Brain lateralization, attention and cognitive control in persistent Attention-Deficit/Hyperactivity Disorder

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Margaretha

ABBREVIATIONS

ACC	Anterior cortex cinguli
ADD	Attention deficit disorder
ADHD	Attention- deficit/hyperactivity disorder
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASRS	Adult ADHD Self-Report Scale
BOLD	Blood oxygen level-dependent
CC	Corpus callosum
CNVs	Copy number variants
COWAT	Controlled word association test
CPT	Continuous performance test
Cre	Creatine
CV	Consonant-vowel
DIVA	Diagnostic interview for ADHD in adults
D-KEFS	Delis-Kaplan executive function system
DL	Dichotic listening
DMN	Default mode network
DNA	Deoxyribonucleic acid
DRD4	Dopamine receptor D4
DSM	Diagnostic and statistical manual of mental disorders
DTI	Diffusion tensor imaging
EEG	Electroencephalography
EPI	Echo-planar imaging
FA	Fractional anisotropy

FL	Forced-left
fMRI	Functional magnetic resonance imaging
FR	Forced-right
FSPGR	Fast spoiled gradient recall sequence
Gln	Glutamine
Glu	Glutamate
Glu/Cre	Glutamate to creatine ratio
Glx	Glutamine + Glutamate
HPA	Hypothalamus-pituitary-adrenal
HTR1B	5-hydroxytryptamine (serotonin) receptor 1B
ICD	International classification of diseases
IQ	Intelligence quotient
K-SADS	Kiddie-schedule for affective disorders and schizophrenia
LCModel	Linear combination of model
LEA	Left-ear advantage
LTD	Long-term depression
LTP	Long-term potentiation
MBD	Minimal brain dysfunction
MD	Mean diffusivity
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MST	Multisystemic therapy
NF	Non-forced
NFPP	The new forest parenting programme
PMTO	Parent management training – Oregon

PROBE-PRESS	Single-voxel point-resolved spectroscopy
RAS	Reticular activating system
REA	Right-ear advantage
RNA	Ribonucleic acid
SLC6A3	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 3
SNAP-25	Synaptosomal-associated protein 25
TE	Echo time
TFCE	Threshold-free cluster enhancement procedure
TR	Repetition time
WAIS	Wechsler adult intelligence scale
WASI	Wechsler abbreviated scale of intelligence
WISC	Wechsler intelligence scale for children

LIST OF PAPERS

The present thesis is based on the following papers:

a) Dramsdahl M., Westerhausen R., Haavik J., Hugdahl K., Plessen K.J. Cognitive control in adults with attention-deficit/hyperactivity disorder. Psychiatry Research. 2011 May 4. [Epub ahead of print]

b) Dramsdahl M., Westerhausen R., Haavik J., Hugdahl K., Plessen K.J. Adults with ADHD – a diffusion-tensor imaging study of the corpus callosum. Psychiatry Research: Neuroimaging. Submitted.

c) Dramsdahl M., Ersland L., Plessen K.J., Haavik J., Hugdahl K., Specht K. Adults with attention-deficit/hyperactivity disorder – a brain magnetic resonance spectroscopy study. Frontiers in Psychiatry. Submitted.

PREFACE

"Elise, pay attention! Didn't you hear what I said?" - "Don't you ever do that again, René, your little devil!" - "For the hundredth time, Charles, sit down, and don't leave your chair again, please!"

As for Elise, the daydreamer; René, the bully; and Charles, the clown, children with attention-deficit/hyperactivity disorder (ADHD) will hear similar comments every day, many times a day, often without the possibility to change their behaviour. They do not understand what is wrong, and are often confused about the repeated corrections and yelling from parents, teachers and peers. In school and family settings, those around the child might think that it is a question of willpower and brand the ADHD child as a loser. Inattention, hyperactivity and impulsivity are major handicaps that interfere with daily life. The typical symptoms are difficulties in concentrating and maintaining focus when distractions are present, restlessness and excessive activity, frequent loss of items like gym bag or cell phone, careless interruption of others, or verbal loudness.

More than half of these children continue to have symptoms into adulthood, which causes dysfunction and suffering, and some of them become a burden on their surroundings. Adults with persistent ADHD symptoms may represent a more homogenous subgroup with other neurobiological underpinnings than the children who grow out of the disorder. Treatment and supportive interventions are important strategies, but do not always achieve the desired effect. What is actually wrong? What is the neurobiological basis and pathophysiology of this disorder, and how can preventive interventions and more effective treatment be developed?

