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UNDERSTANDING THE ESSENTIALS OF THE **ADHD** NEUROBIOLOGY

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ADHD is a common neurodevelopmental disorder that typically has onset in childhood, most often between age 6 and 12. Despite thousands of research papers on ADHD are being published each year, our understanding of the neurobiology of ADHD is still limited. It is clear, however, that ADHD is characterized by substantial heterogeneity across many, if not all, levels of analysis. This chapter will review this heterogeneity with respect to the neurobiological mechanisms that underping ADHD, starting with biochemistry and metabolomics, and then continuing with cognition, up to functional and structural alterations of the brain.

NEUROCHEMISTRY AND METABOLOMICS

Knowledge about the neurochemistry of ADHD has thus far largely relied on serendipity and coincidental findings, e.g. from medication studies and work in animal models. Additional evidence for the involvement of those basic pathways comes from genetics as well as first metabolite biomarker studies. For example, a comprehensive meta-analysis of potential biomarkers found several measures, specifically norepinephrine (NE), monoamine oxidase (MAO), 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), zink, ferritin, and cortisol, to be significantly

altered in blood and urine of drug-naïve/drug-free patients with ADHD compared to healthy individuals.[1] Some of the metabolites were also associated with symptom severity of ADHD and/or the response to ADHD medication.

The serendipitous finding that methylphenidate (MPH) treats ADHD symptoms started research into the role of dopaminergic neurotransmission in the pathophysiology of ADHD. This research was soon extended to include norepinephric neurotransmission pathways, since the re-uptake inhibitory action of MPH and other psychostimulants is not selective to the dopamine transporter receptor, but also affects the norepinephrine transporter function. Later, also serotonergic neurotransmission was found to be involved. Thereafter, we review the involvement of other neurotransmission systems in ADHD.

DOPAMINE

The neurotransmitter dopamine is involved in regulation of motor activity and limbic functions, but also plays a role in attention and cognition, especially executive functioning[2] and reward processing.[3] It is a key-contributor to behavioural adaptation and to anticipatory processes necessary for preparing voluntary action following intention.[4] In addition to the fact that the function of dopamine fits well with the signs and symptoms observed in people with the disorder, dopamine circuit dysfunction has been implicated in ADHD based on different experimental evidence.[5] Dopamine-producing cells are localized in the midbrain substantia nigra pars compacta and the ventral tegmental area. From there, three projection pathways can be distinguished: the nigrostriatal pathway, which originates from the substantia nigra and projects to the dorsal striatum (caudate nucleus and putamen); the mesolimbic pathway, which projects from ventral tegmentum to limbic system structures, in particular the ventral striatum (nucleus accumbens), hippocampus, and amygdala; the mesocortical pathway also originating in the ventral tegmental area, which projects to the cerebral cortex, the medial prefrontal areas in particular.[6]

As indicated above, the dopamine transporter – which is the most important molecule in the regulation of dopamine signalling in most areas of the brain – is the main target of stimulants like MPH and also dexamphetamine, the most frequently used prescription drugs for the treatment of ADHD symptoms. These drugs block the dopamine transporter and lead to an increase in dopamine concentration, particularly in the parts of the basal ganglia that are highest in the expression of the transporter, the striatum.[7] This effect is due to the blockade of the transporter molecule in the case of MPH; and due to both transporter blockade and stimulation of dopamine release/block of breakdown through monoamine oxidase in the case of dexamphetamine.[8] The dopamine transporter protein (DAT) and its gene (*DAT1*, official name *SLC6A3*) have thus received most attention in

research of mechanisms underlying ADHD. In animal models, knock-out of the *Dat1* gene produces elevated dopaminergic tone and hyperactivity in the mouse;[9] the latter is also observed upon knock-down of the dopamine transporter in the fruit fly *Drosophila melanogaster.*[10] Implicating the dopaminergic system in ADHD-like behaviour is also the neonatal 6-hydroxy-dopamine lesioned rat model.[11] Neuroimaging studies of the dopamine transporter in humans using positron emission (PET) suggest that more dopamine transporter activity is present in people with ADHD than in healthy individuals,[12] and evidence for depressed dopamine signalling has also been concluded from alterations in dopamine receptors seen in PET. Evidence for disturbances in dopamine signalling have also been suggested by findings of genetic studies. Here, it has again been the dopamine transporter, and in particular a genetic polymorphism in the 3'-regulatory region of the *DAT1* gene, that has been the subject of most studies. Meta-analyses have shown significant associations of this genetic variation in the gene, albeit different versions of the gene were found associated with the disorder in children and adults. Furthermore, an analysis of genetic variants in a larger group of genes involved in ADHD suggested association of this set of genes with the severity of symptoms in children with the disorder.[13]

