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Anatomical and functional brain imaging in adult attention-deficit/hyperactivity disorder (ADHD) – A neurological view

Abstract In this review, we discuss current structural and functional imaging data on ADHD in a neurological and neuroanatomical framework. At present, the literature on adult ADHD is somewhat sparse, and so results from imaging have to therefore be considered mainly from the childhood or adolescence perspective. Most work has considered the impairment of executive functions (motor execution, inhibition, working memory), and as such a number of attention networks and their anatomical correlates are discussed in this review (e. g. the cerebello-(thalamo-)-striato-cortical network seems to play a pivotal role in ADHD pathology from childhood to adulthood).

The core findings in ADHD imaging are alterations in the architecture and function of prefrontal cortex and cerebellum. The dorsal part of anterior cingulated cortex (dACC) is an important region for decision making, and executive control is impaired in adult ADHD. Finally, dysfunction of basal ganglia is a consistent finding in childhood and adulthood ADHD, reflecting dysregulation of fronto-striatal circuitry. The cerebellum, and its role in affect and cognition, is also persistently implicated in the pathology of ADHD.

Key words attention-deficit/hyperactivity disorder (ADHD) · magnetic resonance imaging (MRI) · review

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Introduction

ADHD affects adults with a prevalence of about 2–4 % (Kessler et al. 2005). In forensic populations, ADHD occurs with considerably higher prevalences (between 14 and 72 %; Rösler et al. 2004), revealing the negative impact of this disorder on psycho-social outcome (Biederman et al. 1995; Hechtmann et al. 1992). Unlike its clinical core features and psychopathology in childhood, adults with ADHD tend to be predominantly impaired by attention deficits and disorganization, whereas hyperactivity and impulsivity tend to move to the background (Biederman et al. 1996, 2000; Mannuzza et al. 1993). Emotional dysregulation, mood and anxiety disorders as well as substance abuse are commonly described features and comorbidities with high modulatory impact on the adult patients (Retz et al. 2004). As clinical patterns differ between ADHD children and adults, and given that more than half of the children with ADHD will not be clinically affected as adults, one could hypothesize that adult patients with ADHD represent a distinct subpopulation, with not only a stable pathophysiology, but also a different neurobiological or environmental background. Therefore, scientific investigations of neuroanatomical and neurophysiological substrates in adult ADHD need to be advanced. This need is enhanced as in ADHD, the pathophysiological and neurochemical mechanisms for the impairment of higher cortical functions are not well understood, and the inferences that may be derived from animal models of attention deficit, hyperactivity and impulsivity are limited (Sagvolden et al. 2005).

The principle question to be addressed is to verify whether adults with ADHD also display the extensively described impairments of brain networks of affected children. Thus, a key question in adult ADHD research is whether there is an impairment of fronto-striatal/fronto-subcortical networks. Such pathways represent the highest levels of executive and motor control, as well as inhibition of behaviour and voluntatory

decision making. Fronto-subcortical networks contain a large amount of noradrenergic, dopaminergic as well as serotonergic projections. Areas of particular interest are the prefrontal and dorsolateral prefrontal cortex. The anterior cingulated cortex (ACC) also seems to play a pivotal role in ADHD psychopathology, as it has a variety of widespread connections to forebrain and limbic structures. Besides its function as a conflict monitoring centre, the ACC has the role of integrating polymodal inputs from different brain regions in the control of executive and inhibitory functions (Carter et al. 2000). Striatal structures, such as putamen, globus pallidum and caudate nucleus, form a fronto-striatal network and are typically impaired in ADHD (Casey et al. 1997). Finally, the cerebellum also exerts strong influences on affective and cognitive function via thalamic connections, and increasing attention is being paid to these projections in ADHD pathology (Anderson et al. 2002; Schmahmann 2001).

Like many areas in neurology and psychiatry, research using imaging techniques has intensified in the field of ADHD in the past few years, and this review will focus on recent data from magnetic resonance imaging (MRI) studies, with emphasis on the networks mentioned above.