Cognitive neuroscience focuses on the information processing in the brain and the neuronal substrates of mental processes using different methods. In this thesis, two approaches are used, a neuropsychological paradigm and neuroimaging methods, to explore the expression of some of the pathological processes in persistent ADHD.

ABSTRACT

Objective:

Divergent brain lateralization and dysfunctional attention and cognitive control may be part of the pathophysiology of ADHD, with the corpus callosum (CC) and the anterior cortex cinguli (ACC) as important structures. Adults with ADHD may represent a more homogenous subgroup of the disorder compared to children. Research of ADHD has mainly included children and adolescents, whereas neuropsychological and neuroimaging studies of adults with ADHD are sparse. In the clinical studies, which are the foundation of this thesis, we aimed to contribute to the knowledge about brain lateralization, attention and cognitive control in a group of adults with persisting ADHD. The specific aims were to compare an adult ADHD group with healthy controls to explore lateralization of auditory processing and the ability to direct attention and exert cognitive control during various instructions of dichotic listening (DL). Further we wanted to measure the micro- and macrostructure of the CC, as well as the glutamate levels in the midfrontal brain region including the ACC.

Method:

Adults with ADHD and healthy controls were recruited from the Norwegian ADHD biobank and were subjected to DL tests and three modalities of magnetic resonance imaging (MRI). DL is an experimental behavioural task that measures hemispheric specialization of auditory perception, and the DL paradigm with non-forced and forced instructions is presumed to tap into three different levels of cognition: perception, direction of attention and cognitive control. Structural MRI, diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) were the MRI modalities used in the actual project.

Three different articles constitute this thesis. Results in the three papers are from the same sample of 29 adults with clinically diagnosed ADHD. In study I, DL results from the ADHD

group were compared with data from a group of 58 controls selected from a DL database. In study II, the results from structural MRI and DTI of the CC were analyzed, and the results from the 29 adults with ADHD were compared to the results from the 37 healthy controls. In study III, we focused on the results from MRS, and compared the measures of glutamate in the midfrontal brain region, including the ACC, from the 29 ADHD participants with the measures from 38 healthy controls.

Results:

In study I, we found no group differences during non-forced or forced-right conditions of DL, but adults with ADHD were impaired in their ability to report the left-ear syllables during the forced-left instruction condition, whereas the control group showed the expected left-ear advantage in this condition.

In study II, we found reduced fractional anisotropy (FA) values which may reflect changes of the microstructure, in the posterior part of the CC in the ADHD group compared to the control group, though the size of the CC did not differ across the groups.

In study III, a group difference was found with significant reduction of glutamate/creatine ratio (Glu/Cre) in the left midfrontal region in the ADHD group, as well as a side effect with reduced Glu/Cre in the left compared to the right midfrontal region.

Conclusions:

Adults with ADHD seem to have a deficit in cognitive control, but not in auditory processing or focus of attention when measured by DL tasks. Normal macroscopic size of the CC and reduced FA values in the posterior callosal part contrast the findings of those in children who seem to have both reduced macro- and microstructure of the CC. Our findings may point to a delayed development of the CC in adults with ADHD, but not to a total

normalization. The reduced microstructure may reflect impaired interhemispheric connectivity in the posterior part of the CC. The reduction of Glu/Cre in the left midfrontal region in the ADHD group may reflect a cortical glutamatergic deficit. Glutamatergic deficit in the ACC may result in problems with cognitive control and possibly cause a defect thalamic filter-function, which may in turn result in overload of stimuli to the cortex, although this is a speculative hypothesis. A glutamatergic deficit may be a result of epigenetic factors, and a glutamatergic disturbance during maturation of the brain may have an impact on the cerebral development, which could explain the diversity of brain abnormalities revealed in ADHD research. Lastly, a glutamatergic dysfunction may cause an imbalance in other transmitter systems such as the dopaminergic circuitry.