NOREPINEPHRINE

Norepinephrine signalling is intimately linked to the dopamine system by the fact that norepinephrine is a downstream product of the metabolism of dopamine. Norepinephric neurotransmission regulates important higher cognitive functions such as working memory and inhibitory control, primarily through its projections originating in the locus coeruleus and innervating multiple areas of the cortex, the thalamus, and cerebellum.[5] Especially the innervation of the prefrontal cortex (PFC) by norepinephrine pathways is thought to be important for understanding ADHD. Norepinephrine and dopamine signalling are intimately linked in PFC, i.e. they influence each other in optimizing PFC performance in cognitive tasks.[14] Knowledge about the role of norepinephrine in ADHD mainly comes from the fact that MPH and dexamphetamine inhibit the norepinephrine transporter (NET) in addition to the DAT.[14] Moreover, atomoxetine, a selective NET inhibitor, is effective in the treatment of the cardinal symptoms of ADHD and some of its comorbidities, as are several other prescription drugs with noradrenergic properties, like guanfacine and clonidine[5] While this is clear evidence that altering norepinephrine signalling can ameliorate the symptoms of ADHD, less evidence is available to link it to ADHD neurobiology. This may primarily be due to the concentration of research on the dopaminergic pathways, and the large overlap between dopamine and norepinephrine synthesis and function. No animal models for ADHD based on altering genes involved directly in norepinephrine signalling

have yet been described, but many models actually implicate both dopamine and norepinephrine neurotransmission circuits.[15] PET of the NET has been inconclusive, thus far.[16] Genetic studies of a number of norepinephrine receptors and the NET have not produced convincing evidence for the involvement of these genes either.[17]

SEROTONIN

Serotonin is involved in regulating mood and emotion, and also plays an important role in inhibition, one of the executive cognitive deficits observed in ADHD.[18] The neurons of the raphe nuclei in the midline of the brainstem are the main source of serotonin in the brain. Axons of neurons in the higher raphe nuclei spread out to the entire brain, with strong projections e.g. into the prefrontal cortex, while axons originating in the lower raphe nuclei project to cerebellum and spinal cord. Serotonin signalling is known to affect the regulation of other neurotransmitters, including that of dopamine, which may occur through several mechanisms. Neurotransmission through serotonin was first implicated in ADHD based on paradoxical calming effects of methylphenidate observed in a mouse model lacking the dopamine transporter (DAT). The drug was shown to act by blocking the serotonin transporter in the absence of the DAT in this model. Also, other animal models with altered serotonin signalling show ADHD-like symptoms, inattention as well as hyperactivity.[18] In humans, studies have reported reduced levels of peripheral serotonin in patients with ADHD; but other studies did not find such effects.[18] The exact role of serotonin on ADHD still has to be defined in humans, however. Serotonin neurotransmission may modulate the severity of ADHD symptoms rather than being related to ADHD onset.[13] Other theories suggest that it may be the comorbidity, especially with conduct disorder, obsessive compulsive disorder, aggression and mood disorders (major depression and/or anxiety), rather than the core symptoms of ADHD, which is influenced by serotonin.[18] Genetic studies of the contribution of the serotonergic system to ADHD have not been fully convincing, where it comes to the involvement of serotonin in ADHD. However, the serotonin receptor gene HTR1B and the gene encoding the serotonin transporter (SLC6A4, 5-HTT, SERT) have been implicated in the disorder in meta-analysis.[19] Gene by environment interactions may explain some of the observed inconsistency across studies, as the effect of stress on ADHD symptoms seems to be influenced by genetic variation in the serotonin transporter gene.[20] A recent analysis of a gene-set related to serotonergic neurotransmission suggests that variation in serotonergic genes may be associated with disease severity.[13] Tryptophan depletion, which causes reduction in brain 5-HT synthesis, was found associated with increase of aggression, inattention, and impulsivity.[18] A retrospective pilot study on the administration of precursors of serotonin and dopamine led to promising results

in 85 children and adolescents with ADHD. However, in spite of this supportive evidence for a serotonergic involvement in ADHD, findings from clinical trials with serotonin-noradrenaline reuptake inhibitors (SNRIs) such as venlaflaxine and duloxetine in adults with ADHD are rather mixed (for review, see Banerjee and Nandagopal, 2015).[18]

GLUTAMATE

Glutamate is the most abundant excitatory neurotransmitter in the human central nervous system and is involved in many neuronal functions including synaptic transmission, neuronal migration, excitability, plasticity, and long-term potentiation.[21] The fronto-striatal circuits implicated in impulsivity and compulsivity are notable for their relatively rich glutamatergic receptor density. Glutamatergic projections from the various frontal subregions (orbitofrontal, infralimbic cortex, and prelimbic cortex) to the striatum (and vice versa) play a key role in the regulation of various compulsive behaviours. The signalling effect of glutamate is not dependent on the chemical nature of glutamate, but on how cells are programmed to respond when exposed to it. Because glutamate receptor proteins are expressed on the surface of the cells in such a way that they can only be activated from the outside, glutamate exerts its neurotransmitter function from the extracellular fluid. Consequently, control of receptor activation is achieved by releasing glutamate to the extracellular fluid and then removing glutamate from it. Because there are no enzymes extracellularly that can degrade glutamate, low extracellular concentrations require cellular uptake. Several families of glutamate receptor proteins have been identified and classified as NMDA receptors, AMPA receptors, kainate receptors, and metabotropic receptors.[22] Most, if not all, cells in the nervous system express at least one type of glutamate receptor.