Anatomical findings

Gross neuroanatomical findings

Total cerebral volume reduction is well described in children and adolescents with ADHD (Filipek 1997; Castellanos 1996, 2001, 2002; Kates 2002; Mostofsky 2002; Hill 2003; Durston 2004). There is a marginal volume reduction, most marked in the right hemisphere. The right hemisphere is hypothesised to dominate in decision making, inhibitory control and selective attention (Pardo et al. 1990; Posner and Peterson 1990). Damage to the right hemisphere can lead to desynchronisation of brain activity and neglect of sensory stimuli in both hemispheric spaces (Heilman et al. 1980; Weintraub and Mesulam 1987).

Sowell et al. (2003) showed that brain alterations in children with ADHD were not general, but focused on brain regions with relevance to attention, executive control and linguistic performance. More specifically, these authors showed that brain surface reductions were mainly localized in inferior portions of the dorsal prefrontal cortex and anterior temporal cortex bilaterally, with increases in grey matter also seen in large portions of the posterior temporal and inferior parietal cortex bilaterally (Sowell et al. 2003). In adults, data confirming general volume reductions are not currently available. It would be of particular interest if the findings in childhood and adolescence were to be replicated in adults with ADHD as the prefrontal regions subserve attention and behavioural inhibition.

Frontal lobe

To date only one morphological analysis has been performed in adults with ADHD. Hesslinger et al. (2002) found diminished left orbito-frontal brain volumes in adult ADHD patients, although the number of ADHD patients included in this study warrants confirmatory investigation. However, these affected regions are associated with social behaviour and impulse control.

From the viewpoint of anatomical differences in children with ADHD, the dopamine and noradrenalin-rich prefrontal cortex appeared to have volume reductions. Several studies have confirmed volume reductions of prefrontal cortex, namely its dorsolateral part (DLPFC) (Hynd et al. 1990; Castellanos et al. 1996; Filipek et al. 1997; Mostofsky et al. 2002; Hill et al. 2003; Kates et al. 2002; Durston et al. 2004). DLPFC plays an important role in attention, working memory, planning and organisation of a task (Posner et al. 1990). Ventrolateral prefrontal cortex plays an important role for inhibitory control (Aron et al. 2003; Rubia et al. 1999). Orbitofrontal cortex regulates social behaviour and balance of inhibition and desinhibition as well as emotional attribution to decisions. Detailed structural imaging studies are to date limited to children and adolescents with ADHD, with studies generally describing slight frontal brain volume reductions.

Anterior cingulated cortex

In spite of the observation that the anterior cingulated cortex is impaired in functional studies with ADHD patients (Zametkin et al. 1990; Bush et al. 1999; Ernst et al. 2003), anatomical investigations are limited to one study reporting volume reductions in the right posterior cingulated gyrus in children (Overmeyer et al. 2001). The dorsal part of the anterior cingulated cortex (dACC) is crucial for executive functioning, inhibitory control monitoring, target detection, error processing as well as reward based learning. Hence the functional deficits shown in adults with ADHD (Bush et al. 1999) still remain to be verified by morphological investigations.

Temporal lobe

Temporal lobes have polymodal sensory integration functions in language comprehension as well as object identification ("what system"), emotional regulation and memory function. The right temporal convexity plays a strong role in visuospatial function as it has wider visual association areas. The left temporal convexity has a larger auditory association area which contributes to language comprehension (Devinsky and D'Esposito 2004). Sowell et al. (2003) demonstrated by anatomical brain surface analysis that children with ADHD had reduced anterior temporal lobe volumes bilaterally. Castellanos et al. (2002) have described tempo-

ral lobe volume reductions as a part of the general brain volume reduction in children and adolescents with ADHD compared to healthy controls. However, little is known about the interplay between cognition and affect in sensory processing, and its modulation by temporal lobes in ADHD.

Striatum

The basal ganglia comprise five principal nuclei, the caudate nucleus ("cognitive associative" striatum), putamen (sensorimotor striatum), nucleus accumbens (limbic striatum), globus pallidus and subthalamic nucleus. These are closely related to brainstem structures such as substantia nigra and pedunculopontine nucleus. The striatum comprises the putamen and the pallidum, and displays a high density of dopaminergic neurons. Its main function is procedural learning and automatisation of motor programs and behaviours and it serves to assemble complex response habits to strategically adapted environmental needs (Marsden 1982; Dubois et al. 1995). Lou et al. (1996) have shown that ADHD associated symptoms are associated with striatal damage.