1. INTRODUCTION

1.1. Neurodevelopmental disorders

In neurodevelopmental disorders the normal development of the central nervous system is disturbed, as proposed in diseases like ADHD and autism spectrum disorders. This contrasts neurodegenerative diseases with degeneration of a normally developed central nervous system as observed in Parkinson's disease, amyotrophic lateral sclerosis and Alzheimer dementia. Bipolar disorder and schizophrenia may be of neurodevelopmental origin, though these theories are debated (Brown, 2011; Sanches, Keshavan, Brambilla*, et al*, 2008). To understand the pathophysiology of neurodevelopmental disorders, knowledge about normal brain development and functions is necessary. The cerebral maturation continues throughout childhood and adolescence, representing vulnerability to different pathological processes and epigenetic factors. Modern etiologic theories of neurodevelopmental disorders are multifactorial with focus on disturbances in the interaction between genetic expression and environmental factors that influence normal development and functional neuroplasticity. Deviation from normal brain development may result in the abnormal cerebral lateralization and hemispheric specialization that are reported in different neurodevelopmental disorders (Klimkeit & Bradshaw, 2006). Altered neuromodulation may be part of the pathophysiology or a result of a compensatory mechanism. Neurochemical disturbances are likely to be involved, and imbalance in the dopaminergic-glutamatergic interplay seems to be a key factor.

1.2. Human brain development

The development of the brain starts a few weeks after conception with formation of the neural tube followed by stages of cellular proliferation and differentiation, migration and axonal outgrowth, apoptosis, synaptogenesis and synaptic pruning (Monk, Webb & Nelson,

2001). The process of myelination parallels this neuronal development and continues into adulthood.

Neocortex, also called the isocortex, is phylogenetically the most recently developed part of the mammalian brain and constitutes the majority of the human cerebral cortex (Krubitzer, 2009; Rakic, 2009). It consists of six horizontal morphologically and functionally defined layers with differences in cell types and neural connections. In the neocortex the neurons migrate to one of six layers. Once the immature neurons have reached their destination, the axonal growth and the development of neural circuits start. The establishment of connections between the neurons, synaptogenesis, starts in foetal life and continues throughout life as part of the neuromodulation. With synaptic elimination or pruning, the neural connections are adjusted in accordance with their tasks and activities. The time course of human synaptogenesis and synaptic pruning differs in different cortical regions.

All the processes of proliferation, migration, differentiation, axonal outgrowth, synaptogenesis and apoptosis are regulated by microenvironmental molecular mechanisms like neurotrophic factors and neurotransmitters. This chemical signalling is also sensitive to exogenous factors like oxygenation, nutrition and experiences, and it will influence DNA synthesis and expression of the genes. Neurotrophins are proteins crucial in cerebral development and in survival and function of the neurons (Allen & Dawbarn, 2006). The first neurotrophin discovered was Nerve Growth Factor; it was isolated by the Italian neurologist Rita Levi-Montalcini (Levi-Montalcini, 1952).

The newborn human brain is immature and its development continues into young adulthood through processes of myelination, dendritic and axonal growth, synaptogenesis and synaptic pruning, apoptosis and changes in neurotransmitter sensitivity (Webb, Monk & Nelson, 2001). The changes of grey matter seem to follow an inverted U-shape with increase during pre-adolescence, followed by a post-adolescent decrease of grey matter, whereas white

matter increases linearly up to the twenties (Giedd, Blumenthal, Jeffries*, et al*, 1999). The neurons are organized into different neural circuits or networks, and remodelling and maturation of connections and networks continue during adolescence (Tau & Peterson, 2010).

The developmental trajectories of the brain differ between girls and boys (Lenroot & Giedd, 2010). The peak sizes of cortical and subcortical grey matter seem to be one to two years earlier in females compared to males, and the development of white matter has a steeper rate of increase in boys compared to girls during adolescence. The developmental trajectories may reflect functional differences between boys and girls and correspond to the difference in the average age of pubertal maturation.

The impact on the cerebral development of either biology and the genes or environment and experiences has been debated. Later research has confirmed a unified hypothesis of both intrinsic and extrinsic mechanisms as crucial with a complex interaction between the genetic expression and activity-dependent microenvironmental conditions that start at conception and continue into adulthood (Sur & Rubenstein, 2005). The genes are inherited from our parents and ancestors, but the expression of the genes can be influenced by chemical substances and activity, even during embryonic/foetal life. Cerebral development is sensitive to external conditions like nutrition, exposure to nicotine, cannabis, pollution and stress (Bourre, 2006a; Bourre, 2006b; Dwyer, Broide & Leslie, 2008; Jutras-Aswad, DiNieri, Harkany*, et al*, 2009; Karimi & Arck, 2010;). Neurotrophic factors, cytokines, endorphins, hormonal factors and neurotransmitters are among the chemical microenvironmental ingredients necessary for a normal regulation of the development of the nervous system. The nervous, endocrine and immune system are interwoven in circuits fundamental to homeostatic equilibrium. There are critical periods of vulnerability during brain development where both biological and environmental conditions can disturb development and result in neurodevelopmental disorders with a diversity of dysfunctions and symptoms (Hertzman, 2010; Rice & Barone, 2000).