Several candidate genes within the glutamatergic system have been associated with ADHD. For instance, associations have been found for variation in the *GRIN2B* gene with both inattention and hyperactivity symptoms in ADHD. A genome-wide study investigating rare variants found overrepresentation of variants belonging to the metabotropic glutamate receptor genes in several ADHD cohorts.[23] An analysis of a glutamate gene-set showed significant association to severity of hyperactivity/impulsivity of patients with ADHD.[24] Proton-magnetospectroscopy (MRS) studies suggest a possible increase in Glx (a combination of glutamate, glutamine, and GABA) in the striatum across ADHD, obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD), and further, an increased Glx signal in the anterior cingulate cortex in children with ADHD and ASD but a lower Glx signal in adults with ADHD and ASD. This suggests neurodevelopmental changes in fronto-striatal glutamatergic circuits across the lifespan.[25] Glutamatergic agents such as memantine, an antagonist of he NMDA receptor, are of po-

tential value in the treatment of impulsivity in children and adolescents, including ADHD, but large-scale positive trials have not been published yet.

HISTAMINE

Histamine is one of the key neurotransmitters regulating arousal and attention. The cell bodies of histamine neurons are found in the posterior hypothalamus, in the tuberomammillary nuclei. From here, these neurons project throughout the brain, including to the cortex, through the medial forebrain bundle. Histamine neurons increase wakefulness and prevent sleep.[26] In addition, this neurotransmitter is an important agent in (neuro)immune reactions. Interest in the role of histamine in ADHD stems from the observations that allergies have an increased incidence in people with ADHD. Indeed, a recent meta-analysis shows that children with ADHD are more likely to develop asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis than healthy individuals.[27] Conversely, children with allergies appear to have higher ADHD symptom ratings than non-affected children. The histamine H3 receptor subtype is mainly distributed in the central nervous system and functions as both a presynaptic autoreceptor that reduces histamine release and a heteroreceptor that regulates release of other neurotransmitters. Histamine H3 receptor antagonists and inverse agonists increase release of brain histamine and other neurotransmitters. The H3 receptor antagonists have been shown to promote arousal in various species, without the psychomotor activation seen with stimulants.[28] Potent histamine H3 receptor antagonists are currently being developed and tested for the treatment of ADHD.[29]

NICOTINIC ACETYLCHOLINERGIC SYSTEM

Nicotinic acetylcholine receptors are receptor proteins that respond to the neurotransmitter acetylcholine. Nicotinic receptors also respond to drugs, including the nicotinic receptor agonist nicotine. Nicotine use has been associated with improvement in cognition, attention in particular, in different animal species, healthy human volunteers, and patients with ADHD.[30] In addition to the knowledge about the influence of attention, the nicotinic acetylcholine neurotransmission system is also implicated in ADHD through genetic findings: a large study of copy number variants found duplications of the gene encoding the α7-nicotinic acetylcholine receptor (CHRNA7), located in the mutation-prone region on chromosome 15q13.3, to contribute to the risk for the disorder.[31] The nicotinic acetylcholine system may be one of the new targets for the development of alternative drugs for ADHD. Nicotine appears to exert its beneficial effect selectively on behavioural inhibition and delay aversion tasks, which are known to have good discriminant

validity in distinguishing subjects with ADHD from controls. Stimulation of neuronal nicotinic acetylcholine receptors by nicotine may be mediated directly via changes of cholinergic neurotransmission and/or by modulating activity of other neurotransmitters including dopamine, which in turn has a recognized role in the neurobiology of ADHD (see section on dopamine above). Trials of nicotinic drugs demonstrated beneficial effects in adults with ADHD, with evidence for also positive effects on cognitive and emotional domains, although there are no approved medications for ADHD that target nicotinic acetylcholine receptor function.[32]

COGNITION

For many years, cognitive research in ADHD has been dominated by theories about primary key cognitive impairment that would be causal to the development of the disorders (see Box 2.1). This was followed by theories about dual- and triple pathways models (see Box 2.1). Currently, there is consensus that ADHD is characterized by a fragmented pattern of deficits in relatively independent cognitive domains. The classification of these cognitive domains varies by paper, but include inhibition, working memory, arousal, activation, response variability, temporal information processing, memory span, processing speed, decision making and delay aversion.[33,34] We will review executive function and reward processing deficits in particular in more detail below (Box 2.1).

