) suggesting that the SN could be involved in the pathogenesis of ADHD. Recently, two studies have employed TCS in children and adolescents between the age of 6 and 17 with ADHD (Krauel et al. 2010; Romanos et al. 2010). In both studies, ADHD patients showed an increase in echogenic size of the SN that was independent of age and gender. Hyperechogenicity, defined as echogenic size above the 90th percentile in the control group in one study (Krauel et al. 2010), was present in 48% of ADHD patients. In both studies, SN echogenic size was a significant predictor of ADHD diagnosis. In both samples about half of the ADHD patients had comorbid disorders. However, ADHD patients with SN hyperechogenicity actually had no relevant oppositional defiant disorder (ODD) or conduct disorder (CD) symptom load suggesting that the increase in SN echogenicity was indeed associated with ADHD (Krauel et al. 2010). Although specificity and sensitivity need to be further addressed, TCS is easily applied, well tolerated even in very small children and inexpensive. Recently, normative data in 121 healthy children and

adolescents have become available for ages between 0 and 17 that could allow a first assessment whether an individual measure can be considered as hyperechogenic or not (Hagenah et al. 2010). However, the usability of TCS as a biological marker is compromised by various aspects: so far, the measurement of echogenic size is subjective, even though interrater reliability is high in most studies. Although about 90% of patients with idiopathic Parkinsons's disease show increased echogenicity of the SN, symptom severity or progress of the disease as well as treatment is not reflected in SN echogenic size. So, SN hyperechogenicity could be rather viewed as a vulnerability than a biological marker that varies with symptom load. However, whether SN echogenic size relates to symptom load in ADHD is currently unknown.

### *Genetic and other neurobiological candidates*

*Genetic biomarkers.* Genome-wide association and pedigree linkage studies have considerably contributed to elucidate the molecular genetics of ADHD by identifying possible risk genes such as genes coding for cell adhesion molecules and regulators of synaptic plasticity (Lesch et al. 2008). Further neurotrophic-factor and CLOCK genes have been discussed in this context (Conner et al. 2008; Kissling et al. 2008). As in schizophrenia research, genes involved in dopmaminergic neurotransmission have extensively been researched (Durany et al. 1996; Kopeckova et al. 2008; Gainetdinov 2010), with the most promising candidate genes being DRD4, DRD5, DAT1 (Stergiakouli and Thapar 2010).

However, none of the risk genes identified so far exhibits a sufficiently robust effect in order to fulfil the definition criteria of a true ADHD biomarker. Nevertheless, genetic research remains an important field with the potential of elucidating important pathomechanisms underlying ADHD and revealing possible new treatment strategies. In addition, gene expression profiling may be a promising approach for defining valuable markers as the mRNA-expression levels of DRD4 gene in the whole blood of patients with ADHD and autism spectrum disorders, highly comorbid with ADHD, were lower (Taurines et al. 2011b).

*Putative biochemical markers.* From the 1970s, a considerable number of investigations have been undertaken to reveal the pathochemical mechanisms underlying ADHD, according to DSM-IV (American Psychiatric Association 1994) or child hyperkinetic syndrome (HKS), according to ICD-10 (World Health Organization 1992; for example see Oades et al. 2005; Uzbekov 2006).

It has been shown that changes in the central monoaminergic systems (dopamine, noradrenalin, serotonin) play an important role in the pathology of the condition. There are several approaches for the investigation of monoamine metabolism in ADHD/HKS children. One approach involves the collection and analysis of cerebrospinal fluid (CSF). However, analyzing CSF in the case of ADHD/HKS has no practical value because CSF can be taken for examination only in cases with absolute clinical indications such as bleeding, neoplasma and infections. Nevertheless, occasionally CSF monoamine metabolites have been measured in ADHD. Castellanos et al. (1994) performed a clinical study in boys, aged 6–12 years, to determine homovanillic acid (HVA), 3-methoxy-4-hydroxyphenylglycol (MHPG) and 5-hydroxyindoleacetic acid (5-HIAA) as a measure of the function of monoaminergic systems. It was demonstrated a positive correlation of 5-HIAA concentrations with aggression by using the Brown-Goodwin Lifetime History of Aggression Scale; HVA was positively correlated with several measures of hyperactivity (Castellanos et al. 1994).