1.3. Brain lateralization

1.3.1. Hemispheric specialization

The human hemispheres are both functionally and anatomically asymmetrical, and disturbances in this cerebral lateralization may give neurological and psychological consequences. More than 150 years ago, the British general practitioner Arthur Ladbroke Wigan published "*The Duality of the Mind*" in which he described the theory of functional differences between the two hemispheres, with the left half as generally the dominant, and proposed that mental disorders were due to disharmony between the two hemispheres (Wigan, 1844; Clarke, 1987).

The processing of language in the left hemisphere is the most obvious example and most studied area of functional brain lateralization. The first knowledge of language lateralization came with two discoveries of speech deficits caused by cerebral lesions: one discovered by the French physician and anatomist Pierre Paul Broca (1861) and the other by the German physician and anatomist Carl Wernicke (1871) (Fadiga, Craighero & D'Ausilio, 2009). Damage to the left posterior inferior frontal gyrus results in loss of ability to formulate words and to speak, which is called expressive aphasia. Damage to the posterior part of the left superior temporal gyrus results in loss of the ability to know what to say and to understand what others are saying. In receptive aphasia, speech is meaningless and is referred to as "word salad" in layman's terms.

Experiments with DL have revealed information about auditory lateralization. Fifty years ago the Canadian psychologist Doreen Kimura discovered that healthy subjects had a preference to the stimuli presented in the right ear by using a version of repeated words presented dichotically (Kimura, 1967; Kimura, 2011). This right ear advantage is explained by the auditory pathways mainly crossing to the opposite side, and that the processing of speech sounds is lateralized to the left temporal lobe. Stimuli from the left ear cross over to

the right hemisphere and then pass through the CC to the left temporal lobe before processing. Right ear input, thus, is processed faster than left ear input. The DL paradigm has been developed as a neuropsychological experimental method, and the consonant-vowel syllables paradigm with unforced and forced conditions seems to tap other cognitive processes in addition to speech perception (Hugdahl, Westerhausen, Alho*, et al*, 2009).

The centre of Wernicke's area is termed planum temporale and has been found to be larger in the left hemisphere compared to the right (Geschwind & Levitsky, 1968), but the correlation between anatomic and functional asymmetry is not fully understood (Witelson, 1977). The morphologic asymmetry may reflect functional lateralization, and supports the hypothesis that functional brain asymmetry is rooted in anatomical asymmetry (Steinmetz, 1996). The asymmetries in structural connectivity may be critical components in the development of functional hemispheric specialization (Stephan, Fink & Marshall, 2007).

In the 1970s, the American neuropsychologist Roger Wolcott Sperry performed research on split brains; he was awarded the Nobel Prize in Physiology or Medicine for his discoveries of the functional specialization of the cerebral hemispheres in 1981. Together with his student Michael Gazzaniga, he discovered that the right hemisphere had much more advanced and sophisticated cognitive functions than the classic view that suggested the left hemisphere was dominant (Gazzaniga, 2005). The traditional dichotomical view with the left hemisphere as the analytical and logical half of the brain and the right hemisphere as the holistic and creative part is an oversimplification of the complex interplay between the two cerebral halves and their adaptive flexibility. The two halves of the brain behave like one functional unit with the leading control being in one or the other depending on the task. Research on the cognitive outcome after hemidecortication in humans reveals both hemispheres' ability to support a wide range of cognitive functions (Vargha-Khadem & Polkey, 1992).

The right hemisphere, however, seems to be superior concerning visuospatial, attentional and emotional processing (Heilman, Bowers, Valenstein*, et al*, 1986). The inhibitory function seems to be localized to the right inferior frontal cortex (Aron, Robbins & Poldrack, 2004), and a significant association between disinhibitory dysfunctions and damage of the right hemisphere has been documented (Starkstein & Robinson, 1997). The right hemisphere is also important in language processing and mediates higher order language functions essential in the social aspect of communication and the interpretation of the meaning of words with respect to a given context (Mitchell & Crow, 2005).