EXECUTIVE FUNCTIONS

Executive functions (referred to as executive function and cognitive control) is a umbrella term for a set of cognitive processes that are necessary for the cognitive control of behaviour. Executive functions include basic cognitive processes such as attentional control, cognitive inhibition, inhibitory control, working memory, and cognitive flexibility. Higher order executive functions require the simultaneous use of multiple basic executive functions and include planning and fluid intelligence (i.e., reasoning and problem solving). Executive functioning deficits in ADHD are seen in inhibitory control, visuo-spatial and verbal working memory, vigilance, and planning.[41]

RESPONSE INHIBITION

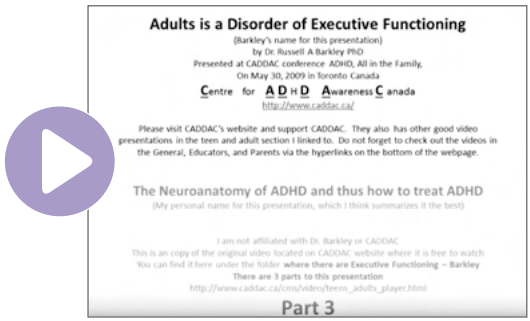
Response inhibition is one aspect of cognitive control. Attention, behaviour, thoughts, and emotions are regulated through inhibition processes executing top-down cognitive control. Response inhibition specifically is the ability to control oneself

Box 2.1
REVIEW OF EXECUTIVE FUNCTION AND REWARD PROCESSING DEFICITS IN ADHA

Key single deficit theories	• Attention deficit[35] • Non-optimal energetic state, in particular activation[36] • Behavioral inhibition[37] • Delay-aversion[38]
Dual pathway theories	Executive functioning deficit ("cold cognition") and reward processing deficit ("hot cognition")[39]
Triple pathway theories	Executive functioning deficit, reward processing deficit, timing deficit[40]

by suppressing or altering intended actions that are no longer required or appropriate. Adequate response inhibition thus enables people to properly adapt to changes in the environment.[42] Impaired response inhibition is central to theoretical models of ADHD.[43] Barkley[37] and others have argued for response inhibition as a central deficit of ADHD in that it affects top-down multiple executive functions, including working memory, self-regulation, internalization of speech and reconstitution. On average individuals with ADHD inhibit their responses more slowly than controls, as reflected in longer stop-signal reaction times and higher error rates. A meta-analysis reported a medium effect-size of 0.62 for the case--control difference in stop-signal reaction time.[44] In addition, a large community study showed that ADHD symptoms in children and adolescents are associated with worse response inhibition and slower response latency.[45]

Response inhibition deficits in ADHD are also observed at the level of the brain. When brain activation is assessed during the administation of response inhibition tasks in the MRI scanner (in socalled functional MRI or fMRI studies),



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healthy participants activate core network of brain regions involved in response inhibition, including a frontal-striatal and frontal-parietal network.[46] Most consistently, children and adolescents with ADHD show decreased activation in frontal, medial and parietal regions during inhibitions when compared with controls,[47] while for adults with ADHD hyperactivation has also been reported. Relative to comparison subjects, not only participants with ADHD but also their unaffected siblings had neural hypoactivation in frontal-striatal and frontal-parietal networks, whereby activation in inferior frontal and temporal/parietal nodes in unaffected siblings was intermediate between levels of participants with ADHD and comparison subjects.[48] Furthermore, neural activation in inferior frontal nodes correlated with stop-signal reaction times, and activation in both inferior frontal and temporal/parietal nodes correlated with ADHD severity. These neural activation alterations in ADHD are more robust than behavioral response inhibition deficits and explain variance in response inhibition and ADHD severity.[48] Together with alterations in brain activation during response inhibition, individuals with ADHD also had lower functional connectivity within the response inhibition network.

The alterations in brain activations in the inhibition network in unaffected siblings described above indicate that response inhibition may serve as a socalled endophenotype. Endophenotypes are biomarkers that share genetic loading with the disease liability, can be measured in all individuals (both affected and unaffected), and that are assumed to provide greater power to identify disease-related genes than clinical phenoptypes.[49] Since ADHD has strong genetic underpinnings and siblings on average share 50% of their genetic variation, unaffected siblings will on average have more ADHD risk genes than healthy controls. Thus, this suggests that part of the genetic loading for ADHD is mediated by alterations of response inhibition at the behavioural and neural level.

WORKING MEMORY

Working memory is considered to be the most central executive function. Three components of working memory are identified in Baddeley's model.[50] The Central Executive (CE) acts as an attentional controller, coordinating tasks and activities of its two sub-systems: the phonological loop (PL) and the visuospatial sketchpad (VS), both storing modality-specific information. Deficient functioning of the separate systems translates into different performance deficits on cognitive tasks: limitations in storage capacity of the VS or PH subsystems is typically characterised by a decline in task performance with increasing memory load or task difficulty. CE dysfunctioning generally translates into a general performance deficit, stable over different memory loads. Evidence suggests that deficits in working memory are one of the key cognitive impairments in ADHD,[51] with the strongest impairments reported for the spatial domain of working memory, as opposed to

the verbal or phonological domain.[51] Visuo-spatial working memory is subserved predominantly by the inferior and superior parietal areas together with dorsolateral prefrontal regions.[52-56] There is additional evidence of activation in the cerebellum during visuo-spatial working memory tasks.[57,58] The available fMRI studies of ADHD reveal a differential activation pattern in the fronto-striatal areas[59] and reduced activation in the dorsolateral prefrontal areas,[60,61] right inferior and superior parietal lobes,[56,62,63] and right caudate nucleus.[63]