Another approach consists in the examination of monoamines, their precursors and metabolites in blood plasma or serum as well as different monoaminergic receptors and enzymes in blood cells. Although plasma/blood biogenic amines are of importance for functions of the peripheral nervous system and metabolic functions (see for example Rubi and Maechlar 2010) their correlation to CNS dysregulations is far from being understood. Nevertheless, knowledge of plasma and urinary concentrations of biogenic amines, their metabolites, blood enzymes or even receptors might be a lead to explore pathobiochemical aspects of various neuropsychiatric disorders including ADHD. Platelet monoamine oxidase (MAO) is the type-B isoform (MAO-B). The MAO-B activity has been associated with aggressive, impulsive and hyperactive behaviour in a longitudinal investigation in 320 adolescents in which also plasma cholesterol was measured (Kiive et al. 2005). Correlations to aggressive and hyperactive behaviour, smoking, alcohol and drug use were studied at ages 15 and 18. Decreased MAO-B activity was associated to increased total and HDL cholesterol. Both these changes were correlated to scores of concentration difficulties. No correlations were seen with alcohol and drug use (Kiive et al. 2005). However, venipuncture can be very stressful for children and therefore the results of the examination can be distorted by adrenergic reactions.

A more appropriate approach, especially for children, therefore is the investigation of the urine. Regarding the pathogenetic mechanisms of ADHD, Campbell and Spencer (1988) contended that "it

remains to be shown where discrete biochemically-based subgroups show a different response to drugs: to psychostimulants, imipramine or neuroleptics". Accordingly, it was attempted to identify possible clinical-biochemical correlates of ADHD/HKS using a number of urinary biochemical indices that reflect catecholamine and serotonin neurotransmitter metabolism. Of particular interest is the detection of specific features of monoamine metabolism correlating with ADHD/HKS severity. This may be important both in the understanding of the pathogenetic mechanisms of ADHD/HKS and in deciding between different pharmacotherapeutic approaches depending on symptom severity (Uzbekov and Misionzhnik 2003; Uzbekov 2006).

According to the degree of motor hyperactivity and inattention, two groups of children with HKS were selected; a third group of children acted as a controls. Group 1 consisted of patients with a mild form of HKS. Group 2 included patients with a severe form of HKS. Both these groups consisted of patients with borderline mental insufficiency (Kovalev 1975). Group 3 (control) consisted of patients without any features of HKS (in all groups the patients were 7–11 years old children). Clinical delineation of different ADHD/HKS forms was carried out as described by Krasov (1988). Methods for the determination of monoamines and their metabolites in urine samples were described elsewhere (Uzbekov and Misionzhnik 2003). It was found that there are significant differences between severe and mild forms of HKS. In severe HKS, urine excretion of L-dopa (L-3,4-dihydroxyphenylalanin, the precursor of dopamine, 186.2%, $P<0.05$), dopamine (201.4%, $P<0.02$), noradrenalin (186.2%, $P<0.05$) and adrenalin (160.4%, $P<0.02$) was significantly higher when compared with the mild form of the syndrome (Uzbekov and Misionszhnik 2003; Uzbekov 2006).

Platelet MAO-B activity levels were also measured according to the method of Voloshina and Moskvitina (1985). It was found that MAO activity in children with severe HKS was almost twice the level shown in the mild form of the disease (187.5%, $P<0.02$). The degree of association between performance on a sustained attention task requiring visual discrimination and urinary excretion of catecholamine metabolites was examined in a cohort of 6–12-year-old children with ADHD (Llorente et al. 2006). All tests of variables of attention indices were significantly correlated with urinary excretion of noradrenalin metabolites at a low-to-moderate magnitude (0.37–0.50). Dopamine metabolites did not show any correlation (Llorente et al. 2006).

Medication-free hyperactive patients and controls had similar concentrations of plasma noradrenalin and blood pressures while recumbent and a similar increase in noradrenalin on standing but the patients had a longer pressor response on standing (Mikkelsen et al. 1981).

There are only few studies comparing urinary amine metabolites in ADHD and controls that show controversial findings. For example, Wender (1971) found that there are no differences in the urinary MHPG excretion between untreated hyperkinetic children and respective controls, while Shekim et al. (1978, 1982) reported a significant decrease of MHPG. Khan and Dekirmenjian (1981) found a significant increase in urinary MHPG creatinine ratio as well as MHPG concentration, while there were no changes in the concentrations of metanephrine, normetanephrine and creatinine. In the study of Wender (1971) in addition to 24-h urinary MHPG other parameters like noradrenalin, adrenaline, metanephrine, normetanephrine, vanillylmandelic acid (VMA), HVA and 5-HIAA also did not show any changes in nine children with "minimal brain dysfunction" versus controls.