Many cross-sectional studies have shown brain development with a rightward frontal and a leftward occipital asymmetry (brain torque), and a recent developmental study confirms the same pattern (Shaw, Lalonde, Lepage*, et al*, 2009). Hemispheric specializations have been revealed at micro-level involving cortical microcircuits of the neocortical columns of pyramidal cells (Hutsler & Galuske, 2003). This left-right hemispheric specialization of microcolumns may be a result of early asymmetries in gene transcription (Sun, Patoine, Abu-Khalil*, et al*, 2005). A genetic determined structural asymmetry of the microcolumns may guide functional lateralization and the development of macrocolumns. These findings underline the functional importance of cerebral organization and its consequences for complex cognitive processing, and disturbances in the development of cortical asymmetry may result in the cognitive dysfunctions seen in different neuropsychiatric disorders.

The influence of gender and handedness on brain lateralization has been debated. A recent study reports no differences between men and women in asymmetries of planum temporale or in functional language lateralization, but there is gender difference in handedness with men more often non-right handed than women (Sommer, Aleman, Somers*, et al*, 2008). Handedness seems only moderately related to language lateralization with approximately 60%

non-right-handers and 90% right-handers having a left temporal dominance for speech (Risse, Gates & Fangman, 1997).

The evolutionary benefits of hemispheric specialization in humans are not known, though research on animals indicates that lateralized brains are advantageous in regards to enhanced vigilance to potential dangers compared to non-lateralized brains (Rogers, 2000). Interhemispheric transfer and transcortical processing are time consuming and may explain the benefit of hemispheric specialization in larger brains, and research on callosal transfer time supports this hypothesis (Jancke, Preis & Steinmetz, 1999; Ringo, Doty, Demeter*, et al*, 1994).

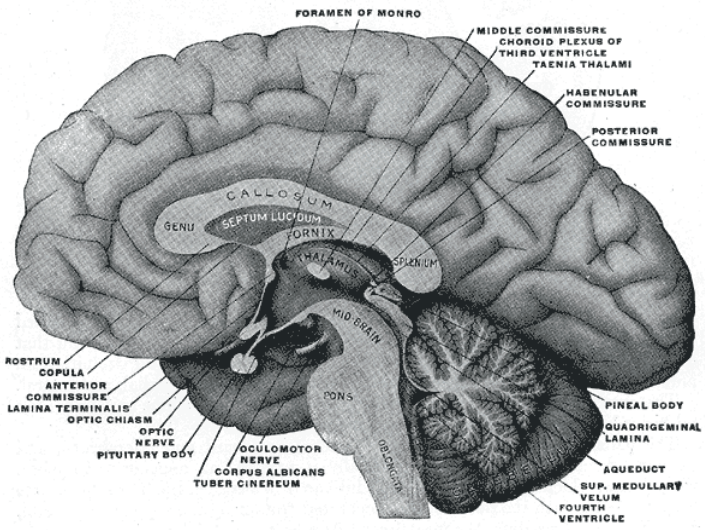
In neurodegenerative disorders like Parkinson's and Huntington's disease, there seems to be normal cerebral lateralization, whereas results from neuropsychological and brain imaging studies of neurodevelopmental disorders suggest disturbances of lateralization, and abnormalities in the right hemisphere have been revealed in persons with ADHD, autism and OCD (Klimkeit & Bradshaw, 2006). The disturbed pattern of lateralization may reflect developmental pathology, but it may, as well, be a result of compensatory processes during cerebral maturation. Altered anatomical and functional lateralization may have served an adaptive evolutionary function, but high genetic penetrance and/or changes in environmental demands may have unfavourable consequences (Bradshaw & Sheppard, 2000).

1.3.2. The Corpus Callosum

Communication between the two hemispheres is crucial for hemispheric specialization. The CC is the main commissural white matter bundle interconnecting the two cerebral hemispheres (Figure 1). Callosal projections link areas with corresponding localizations in the two cerebral halves; homotopic areas, as well as heterotopic areas. The development of the CC and refinement of the connections continue after birth with myelination, pruning and reorganization (LaMantia & Rakic, 1990). This callosal maturation is reflected in increased

size of the CC into young adulthood (Keshavan, Diwadkar, DeBellis*, et al*, 2002; Pujol, Vendrell, Junque*, et al*, 1993).