REWARD SENSITIVITY

Reward sensitivity is an evolutionary important construct; because rewards are accompanied by positive feelings, they reinforce reward-linked behaviour. This process of reinforcing behaviour forms the basic principle of learning.[64] Yet, if an individual is highly sensitive to rewards, this can lead to maladaptive behaviour, such as risky behaviour and addictions. Especially during adolescence, reward sensitivity is heightened, which is demonstrated by increased risky behaviour when rewards are at stake.[65] Current theoretical models of ADHD consider altered reward sensitivity to be a key cognitive mechanism.[66,67] In general, studies of reward processing show that individuals with ADHD patients make suboptimal and more risky decisions, prefer immediate compared with delayed rewards[66] and overestimate the magnitude of proximal relative to distal rewards. The greater sensitivity to rewards in individuals with ADHD is further demonstrated by faster behavioural responses to trials which lead to rewards than to non-reward trials in the socalled monetary incentive delay task.[67]

Alterations in reward sensitivity in ADHD have alo been observed at the neural level, using fMRI paradigms. Various brain regions, including the orbitofrontal cortex, medial prefrontal cortex, and the ventral striatum are activated in healthy subjects when receiving or anticipating rewards. Findings in ADHD are mixed, with increased activations in the anterior cingulate and anterior frontal cortex during reward anticipation, and in the orbitofrontal cortex and nucleus accumbens during reward receipt[68] and a community study associating increased activation with impulsivity, a related concept. Other studies in adolescents and (young) adults with ADHD however have reported less striatal activation during reward anticipation compared to controls.

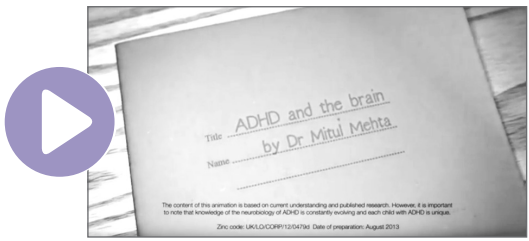
OTHER COGNITIVE DEFICITS

Among other domains that have found to be impaired in ADHD are temporal information processing and timing,[69] speech and language functions,[70] motor control problems,[71] memory span, processing speed, arousal/activation; and reaction

time variability.[72] Slower and more variable reaction times are robust markers of ADHD not only compared to typically developing controls but also to individuals with autism.[73] Last, but not least, it is frequently reported that children with ADHD have on average a lower IQ (about 9 scale points) than controls.[74] This reduction appears to be attenuated in adults with ADHD and is not fully caused by inattentiveness during test performance. This lower IQ may not be specific for ADHD and be found in individuals with other psychiatric disorders as well and might reflect executive deficits that are are assessed as part of the IQ battery tests.

THE AVERAGE INDIVIDUAL WITH ADHD VERSUS INTERINDIVIDUAL VARIATION

All of the above described ADHD case-control cognitive differences were based on group effects. These group effects report on the "average" individual with ADHD but may disguise substantial interindividual variation.[75] Although most individuals with ADHD show deficits in one or two cognitive domains, about 10-25% have not any cognitive deficit with the test batteries used, and at the other side of the spectrum, only very few show deficits in all cognitive domains[34]. It is further of note that also 10% or more of all healthy controls (without ADHD) present with cognitive deficits in 2-3 domains.[34] This has led to attempts to identify subgroups of ADHD with a more homogenous cognitive profile. One study revealed four cognitive subtypes, the first characterized by high response variability, the second by low performance on memory, inhibition and response speed, the third by inaccurate temporal information processing, and the fourth by sub-optimal arousal. Remarkably, very similar cognitive subgroups were found in a community sample of control children.[33] This supports the view that at least part of ADHD's cognitive heterogeneity is nested within normal variation. Similarly, van Hulst and coworkers[76] identified three neuropsychological subgroups within children with ADHD: a quick and accurate, a slow and variable timing and a poor cognitive control subgroup. The first two of these subgroups were also present in the control



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group. Also in adults with ADHD, very similar cognitive subtypes have been identified.[77] It is, however, unclear whether these cognitive subtypes of ADHD have external validity, and for example predict treatment response or course. It is also unclear whether cognitive deficits cause ADHD symptoms and drive the development of the clinical phenotype[38] or reflect the pleiotropic outcomes of risk factors.

BRAIN IMAGING

Brain imaging techniques allow researchers to visualize, measure and analyze the interior of the human brain, i.e. its structure and function, with unprecedented power (see Box 2.2). Alterations have been observed in virtually all neuroimaging modalities applied to the study of the ADHD brain, including structural and functional magnetic resonance imaging (MRI), electroencephalography (EEG), and magnetoencephalography (MEG).