Basal ganglia volume reductions have been shown in several studies, with most studies showing reductions in caudate volumes, uni- or bilaterally (Castellanos et al. 1994, 1996, 2001, 2002, 2003; Filipek et al. 1997; Hynd et al. 1993; Mataro et al. 1997). Schrimsher et al. (2002) could predict the cumulative severity ratings of inattentive behaviours by measuring caudate volume asymmetry from serial sagittal magnetic resonance images from childhood to adolescence. Unilateral volume reductions of the pallidum have also been shown in several studies in children with ADHD (Aylward et al. 1996; Castellanos et al. 1996, 2001, 2002; Overmeyer et al. 2001).

Until now no evidence for basal ganglia volume reduction in adult ADHD has been reported. A possible explanation is that differences between controls and ADHD almost disappear with increasing age before adulthood (Castellanos et al. 2002).

Corpus callosum

The corpus callosum connects homonymous regions of the cerebral hemispheres. Injury of callosal structures can lead to problems in holding sustained attention (Ellenberg et al. 1979), with associated deficits in learning and memory (Zaidel et al. 1990). The neuropsychological deficits after injury of the corpus callosum are often subtle or lacking.

Volume reduction of the corpus callosum is a common finding in studies with ADHD children and adolescents. Posterior regions of the corpus callosum are mostly affected (Baumgardner et al. 1996; Giedd et al. 1994; Hill et al. 2003; Hynd et al. 1991; Lyoo et al. 1996; Semrud-Clikeman et al. 1994). Data from adult ADHD is presently lacking.

Parietal lobe

Posner et al. (1990) have described a posterior attention system located in the parietal lobe, which seems to be mainly modulated by noradrenergic transmission in contrast to the predominantly dopaminergic modulation of the frontal attention system. The posterior parietal cortex plays an important role in orienting and selective attention networks (Fan et al. 2005). It disengages the attentional focus from the contralateral target (Rafal et al. 1995), and lesions of this region can lead to impaired attention (hyperattention to the ipsilateral, impaired attention to the contralateral side (Posner 1995; Ro et al. 2001)). Only a handful of studies have addressed the parietal lobe structure and functioning in ADHD. Castellanos et al. (2002) have shown that there is a reduction in posterior parietal volume, whereas conversely Sowell et al. (2003) have demonstrated an increase in cortical volume in children with ADHD. Given its importance in visuo-spatial orienting and as a region for polymodal sensory integration, the parietal brain seems to be generally underestimated when dealing with attention deficits in ADHD.

Occipital lobe

In line with the general findings of Castellanos' work (2002), Durston et al. (2004) showed a pronounced reduction of occipital brain volume in children with ADHD which was localised unilaterally to the left hemisphere. There is no data presently concerning occipital lobe anatomy in adult ADHD.

Cerebellum

The role of the cerebellum in cognitive and affective function has been described in 20 patients with cerebellar lesions with divergent reasons (Schmahmann and Sherman 1998). Aside from the well known motor coordination problems, patients with cerebellar lesions display impairment of executive functions, visuospatial cognition deficits as well as blunting of affect and disinhibition of behaviour. Cognitive cerebellar functions are located mainly in the posterior lobe, lobules VI and VII (neocerebellum), whereas executive, visuospatial, and memory functions of neocerebellum are impaired when the lesions are located in the hemispheres and dentate nucleus (Schmahmann and Sherman 1998). When lesions are in the lateral hemispheres of the posterior regions, the cerebellum is hypothesised to modulate actions via a dysmetria of thought, while the vermis is shown to be involved with affective disturbances (Schmahmann 2004).

The cerebellum projects via the thalamus to areas in the prefrontal cortex (Middleton and Strick 2001) and there are reciprocal projections from the prefrontal cortex to the cerebellum, thus forming a functional network

that influences rather than generates motor control, inhibitory and executive functions.