By measuring noradrenaline, adrenaline and their metabolites in children with ADHD in a 2-h urine sample, they excreted, regardless of co-morbid anxiety, more normetanephrine as well as VMA. Children with ADHD alone had a lower noradrenaline/normetanephrine as well as adrenaline/metanephrine ratio than controls (Pliszka et al. 1994). Children with ADHD plus anxiety excreted more adrenaline than ADHD children without anxiety (Pliszka et al. 1994).

Rogeness et al. (1989) found that boys with "conduct disorder, socialized" had a higher 24-h urinary noradrenaline and VMA excretion. This was at variance to "conduct disorder, under-socialized" and subjects without conduct disorder. All groups of emotionally disturbed boys were divided into two groups based on their plasma dopamine-β-hydroxylase activities (DBH). Boys with low DBH showed significant correlations between ADHD symptoms and biochemical measures (Rogeness et al. 1989).

MHPG and normetanephrine have been measured in the 24-h urines of children with ADHD and controls. There was no difference in the excretion of both parameters between the groups (Baker et al. 1993).

Another clinical study showed a significant increase in the urinary concentrations of catecholamines in ADHD patients compared to healthy children (Dvorakova et al. 2007). Moreover, noradrenalin concentrations correlated positively with the degree of hyperactivity in ADHD. In addition, in ADHD adrenaline as well as noradrenaline concentrations correlated positively with plasma concentrations of oxidized glutathione (Dvorakova et al. 2007).

Twenty-four-hour urinary measures of biogenic amines activity (noradrenaline, dopamine, serotonin)

were correlated to "sustained attention". In all children, immediate response-feedback reduced omissions, and modestly improved perceptual sensitivity for ADHD. Continuous Perfomance Test (CPT) characterizing working memory related negatively to dopamine metabolism in control subjects and serotonin metabolism in the ADHD-group. But comparison between the metabolites in the ADHD-group suggest that increased serotonin and decreased noradrenalin with respect to dopamine metabolism, may detract from CPT performance in terms of perceptual sensitivity. The activity of biogenic amines was implicated in the promotion of perceptual processing in normal and ADHD-children, but serotonin may contribute to poor working memory performance in ADHD patients (Oades 2000).

Over the last 10–15 years, there has been an increasing interest in the potential involvement of serotonin in the pathogenetic mechanisms of ADHD (Askenazy et al. 2000; Rubia and Smith 2001; Oades et al. 2005). However the results of our studies have shown that there are no significant changes in 5-HIAA excretion in children with mild and severe HKS forms in comparison to controls (Uzbekov and Misionzhnik 2003). It has been shown (Lapin 2004; Vamos et al. 2009; Zadori et al. 2011; Mandi and Vecsei 2012) that the kynurenine pathway of the metabolism of tryptophan, the precursor molecule for both the serotonin and the kynurenine metabolic pathways, is the main one found in humans and in other mammals: about 90–95% of tryptophan molecules are metabolized via the latter pathway and only about 5–10% of these molecules are used for serotonin synthesis. We have examined the possible involvement of kynurenine pathway in the HKS pathogenetic mechanisms. For this purpose, the level of *N*-methylnicotinamide (N-MNA) excretion, one of the main metabolites of the kynurenine pathway of tryptophan metabolism, was measured in HKS patients (Uzbekov, 2006). We have found that drug-naive HKS children both with mild and severe forms exhibited a decreased excretion of N-MNA (35%, $P < 0.05$) (Uzbekov 2006). Thus, the kynurenine pathway could play a role in HKS pathogenesis.

With respect to the involvement of kynurenines in the pathophysiology of ADHD/HKS it is necessary to note that a lot of different kynurenine metabolites that are formed along the kynurenine pathway (Lapin 2004) possess neuroactive properties. For example, some endogenous kynurenine metabolites – L-kynurenine, 3-hydroxykynurenine, indolepyruvic and picolinic acid – diminish locomotor excitement in animals after acute ethanol intoxication (Lapin et al. 1991).

However, total and free plasma tryptophan were not different in hyperactive or learning disabled and normal siblings of these subjects. There was no significant correlation to hyperactivity, presence of food allergies, brain dysfunction or favourable response to methylphenidate. In addition, there was no correlation to blood serotonin (Ferguson et al. 1981).

It is evident, that the discrepancies reported for urinary concentrations of biogenic amines and their metabolites are not only due to the various methods used for their detection. Rather these discrepant values are due to environmental factors like nutrition (e.g., ice cream, nuts, chocolate, high fat diet, bananas, etc.), physical activity, 2-h urinary fractions versus 24-h concentrations, health condition (e.g. renal system failures, liver function) and small number of cases. Therefore, any conclusions drawn from such studies are only relevant, if rigorous methodological issues are being considered.