STRUCTURAL MRI

Earlier studies had found that ADHD is associated with a 3-5% smaller total brain size compared to controls[78] due to a reduction of gray matter.[79] Consistent with genetic data suggesting ADHD is the extreme of a population trait, total brain volume correlates negatively with ADHD symptoms in the general population.[80] Meta-analyses further document smaller volumes in ADHD across several brain regions, most consistently in the right globus pallidus, right putamen, caudate and cerebellum. The most recent and largest meta-analysis included in total 1713 participants with ADHD and 1529 controls from 23 sites with a median age of 14 years (range 4-63 years).[81] The results of the mega-analysis (in which not just the case-control differences per site were aggregated but all individual data points were taken in to account) indicated that the volumes of the accumbens, amygdala, caudate, hippocampus, putamen, and intracranial volume were smaller in individuals with ADHD compared with controls. The effects sizes were small and between 0.10 and 0.19 in terms of Cohen's d. There was no difference in volume size in the pallidum and thalamus between people with ADHD and controls. Effect sizes were highest in most subgroups of children (<15 years) versus adults (>21 years), and case-control differences in adults were non-significant. Psychostimulant medication use or symptom scores did not influence the results, nor did the presence of comorbid psychiatric disorders. The greater case-control differences at younger age and absence of such differences at older age support the brain maturation delay theory for ADHD. This theory states that ADHD is due to a delayed ma-

turation of brain structures that mature earlier in healthy controls, and that brain maturation in ADHD may catch-up at later age.[82] This theory was developed given earlier observations that ADHD is associated with delayed maturation of cerebral cortex. Shaw et al.[83] reported that the age of attaining peak cortical thickness was 10.5 years for individuals with ADHD and 7.5 years for controls. This delay was most prominent in prefrontal regions important for control of executive functioning, attention, and motor planning.[83] The development of cortical surface area was delayed in ADHD, but ADHD was not associated with altered developmental trajectories of cortical gyrification.[84]

Although the work reviewed above suggests that age-dependent decline in the prevalence of ADHD may be due to a late development of ADHD-associated brain structures and functions, most patients with ADHD do not show complete developmental "catch up". Indeed, widespread reductions in cortical thickness have been implicated in ADHD not only in children but also in adults. Findings include both cortical thinning (superior frontal cortex, precentral cortex, inferior and superior parietal cortex, temporal pole, and medial temporal cortex[84,85] and cortical thickening (presupplementary motor area, somatosensory cortex and occipital cortex).[86]

Changes across age in the brains of ADHD patients are of much interest given the age dependent prevalence of ADHD.[87] Some brain volumetric alterations observed in childhood normalize with age.[88] A longitudinal MRI study found basal ganglia volumes and surface area to be smaller in adolescents with ADHD compared to controls; this difference was fixed and not-progressive over age.[89] In contrast, for ventral striatal surfaces, controls showed surface area expansion with age, whereas ADHD patients experienced a progressive contraction of the surface, which may explain abnormal processing of reward in ADHD.[89]

VOXEL-BASED MORPHOMETRY

Voxel-based morphometry (VBM) analyses (see Box 2.2) on brain scans of adolescents with ADHD observed significantly smaller grey matter volume in 5 clusters located in the precentral gyrus, medial and orbitofrontal cortex, and (para)cingulate cortices, compared to controls.[90] Unaffected siblings of the ADHD probands had also smaller volumes that were significantly different from controls in 4 of these clusters (all except the precentral gyrus). The brain areas that are smaller in ADHD are involved in decision making, motivation, cognitive control and motor functioning, all functional domains that may be affected in ADHD. The alterations in the unaffected siblings indicate the familiality of four of the structural brain differences, supporting their potential as endophenotypes (see above).

Box 2.2
MEASURES OF BRAIN STRUCTURE AND FUNCTION

Neuroimaging has provided a tremendous boost to neuroscience, by enabling a non-invasive study of the brain in health and disease. This chapter describes research into measures of brain structure, activity, and functional network connectivity in individuals with ADHD and control participants. **Structural magnetic resonance** imaging (sMRI) scans are used predominantly to study aspects of brain grey matter, containing neuronal cell bodies and synapses, and white matter, consisting mostly of the myelinated axons that connect brain areas. sMRI scans allow both for assessing the volume of apriori defined volumes of cortical and subcortical volumes and for bottom-up brainwide analyses of brain voxels (voxel-based morphometry-VBM). Finally, sMRI scans enable to quantify various aspects of the cortex, such as cortical thickness, surface area and gyrification. **Diffusion-tensor imaging** (DTI) or diffusion-weighted imaging (DWI) scans make it possible to estimate the location, orientation and functional integrity of the brain's white matter tracts.