Figure1. Sagittal section of the brain



Gray, H. (1918) The Anatomy of the Human Body

Studies of the callosal micro- and macrostructures and the functional aspects of its structure have contributed to a more complete picture of brain lateralizaton. Transcallosal conduction time seems to increase in larger brains, and forebrain volume correlates inversely to the midsagittal size of the CC in both children and adults (Jancke, Preis & Steinmetz, 1999), which supports the theory of increased hemispheric specialization due to increased interhemispheric transfer delay in larger brains (Ringo, Doty, Demeter*, et al*, 1994). The primate CC is not one cable with similar fibres; it consists of fibres of different diameters. Fast-conducting fibres of large diameter connect sensory-motor areas, whereas slow-conducting fibres of small diameter connect prefrontal and temporoparietal association areas

(Aboitiz & Montiel, 2003). The CC seems to exert an important role in the interaction between facilitatory and inhibitory functions of the two hemispheres (Bloom & Hynd, 2005).

An often used operational definition of the CC, proposed by Witelson, divides the CC into five subregions: rostrum, genu, truncus or body, isthmus and splenium (Witelson, 1989). The posterior part of the CC connects cortical regions in the temporal, parietal and occipital lobes. Tractography of the transcallosal fibres has revealed a pattern of projections in the anterior and middle part of the CC different from those described by Witelson, and a modification of the CC division has been suggested (Hofer & Frahm, 2006).

Altered structure of the CC is an often reported finding in various neuropsychiatric disorders such as ADHD (Valera, Faraone, Murray*, et al*, 2007), autism (Brambilla, Hardan, di Nemi*, et al*, 2003), bipolar disorder (Bellani, Yeh, Tansella*, et al*, 2009), obsessive-compulsive disorder (Bora, Harrison, Fornito*, et al*, 2011) and schizophrenia (Patel, Mahon, Wellington*, et al*, 2011). The functional consequences of these callosal abnormalities are not known, but they may reflect abnormal brain lateralization as part of the pathophysiology.

1.4. Neuronal communication

1.4.1. Synapses and transmitters

The mammalian neurons communicate mainly through synaptic transmission where the action potential leads to depolarization of the axon terminal and release of transmitters into the synaptic cleft. The released neurotransmitter influences the membrane of the postsynaptic neuron, either as an excitatory transmitter making depolarization and generation of an action potential or as an inhibitory transmitter resulting in a hyperpolarization and increased threshold for initiating an action potential. The myelin, the fat-sheath of oligodendrocytes surrounding the axons, increases the velocity of transmission of neuronal signals.

The theory of chemical transmission of signals across the synapses was confirmed by Otto Loewi's discovery of acetylcholine in 1921 (Lopez-Munoz & Alamo, 2009). After this finding, numerous of other neurotransmitters have been described; some of the subfamilies are catecholamines, indoleamines, enkephalins and endorphins. The neurotransmitters dopamine and glutamate are relevant in my thesis, and will, therefore, be described in more detail.

In the 1950s the Swedish scientist and medical doctor Arvid Carlsson identified dopamine as a neurotransmitter in the mammalian brain (Carlsson, 1959). Since this discovery, dopamine has been one of the most studied neurotransmitters as the key factor in the dopamine hypothesis of schizophrenia (Meltzer & Stahl, 1976). Five major dopaminergic pathways have been described: the mesocortical, the mesolimbic, the nigrostriatal, the tuberoinfundibular and a pathway from subcortical nuclei to the thalamus (Stahl, 2008). These pathways reflect dopamine's widespread influence on different brain functions: cognitive, motor, affective and hormonal.

The level of dopamine is regulated through an interplay between tonic, extrasynaptic dopamine and phasic, spike-dependent dopamine (Grace, 2000). The amino acid L-glutamate interferes with the tonic-phasic dopamine interplay, and a hypoglutamatergic prefrontal condition may cause imbalance in the dopaminergic homeostasis. Glutamate is a major excitatory neurotransmitter with a key function in long-term potentiation and cognitive functions (Anwyl, 2009; O'Neill & Dix, 2007). The ACC, an area of huge importance in cognitive control, has a high density of glutamate receptors (Vogt, 2009). Glutamate is a crucial component in the development of the brain with a major role in the neural migration and differentiation, axonal outgrowth, synaptic induction and pruning (Danbolt, 2001). The development of neural circuits is activity-dependent, and glutamate exerts a main effect in this

process. Excess of glutamatergic excitation is neurotoxic, but its importance in developmental apoptosis is not known.