*Putative proteomic biomarkers.* Proteomics approaches have recently been applied to psychiatric research in an attempt to systematically analyse all expressed proteins in an hypotheses-generating process. In this context, the expression "proteome" refers to the pool of expressed proteins of the genome at a specific point in time. Proteomics projects are often complemented by transcriptomic or metabolomic projects dealing with the analysis of transcripts/mRNA (Hegde et al. 2003) and metabolites/small molecules acting in biochemical networks (Oldiges et al. 2007).

As complexity and diversity increases from the level of genes to their final products via alternative mRNA splicing and post-translational modifications, the expression of one single gene may result in multiple proteins that can vary in their structure and function. A main advantage of proteomics consists in the fact, that it provides the opportunity to assess modifications at the higher protein level, therefore possibly being more closely related to the underlying pathophysiological mechanisms of neuropsychiatric disorders, such as ADHD. Searching for proteomic biomarkers, the expression level, amino acid structure, post-translational modifications (e.g., phosphorylation, oxidation, glycosylation), interactions and functions of proteins can be determined in human post-mortem tissue and in animal models as well as ex vivo, comparing findings in peripheral tissue of patient and control groups. Proteomic techniques additionally facilitate an automated, technology-driven large-scale mode of analysis and the opportunity to carry out biomarker screening methods analysing the whole proteome in a certain tissue without the necessity of a priori hypotheses about candidate molecules.

In a proteomic biomarker project, the proteome is typically separated and fractionated by gel-based or gel-free (e.g., pre-coated chips, magnetic beads, centrifugal filters, isotope labelling) methods (Taurines et al. 2010a), after protein isolation from a certain

tissue has been conducted. Mostly, the final biomarker identification is based on mass spectrometric (MS) tools, such as matrix-assisted laser desorption/ionization time of flight-MS (MALDI-TOF-MS) and (tandem) electrospray ionization liquid chromatography-MS (ESI-LC-(MS/)MS; for more details see, e.g., Aebersold and Mann 2003).

To date, there are only limited and preliminary results available from proteomic approaches which can be used in the field of ADHD biomarker research. Searching for potential candidate molecules involved in ADHD pathophysiology, Maiya and co-workers (2007) used a proteomics approach and determined proteins that interact with the dopamine transporter (DAT) protein, a key target of methylphenidate. Twenty interacting proteins with diverse cellular functions were identified and could be classified as trafficking proteins, cytoskeletal proteins, ion channels and extracellular matrix-associated proteins. DAT was, for example, found to associate with the voltage-gated potassium channel Kv2.1 and synapsin Ib, a protein involved in the regulation of neurotransmitter release. In a further proteomic study, protein expression was determined in the frontal cortex, striatum and midbrain of the Wig rat, a possible animal model of ADHD (Hirano et al. 2008). Nineteen differentially expressed proteins were found, amongst them five involved in neurotransmitter release (dynamin1, *N*-ethylmaleimide sensitive fusion protein attachment protein (SNAP)-beta, syntaxin binding protein 1, calbindin 2, and CDCrel-1AI). The other up- or downregulated proteins played a role in energy metabolism, cellular transport, protein synthesis, cytoskeleton and cell rescue. Some of them had previously been reported in studies involving neurodegenerative diseases and psychiatric disorders, such as Alzheimer's disease, Parkinson's disease, and schizophrenia. Studies like these may help to identify potential candidates for further hypothesis-driven biomarker studies.

With respect to protein biomarkers in the peripheral tissue of ADHD patients, there is to date only one pilot study using a proteomic screening approach; in this study 16 children and adolescents with autistic spectrum disorder (ASD) and age matched controls were included (Taurines et al. 2010b). About half of the patient group, however, was diagnosed with co-morbid ADHD. After fractionation of the serum proteome via magnetic beads, MALDI-ToF-MS revealed three potential biomarker peaks that differentiated the ASD sample from the control group. Sub-grouping the ASD patients into children with and without comorbid ADHD (ASD/ADHD +, ASD/ADHD–), one peak at about 10.4 kDa distinguished the ASD/ADHD + patients from controls and ASD/ADHD– patients and therefore might constitute a potential marker for ADHD, but not for ASD. Although these results have certainly to be replicated and validated in sufficiently large samples, including ADHD patients without autistic features, in this pilot study an easily manageable, clinically applicable proteomics method was established to determine protein patterns representing potential biomarkers.

## Conclusions and future perspectives

To date, available data has not yet revealed one reliable biomarker to diagnose ADHD, but some promising biomarker candidates such as an increased olfactory sensitivity, and an increased SN echogenicity exist. However, further studies are required in order to validate these novel putative biomarkers.