Functional MRI (fMRI) takes advantage of changes in the magnetic properties of blood passing through the brain as an indicator of the relative activity of a region over time. The blood-oxygen level dependent (BOLD) signal is usually recorded while subjects perform a cognitive task, and then compared to a baseline recording to isolate the task-associated activity. FMRI data may also be used to study brain functional connectivity by calculating the coherence of activation patterns over time between regions. This may be done with task-based fMRI data, as well as with recordings while individuals are not engaged in any specific task, known as **resting-state MRI** (rsMRI). Studies into functional connectivity have identified several brain networks, collections of regions that are consistently co-activated. The activation of these networks depends on the subjects' current state of mind. For instance, activity in the executive function network is most prominent when performing a working memory task, and the default mode network becoming more active while mind wandering during resting conditions.[93]

Information about brain function can also be obtained by **electroencephalography** or EEG; this is the physiological method of choice to record all of the electrical activity generated by the brain from electrodes placed on the scalp surface, and allows to study the power of frequency patterns of brain oscillations (delta, 1-4 Hz, theta 4-7 Hz, alpha 7-12 Hz, beta 12-30 Hz , and gamma > 30 Hz).

Event-related potentials (ERP) assess the change in electrical activity time-locked to certain cognitive or attentional tasks.

Magnetoencephalography, or MEG, is an imaging technique that measures small magnetic fields produced by the electrical activity in the brain.

Proton magnetic resonance spectroscopy (MRS) is an imaging technique allowing for in vivo quantification of several neurometabolites in small volumes of the brain.

Positron emission tomography (PET) and **single photon emission computed tomography** (SPECT) use radioactive tracers for targeting different steps in the process of for example dopaminergic neurotransmission.

DIFFUSION TENSOR IMAGING (DTI)

A meta-analysis of whole-brain analyses DTI studies that combined voxel-based analysis (VBA) and tract-based spatial statistics (TBSS) documented widespread alterations in white matter integrity, especially in the right anterior corona radiata, right forceps minor, bilateral internal capsule, and left cerebellum[91] A later meta--analysis on a larger set of TBSS studies found altered white matter microstructure, as reflected in low fractional anisotropy values, in the splenium of the corpus callosum (CC) that extended to the right cingulum, right sagittal stratum, and left tapetum.[92] These findings indicate that altered WM matter tracts that integrate the bilateral hemispheres and posteriorbrain circuitries play a crucial role in the pathophysiology of ADHD.

FUNCTIONAL MRI (FMRI)

Task-related fMRI studies using inhibitory control, working memory, and attentional tasks have documented under-activation of frontostriatal, frontoparietal and ventral attention networks.[94] The frontoparietal network supports goal-directed executive processes while the ventral attention network facilitates attentional reorienting to salient and behaviorally relevant external stimuli. In reward processing paradigms, most studies report lower activation of the ventral striatum in ADHD compared to controls in anticipation of reward.[67] ADHD is also associated with hyperactivation in somatomotor and visual systems,[94] which possibly compensates for impaired functioning of the prefrontal and anterior cingulate cortices.[95]

Remission of ADHD has been associated with normalization of abnormalities as measured by activation during functional imaging tasks,[96] cortical thinning[97] and functional and structural brain connectivity.[98,99]

RESTING-STATE MRI

Resting-state MRI studies report that ADHD is associated with reduced or absent anti-correlations between the default mode network (DMN) and the cognitive control network, lower connectivity within the DMN itself, and lower connectivity within the cognitive and motivational loops of the fronto-striatal circuits.[100] In simple words, individuals without ADHD tend to activate in a MRI scan during mindwondering this DMN. When requested to focus or execute an action, connections inside this DMN weaken while connections in the areas needed to the task are activated. This process seems to be disturbed in ADHD. Some previous investigations suggest that individuals with ADHD do not decrease activity in the

DMN as controls while changing from a resting state to a task, making them "work with a background noise".

In summary, both structural and functional MRI imaging findings are very variable across studies, suggesting that the neural underpinnings of ADHD are heterogeneous, which is consistent with studies of cognition. Of note, ADHD has also been associated with more global brain changes (i.e., decrease in total brain volume), as well as with localized brain changes in areas outside the frontal-striatal circuits such as the parietal cortices, thalamus, amygdala, and cerebellum, and altered activation patterns within other networks such as the default-mode network.

NEUROPHYSIOLOGICAL STUDIES. ELECTROENCEPHALOGRAPHY (EEG) AND EVENT-RELATED POTENTIALS (ERP)

Neurophysiological studies, EEG and ERP studies report altered electrical brain activity in relation to several cognitive processes as attention, inhibition, and performance monitoring.[101] In the attention domain, selective attention and continuous performance (CPT) tasks indicate issues with orienting to cues and selection/resource allocation processes to target stimuli, oddball studies indicated stimulus discrimination and evaluation problems, and distraction tasks indicating attention switching/orienting problems. When considering response inhibition tasks, Stop-signal studies have indicated deficits in response inhibition that were often preceded by differences in earlier attentional components. Similar effects were reported for the Go/Nogo task, with the CPT task indicating issues with response preparation and response inhibition. The flanker task has indicated conflict processing and resource allocation issues. Deficient error detection and/or evaluation were identified by attenuated ERN and Pe components in ADHD, with feedback-processing effects also consistently reported. Similarly, atypical patterns of socalled resting-state EEG frequency power have been observed, mostly as increased power of low frequency theta activity and/or decreased power of fast beta activit.[102] Excessive theta-beta ratio, however, cannot be considered a reliable diagnostic measure of ADHD, but may be useful as a prognostic measure.[103]