Glutamate is important in intracortical communication through glutamatergic cortico-cortical neurons and has a regulatory effect on other parts of the brain through descending glutamatergic pathways to the brainstem and the thalamus via the basal ganglia (Stahl, 2008). Glutamatergic synapses are modulated both pre- and postsynaptic by activity-dependent release of neurotrophins, but the exact molecular mechanisms of synaptic plasticity are still unclear (Bramham & Messaoudi, 2005).

Dopamine and glutamate are involved in many neural circuits and are crucial in various cerebral processes, and a dopaminergic-glutamatergic imbalance may be involved in the pathophysiology of neuropsychiatric disorders. Symptoms of ADHD and obsessive-compulsive disorder may be a result of dopaminergic-glutamatergic disturbance, in addition to other transmitter-systems that are likely to be involved (Carlsson, 2001). In schizophrenic research the dopamine hypothesis has been complemented by the theory of hypofunction of the glutamatergic NMDA receptor with different suggestions about the modes of interaction with the dopamine system (Olney, Newcomer & Farber, 1999; Stone, Morrison & Pilowsky, 2007).

1.4.2. Neuromodulation and neuroplasticity

Neuromodulation is the influence on synaptic transmission and plasticity in order to regulate neural information processing. Through neuromodulators, the synaptic connections are refined by activity-related synaptic remodelling with alternating development of new synapses and elimination of others. A neuromodulator tends to have a slower onset and longer duration of effect than a neurotransmitter. Some of the neurotransmitters, like glutamate and acetylcholine, act as neuromodulators as well as neurotransmitters (Giocomo & Hasselmo, 2007).

As a neuromodulator, glutamate acts via astrocytes and the tripartite synapse (Araque, Parpura, Sanzgiri*, et al*, 1999). As an excitatory neurotransmitter, glutamate works mainly through ionotropic receptors; NMDA and AMPA/kainate, or metabotropic receptors (Danbolt, 2001). Astrocytes, the most abundant glial cells of the brain, are involved in maintaining the blood-brain barrier and have a key role in the metabolism and homeostasis of the brain. They seem to be crucial in the modulation of synaptic transmission and network activity through a dynamic and activity-dependent interplay with the neurons (Fellin, 2009).

Adult human neurogenesis seems to be restricted to the hippocampus and the olfactory bulb and is not part of the neuroplasticity in the adult neocortex (Sierra, Encinas & Maletic-Savatic, 2011). Synaptic plasticity, however, contributes to cerebral plasticity to a large extent. The Canadian psychologist Donald O. Hebb stated in 1949 that a synaptic connection will strengthen if a synapse and a postsynaptic neuron are simultaneously active (Hebb, 1949). This statement started an era of research in neuroplasticity that lead to the discovery of long-term potentiation (LTP) (Bliss & Lomo, 1973), the phenomenon where repetitive stimulation of axons results in a long-term increase of excitatory postsynaptic potentials. The neural connections are strengthened through the generation of LTP, whereas in long-term depression (LTD), low-frequency stimuli cause a long-lasting decrease of the postsynaptic response. Both LTP and LTD are phenomena of crucial importance in the experience-dependent plasticity of learning and memory that involve glutamatergic receptors (Rebola, Srikumar & Mulle, 2010).

Synaptic plasticity has been extensively studied in the hippocampus, but recent research has revealed the importance of synaptic plasticity in the prefrontal cortex (Goto, Yang & Otani, 2010). This plasticity represents a vulnerability to environmental and genetic factors, and the deleterious effects of stress-exposure on higher cognitive functions may work through this mechanism. Dysfunctions of the prefrontal cortical synaptic plasticity may also be