Several studies in ADHD in childhood and adolescence have shown structural cerebellar impairment (Berquin et al. 1998; Bussing et al. 2002; Castellanos et al. 1996, 2001, 2002; Durston et al. 2004; Hill et al. 2003; Mostofsky et al. 1998). Indeed, the most marked neuroanatomical anomaly in ADHD has been described in the cerebellum, with volume changes more marked than in the prefrontal cortex (Castellanos et al. 2002). In children, reductions in right cerebellar hemisphere and vermis volume have been reported (Durston et al. 2004; Castellanos 2001; Bussing et al. 2002; Berquin et al. 1998; Hill et al. 2003; Mostofsky 1998). These volume reductions correlated with attentional problems and global clinician ADHD ratings (Castellanos et al. 2002). At present there are no data on cerebellar volume in adult ADHD.

Functional studies

In defining functional deficits associated with ADHD, functional MRI (fMRI) techniques are of interest, as well as MRI relaxometry and ligand bound imaging techniques like SPECT or PET. All of those imaging techniques display strength and weakness in topographical and temporal resolution. There is a paucity of functional imaging studies in adult ADHD patients and thus the bulk of data that will be discussed here are from children and adolescents with ADHD.

Attention networks

In ADHD pathophysiology, research originates from either anatomically or from functionally defined cerebral networks, with particular interest centring on the impairment of attention networks. From a neurological viewpoint, attention networks can be roughly distinguished into three components (Posner and Petersen 1990; Coull et al. 1996; Fan et al. 2005). The first one contains mainly subcortically located arousal and alerting networks, which are constituted of the ascending reticular activating system, and project to the whole brainstem and thalamus and, through the striatum, up to the limbic system to form cortical projections. The main function of this component is the activation and synchronisation of the cerebral cortex during behaviour and motivation, and has affinity to salient stimuli and memorisation.

The mixed cortical-subcortical orienting networks detect novel stimuli (superior colliculi), filter out irrelevant stimuli (pulvinar) or disengage attention focus (posterior parietal cortex).

The third attentional network that is especially interesting in ADHD pathophysiology is the selective (or directed/cortical) attentional network. This involves frontal brain structures for generation of volitional saccades (frontal eye fields), induces motor intention (premotor cortex), is linked to working memory (dorsolateral prefrontal cortex) and is modulated by the anterior cingulate cortex (ACC/target detection, response selection and inhibition, conflict monitoring, motivation (Bush et al. 2000)). Such a network is also called the executive (conflict) network, and this has been shown to display high heritability (Fan et al. 2001). Within this network, the dorsal part of ACC (dACC) has strong connectivity to frontal brain structures with dense serotonergic and dopaminergic components. Regions of the parietal cortex also play an important role in mediating sensory functions. The posterior parietal cortex disengages the attentional focus to a target (Rafal and Robertson 1995) and the superior parietal lobule has the function of voluntary shifts of attention (Devinsky and D'Esposito 2004). A right hemisphere dominance could be found for orienting as well as selective attention (Pardo et al. 1990; Posner and Petersen 1990).

Konrad et al. (2005) have used event related fMRI to investigate brain activations related to these three particular aspects of attention, and have shown that relative to controls, children with ADHD recruited deviant brain regions for all three of the above mentioned attentional networks. ADHD children had less right-sided activation in the anterior cingulated gyrus during alerting, more fronto-striatal-insular activation during reorienting, and less fronto-striatal activation for executive control. Dysregulation of the blood oxygenation level dependent signals was described in the putamen during reorienting and executive control, suggesting altered strategies in children with ADHD.

Smith and colleagues (2006) showed with medication naïve children and adolescents with ADHD that functional abnormalities are task-specific and extend not only from frontostriatal but also to parietal and temporal cortices. Thus, recent data confirm the hypothesis that functional networks rather than specific brain regions are affected in ADHD.

Anterior cingulated cortex (dorsal part/dACC)

Zametkin et al. (1990) were the first to describe hypoactivity of dACC with positron emission tomography (PET) in adult ADHD patients. According to the hypothesis of impairment of selective attention, several studies in adult ADHD have shown hypofunctionality of the ACC (Durston et al. 2003; Tamm et al. 2004; Bush et al. 1999; Rubia et al. 1999; Zametkin et al. 1990). Following the executive attention hypothesis, the earliest fMRI study in adult ADHD was performed by Bush et al. (1999), using a specially designed counting Stroop paradigm, and demonstrated that the "cognitive division" of the dorsal part of the anterior cingulated cortex was not activated in adult ADHD patients during interference conditions. As a compensatory mechanism, ADHD patients activated an alternative frontostriatal network by using different regions of the lateral prefrontal cortex