Neurophysiological methods are very well suited to assess and identify characteristic neuronal alterations in ADHD patients for different putative endophenotypes of the disease, involving the frontal lobe functions of response inhibition and action control (ERPs), cortical inhibition in motor cortex (double-pulse TMS), verbal fluency and working memory (lateral PFC, NIRS) as well as delay aversion (OFC, NIRS). Therefore, different neuroimaging methods and regions of interest are optimally suited for the investigation of different endophenotypes and neuropsychological dysfunctions. Future research will show whether this approach will contribute to shed further light on the aetiopathogenesis of psychiatric disorders such as ADHD and if individual assessments will help to solve diagnostic and therapeutic problems. Such an approach of multimodal functional imaging aims at developing individually tailored therapeutic approaches based on individual brain physiology.

Deficits in all domains of cognitive functioning have been reported in children and adults with ADHD. However, these findings are inconsistent across studies. The most robust findings are impairments in vigilance/sustained attention and working memory. Impairments of these functions therefore appear to be the most reliable neuropsychological markers of ADHD. However, meta-analyses (Frazier et al. 2004; Martinussen et al. 2005; Willcutt et al. 2005) have shown that a considerable number of studies failed to find these differences between patients with ADHD and healthy individuals (vigilance/sustained attention: 23–39% of studies depending on the outcome measure; working memory: 25–46% of studies). Furthermore, effect sizes indicated only small to moderate differences between patients with ADHD and healthy participants (vigilance/sustained attention: $d = 0.51$–$0.64$; working memory: $d = 0.43$–$0.75$). Although there is convincing evidence of cognitive dysfunctioning in ADHD, there is no

clear, valid and reliable neuropsychological test profile sensitive or specific for ADHD. Individuals with ADHD have unique profiles of neuropsychological functioning, with some patients showing impairments in one function and other patients displaying deficits in another function. On group level, patients may differ from healthy participants with regard to cognitive functioning. However, there is no neuropsychological marker that is distinctive regarding the individual diagnosis of ADHD.

Imaging in ADHD research moved from the assessment of single structures to the assessment and acknowledgment of the importance of networks and the investigation of trajectories. Although imaging studies provided important findings for the conceptualization and understanding of ADHD to date it remains unresolved whether structural or functional measures are suitable biomarkers, given that a biomarker should be among other features accurate, reproducible, and feasible. Functional imaging is in general not applied before the age of eight, and hyperactivity often severely compromises data quality or feasibility of imaging protocols. So far there are very few studies that have focused on the reliability of functional imaging measures (Brown et al. 2011). Nevertheless recent innovative statistical procedures in longitudinal structural MRI studies have facilitated a high predictive value of $>90\%$ to determine which individual of a high-risk sample for psychosis will actually develop psychosis suggesting that these advances may be applicable to other neuropsychiatric disorders, as well (Koutsouleris et al. 2009).

Recent replicated findings suggest that SN echogenicity assessed by TCS may be a useful diagnostic marker for ADHD, even though sensitivity and specificity have not quite reached the here-proposed definition. Being reliable, reproducible, non-invasive, simple to perform, and inexpensive, it may still provide useful structural data within a set of biomarkers.

Although proteomic findings on potential biomarkers in ADHD to date are scarce and preliminary, this modern high-throughput technology provides the opportunity to analyse the complexity and dynamics of pathophysiological processes in ADHD at the protein level. This promising research tool helps to reveal the function of so far uncharacterized proteins, thus refining our knowledge of ADHD pathophysiology and possibly identifying diagnostic and prognostic biomarkers.

One factor hampering the development of a biological diagnostic marker in ADHD is sample heterogeneity arising from aetiological and phenotypic complexicity. In addition, there are age-dependent different co-morbidities (Taurines et al. 2011a). Therefore, it is very likely that one biomarker cannot exist for the diagnosis of ADHD. On the other hand, the use of biomarkers may reduce heterogeneity and identify homogeneous subtypes of ADHD.

Psychiatric nosology is largely based on clinical symptoms and diagnostic schemes and uses conventional and established diagnostic systems (DSM-IV, ICD-10) that do not reflect underlying neurobiological systems and pathomechanisms. While progress has been made in molecular biology of ADHD and neuropathology underlying the disorder, phenotypic characterization in ADHD has not been improved. Therefore, biomarkers were conceived of as markers more directly linked to the underlying pathology than is the psychiatric "diagnosis", and therefore, if validated, should constitute an objective measure for a psychiatric disease.

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## Statement of Interest

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