Longitudinal work has identified consistent neurophysiological patterns related to differential outcomes. Children with ADHD persisting into adulthood show increased beta and reduced frontal theta EEG at rest,[104] and ERP markers for reduced cognitive preparation (CNV) and error processing.[105-107]

MAGNETOENCEPHALOGRAPHY

There are few magnetoencephalography (MEG) studies in ADHD. A study explored neural interactions between auditory cortices and the frontal cortices during

an auditory attention task in adults with ADHD and controls. ADHD was associated with a greater phase coherence in the beta (14-30Hz) and gamma frequency (30-56Hz) range in attend and no-attend conditions compared to controls. Stimulant medication attenuated these differences but did not fully eliminate them. These results suggest that aberrant bottom-up processing may compromise executive resources in ADHD.[108]

PROTON MAGNETIC RESONANCE SPECTROSCOPY

Proton magnetic resonance spectroscopy (MRS) is a non-invasive method allowing for in vivo quantification of several neurometabolites in small volumes of the brain. MRS studies in ADHD and other neurodevelopmental disorders as autism and obsessive compulsive disorder (OCD) are limited by small sample sizes and varying methodology. Nevertheless, some consistent findings were identified in a systematic review:[25] 1. possible increased Glx (which is a combination of combination of Glu, glutamine and GABA) signal in the striatum across ADHD, OCD and autism; 2. increased Glx in the anterior cingulate cortex (ACC) in children and adolescents with ADHD and autism, and 3. decreased Glx in the ACC in adults with ADHD and with autism. This suggests neurodevelopmental changes in fronto-striatal glutamatergic circuits across the lifespan.

RADIOTRACER IMAGING

Radiotracer techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) can provide more direct evidence of altered dopamine binding patterns in the striatum of patients with ADHD. A meta-analysis of SPECT and PET studies investigating striatal dopamine transporter density in individuals with ADHD and matched healthy comparison subjects found that the striatal dopamine transporter density was 14% higher on average in the ADHD group than in the controls.[12] However, there was marked heterogeneity across studies, and density was higher in patients with previous medication exposure and lower in medication-naive patients. Thus, striatal dopamine transporter density in ADHD appears to depend on previous psychostimulant exposure, with lower density in drug-naive subjects and higher density in previously medicated patients.

SUMMARY AND CONCLUSION

ADHD is a highly heritable, multifactorial disorder, in which genetic factors – often in combination with environmental factors – form risk factors for disease onset.

The mechanisms underlying ADHD are complex and can be defined at different levels. Cognitive deficits are often but not always part of the disorder and include problems in executive functioning, reward processing, timing deficits, various aspects of attentional regulation and orientation, perceptual processes, arousal regulation and reaction time variability. The brain alterations seen in ADHD are very heterogeneous, found in all imaging modalities and both in brain structure and brain function and present a mixture of deviancy and delay. Alterations of the fronto-striatal, fronto-cerebellar and fronto-parietal circuits have been most often reported but this certainly is not the whole picture. The fronto-amygdalar circuits and the limbic brain, and the posterior areas of the brain seem to be involved as well. Individuals with ADHD show different patterns of alterations, and a focus on the "average individual with ADHD" and thus on case-control differences can be somewhat misleading and disguise substantial interindividual variation.[75, 109] Single neuroimaging findings have mostly very limited effect sizes.

Sofar, despite clear evidence that individuals with ADHD have brains that at the group level are different from the "typical brain", no single cognitive or biological marker for ADHD has sufficient diagnostic or predictive value to be incorporated in clinical work. There are several explanations for this disappointing situation. First, the clear limitations of our current categorical diagnostic systems as the DSM[110] and ICD[111] that force both clinicians and researchers into a binary decision: ADHD is present "yes or no". In reality, ADHD can be conceptualized better as a high score (but with a still arbitrary cutoff point) on a complex continuous trait with a normal distribution in the population. Second, the reliance on overly simplistic case-control designs in the study of biomarkers that underestimate heterogeneity in both cases and controls.[75] Third, the lack of a stable, agreed upon and biologically valid concept of ADHD, and for matter of any psychiatric disorder,[112] which makes the current classification an even more unclear basis for informed biological research. The way forward is to define biologically more homogeneous subtypes ("biotypes") of ADHD, and such studies are under way but have still to deliver.[114] The Research Domain Criteria (RDoC) project has been initiated to develop and biologically validate new ways of classifying and understanding mental health.[114] RDoC focuses on altered cross-disorder dimensions of functioning that span the full range of human behavior from typical to atypical and aims to integrate many levels of information from genetics/genomics and neural circuits to observable behavior and self-reports. Again, the promise of RDoC to improve understanding of ADHD in terms of varying degrees of dysfunctions in biological systems has still to be realized.

Conflicts of interest

Jan K. Buitelaar has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Medice, Shire, Roche, and Servier. He is not an employee of any

of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. Other authors report no conflict of interest.

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