(BA 45 instead of BA 9), insular cortex, as well as unilateral activation of the caudate, putamen, thalamus and pulvinar. These results may be interpreted as impairment of dACC function in ADHD subjects under conditions where interferences occur, while under conditions where subjects could focus on salient stimuli, there was no difference in dACC activation. This "normal attention but abnormal stimulus alerting and conflict effect" has also been demonstrated from a neuropsychological point by Oberlin et al. (2005). Only ADHD subjects with the combined type were impaired in their reactions to abrupt visual cues or those that contain conflicting spatial cues. These features were not shared by adult ADHD patients with the inattentive type. Hypoactivation of the dACC has been consistently described in children and adolescents with ADHD using continuous performance paradigms, with results being similar using fMRI of PET imaging techniques (Durston et al. 2003; Tamm et al. 2004; Bush et al. 1999; Rubia et al. 1999; Zametkin et al. 1990). These findings have led to the hypothesis that dACC plays a significant role in ADHD pathophysiology.

Aside from the role of dACC in selective attentional processing, response selection and inhibition and performance monitoring (Ernst et al. 2003), dACC is also thought to influence reward-based decision making (Bush et al. 2002). The larger the gain the higher the activity is especially in the pregenual ACC during the decision phase (Rogers et al. 2004). Ernst et al. (2004) found differences in motivational behaviours in ADHD, especially when the patients had to weigh long-term versus short-term rewards. The patients used more parts of the right anterior cingulated cortex than healthy controls.

Motor system

The execution of simple motor tasks reveals distinct cerebral activation pathways. Using a simple finger tapping task, Mostofsky et al. (2006) reported that children with ADHD had decreased contralateral motor cortex and right parietal cortex activation during right- and left-handed finger sequencing. These findings could be interpreted as anomalous development of cortical systems necessary for execution of patterned movements.

In a study with PET, Jucaite et al. (2005) showed that motor hyperactivity in adolescents with ADHD was correlated with lower binding potential values for dopamine transporter (DAT) in the midbrain. Thus, altered dopamine signalling might have a causal relationship to hyperactivity.

Frontal brain

Variable findings have been described for the ventrolateral and dorsolateral prefrontal cortex (VLPFC, DLPFC). These brain regions also monitor attention, planning, working memory and executive control, especially with regard to inhibitory control (Posner and Petterson 1990; Duncan and Owen 2002). Rubia et al. (1999) found hypoactivation in the right VLPFC and left caudatus of adolescents with ADHD, whilst Durston et al. (2003) reported different activation of frontostriatal regions. Children with ADHD displayed more diffuse network activations including more posterior and dorsolateral prefrontal regions. Rubia et al. (2005) reported that medication naïve adolescent patients with ADHD showed significantly reduced brain activation in the right inferior prefrontal cortex during successful motor response inhibition and in the precuneus and posterior cingulate gyrus during inhibition failure. These deficits correlated with behavioural scores of ADHD and persisted when corrected for medication history and performance discrepancies. Conversely, Ernst et al. (2003) showed using PET that adult ADHD patients, as well as healthy controls, activated the ventral and dorsolateral prefrontal cortex including insula during a decision making task. However, the activation of the dACC and hippocampus, subserving emotional and memory processes, was less extended in the ADHD group, who instead recruited the caudal part of the right anterior cingulated cortex. These results were interpreted as a basis for problems of motivated behaviour in ADHD.

Role of the cerebellum in ADHD

The cerebellum is increasingly of interest in ADHD research due to its involvement in cognitive, emotional processing and behavioural control (Schmahmann and Sherman 1998). In primates, the cerebellum has intense projections to the prefrontal cortex and therefore disturbances of these projections might lead to such cognitive and emotional problems as are associated with ADHD (Middleton and Strick 2001). Several studies have shown that the cerebellum has modulatory effects on forebrain dopamine outflow (Snider et al. 1982; Tellerman et al. 1979; Glowinski et al. 1978; Nieoullon et al. 1979). Anderson et al. (2002) have reported a role of the cerebellum in ADHD pathophysiology, with relaxometry of the vermis suggesting an abnormality that could be influenced by methylphenidate in children and adolescents. The effects of methylphenidate in the cerebellar vermis were dependent on pre-treatment activity level. With fMRI, Schulz et al. (2004) described a higher activity of the cerebellum in adolescents with ADHD, whilst in contrast, Valera et al. (2005) found significantly decreased activity in the cerebellum and also occipital lobe of adult ADHD, even though working memory performance did not differ significantly between ADHD and controls. Kim et al. (2002) examined ADHD children with PET and found decreased bilateral cerebellar blood flow in ADHD compared to controls. Volkow et al. (1997, 1998) reported that methylphenidate could increase metabolic activity of the cerebellum in normal adults, dependent on dopamine receptor activity.

A preliminary study (Ashtari et al. 2005) has hinted for the hypothesis at a connectivity between cerebellum,

forebrain and ADHD symptomatology. In children with ADHD, the diffusion tensor imaging technique (DTI) revealed that white matter abnormalities were especially prominent in the right premotor, right striatal, right cerebral peduncule, left cerebellar peduncule, left cerebellum and left parieto-occipital areas. These results add to the evidence for cortico-ponto-cerebellar circuit deficits in ADHD, with further studies needed to analyse these aspects in adult ADHD.

Parietal cortex

Parietal cortex belongs to an attentional system that includes fronto-parietal network structures (Mesulam 1990; Posner et al. 1990). For example, orienting networks include the superior parietal lobe, as well as the temporal parietal junction and frontal eye field (Corbetta and Shulman 2002). Together with frontal brain areas, alerting attentional network activates the parietal and thalamic areas that are potentially susceptible to the actions of norepinephrine (Coull et al. 1999, 2000, 2001).

Superior parietal and middle frontal areas are involved in visuospatial processing (Booth et al. 2000). Silk et al. (2005) have shown that, with a mental rotational task, fMRI reveals that ADHD children with combined subtype have lower activation of the action-attentional system including the superior parietal cortex as well as middle frontal areas. Patients had also increased activation of the posterior midline attentional system. This indicates that ADHD patients might also have parietal dysfunction as well as dysfunction of the widespread frontal and striatal system. As is the case with many of the networks discussed so far, these findings in children have yet to be extended to adults with ADHD. A first step towards this direction has recently been performed by Tamm and colleagues (2006) who showed that adolescents with ADHD had significant impairments in their ability to direct and allocate attentional resources. This was associated with bilateral aberrations in the parietal attentional system.

ADHD and comorbid disorders

Studies dealing with patients who have comorbid disorders or brain lesions are of special interest because they can verify the hypothesis of fronto-striatal(-cerebellar) dysfunction, its specificity and compensatory mechanisms in ADHD.

Lesions of orbital or mesial frontal brain can lead to symptomatic ADHD. Children with focal brain lesions in the attention executive network have marginal ADHD-like symptomatology whereas lesions within the above mentioned forebrain regions show a significant symptomatology associated with acquired ADHD (Max et al. 2005).

Adler et al. (2005) have used a simple attention task in adolescents with bipolar disorder and shown that comorbidity with ADHD is associated with less activation of the ventrolateral prefrontal cortex, anterior cingulate cortex and higher activation in posterior parietal cortex as well as middle temporal gyrus. Thus, comorbidity with ADHD has the consequence that prefrontal regions are underrecruited while portions of the posterior parietal and temporal cortex are preferentially recruited as an alternative pathway. Facial recognition is also impaired in ADHD in a similar way when compared with patients with schizophrenia (Marsh et al. 2006). Both groups display reduced activity in the medial prefrontal and amygdala brain regions required to process emotional faces.

Bussing et al. (2002) have suggested that no differences in cerebellar morphology could be found between ADHD children and those with comorbid conduct disorder. Also, in this study no differences were reported in volume measurements of frontostriatal structures. On the other hand, electrophysiological studies with event related potentials showed abnormalities in prefrontal lobe activation in teenagers with conduct disorder (Bauer et al. 2003).

Tourette's syndrome (TS) is frequently comorbid with ADHD (Comings et al. 1985; Spencer et al. 1995). In TS, basal ganglia volume reduction and loss of asymmetry of the globus pallidus (usually left > right side) is described (Peterson et al. 1993; Singer 1997), although these findings are controversial (Spencer et al. 1995). Some studies could not differentiate between TS and comorbid ADHD in terms of brain structure alterations; some could find that in addition to smaller caudate nucleus volumes, patients with comorbid ADHD tended to have larger volumes across all cortical portions of those circuits to dorsal prefrontal and parieto-occipital regions (Peterson 2001).

Autism may occur with ADHD. Impairments of attention are among the most consistently reported cognitive deficits in autism (Allen et al. 2001). In anatomical studies, as opposed to ADHD, patients with autism display larger total brain and white matter volumes in caudate, globus pallidum, most cortical brain regions and in the cerebellum (Piven et al. 1996). Reduced fMRI activation was found primarily in the amygdala of autistic patients during social tasks (Baron-Cohen et al. 1999), but autistic spectrum disorders also display a dysfunctional cerebello-frontal spatial attention system (Allen et al. 2004; Haist et al. 2005) similar to ADHD. Further studies are needed to specify attention deficits in autism with comorbid ADHD.

Summary

Despite of the amount of imaging data in children and adolescents with ADHD, the literature on adults is still sparse. Investigations in this field have only started relatively recently. Imaging data are often confounded by small numbers of patients and sometimes contradictory results. However, recent findings have shown similarities

in adult ADHD and ADHD in children, such as the impairment of cerebello-striato-frontal networks. Consistent findings are in dysfunction of striatal brain structures as well as the anterior cingulated cortex. Prefrontal cortical structures also seem to play a pivotal role in ADHD psychopathology, whereas these findings were not specific to ADHD. As in children, the cerebellum is also dysfunctional in adults with ADHD. Moreover, there is increasing evidence that also parts of the posterior attention networks are less active in both ADHD of childhood and adulthood. In a task-specific manner functional abnormalities extend from frontostriatal to parietal and also temporal cortices. Attention orienting is less affected than salient stimulus or conflict alerting. Also, several "vertical" levels of attention networks – beginning from the arousal to the orienting up to the selective attention network – are affected in ADHD.

Data on ADHD patients with comorbid psychiatric disorders are presently inconsistent and can contribute to our understanding of ADHD pathophysiology only in a limited manner. Nevertheless, most investigated psychiatric disorders display comorbid ADHD symptomatology when fronto-striatal brain regions are dysfunctional.

Aside from the lack of structural and functional imaging data in adult ADHD, there is also a paucity of evidence concerning whether persisting ADHD represents a subgroup of childhood ADHD with possibly different genetic or environmental backgrounds. In future studies, brain imaging should focus more on ADHD subtypes or classification by endophenotyping the patients or responders and non-responders to stimulant drugs, respectively.

Given that ADHD symptomatology undergoes changes with adulthood in terms of decline of hyperactivity and impulsivity, while disorganization and emotional dysregulation come to the fore, a more focussed approach to understanding emotional dysregulation in adult ADHD should reveal insights into the pathophysiology of this condition. It is important to bear in mind that comparison of results between young and adults with ADHD could be confounded by maturational or developmental effects with increasing age. Additional longitudinal imaging studies are therefore necessary to follow-up these aspects.

Finally, in animal models emerging evidence suggests that methylphenidate alters the dopaminergic system with long-term effects beyond the termination of treatment (Grund et al. 2006). On the other hand, long-term treatment did not show functional differences after termination of medication compared to treatment-naïve ADHD patients (Pliszka et al. 2006). Whether stimulant medication has long-term influence on brain morphology or neuroregenerative effects is not clarified. Thus, controversies between structural and functional results have still to be resolved.

Nevertheless, until now structural and functional brain imaging techniques can help in understanding ADHD pathophysiology on the level of statistic effects. They have not yet reached sufficient specificity and sensitivity to be clinically implemented as a diagnostic tool on the individual patient's level. This might be due to technical reasons in view of limited spatial and temporal resolution as well as lack of specificity of ADHD activation patterns regarding the imaging data especially in adults.

The better understanding of pathomechanisms leading to ADHD concomiting with the technical progress in brain imaging techniques will in the future lead to data qualities giving possibly also answers on the single patient's level.

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