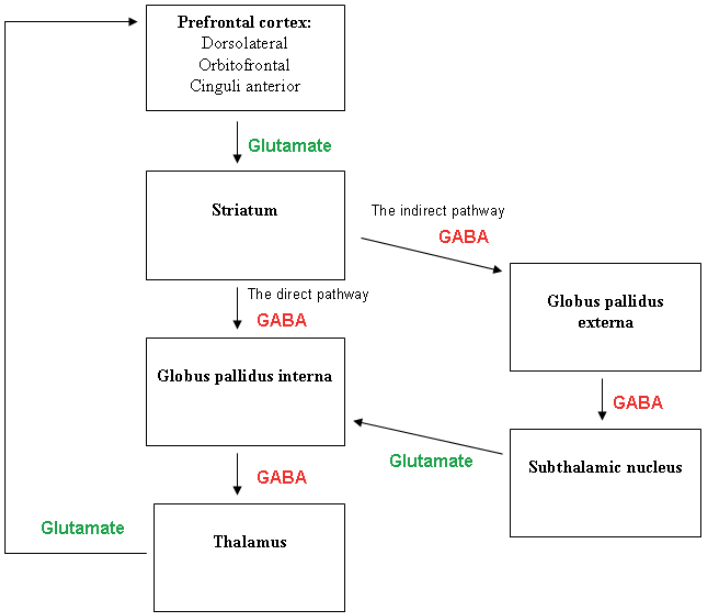
involved in the pathophysiology of neuropsychiatric disorders (Arnsten, Paspalas, Gamo*, et al*, 2010; Goto, Yang & Otani, 2010).

1.4.3. Neural circuits

Sir Charles Scott Sherrington received the Nobel Prize in Physiology or Medicine in 1932 for his discoveries regarding reflexes and the integrative action of the nervous system (Levine, 2007; Sherrington, 1906), and some years later Donald O. Hebb proposed the theory of neural ensemblies as the basis of behavior (Brown, 2006; Hebb, 1949). The ability to measure the firing of groups of neurons, ensemblies, in different brain regions, however, has not been possible until simultaneous multineuron-recording and adapted analysis techniques were developed in recent years (Deadwyler & Hampson, 1997).

Neural networks may be intracortical or intercortical to ensure the corticocortical communication. The intracortical networks are polysynaptic microcircuits with a dynamic interplay between excitatory and inhibitory connections between the six layers of neocortex (Silberberg, 2008; Watts & Thomson, 2005). Five fronto-subcortico-frontal loops originate from different neocortical regions (Cummings, 1993; Tekin & Cummings, 2002). They project to the basal ganglia and further to the thalamus from which they project back to neocortical regions. Within each circuit two pathways through the basal ganglia are described: a direct, excitatory pathway and an indirect, inhibitory pathway, which involves the subthalamic nucleus. Both exert a modulating effect on the thalamus. Two of the fronto-subcortico-frontal circuits, the motor and the oculomotor circuits, are involved in motor functions. The other three circuits originate in prefrontal cortical areas and are mainly involved in cognitive, emotional and motivational processes: the dorsolateral prefrontal, the orbitofrontal and the anterior cingulate circuits (Figure 2). The cerebellum has traditionally been regarded as an executant of motor control, but seems also involved in cognitive and emotional regulation and has dynamic interactions with the fronto-subcortico-frontal circuits.

Figure 2. Diagram of the three prefronto-subcortico-frontal circuits



Modified after Tekin & Cummings, 2002

The regulative function of the prefrontal cortex on attention, emotion and behaviour occurs through extensive reciprocal connections with other parts of the brain. The "cool" executive functions include attention, working memory, planning and response inhibition, whereas the "hot" cognitions are linked to emotions, motivation and reward (Rubia, 2010). The dorsolateral prefrontal network seems to mediate the "cool" cognitions, whereas "hot" cognitions are mediated by the orbitofrontal and the anterior cingulate networks (Taber, Hurley & Yudofsky, 2010). These networks are, however, not separate units, and the cognitive-emotional interaction depends on networks ensuring the communication between

several cerebral regions (Banich, Mackiewicz, Depue*, et al*, 2009; Pessoa, 2008). Development of the affective networks seems to be more protracted than the "cool" cognitive network, and may be reflected in the common emotion-related and impulsive behaviour observed during adolescence (Prencipe, Kesek, Cohen*, et al*, 2011). The activity through the fronto-subcortico-frontal circuits is sensitive to the neurochemical environment and the balance between tonic and phasic noradrenaline and dopamine (Arnsten & Pliszka, 2011). Disturbances in the neurochemical homeostasis in these networks may result in symptoms of different neuropsychiatric disorders (Bonelli & Cummings, 2007).

The hypothalamus-pituitary-adrenal (HPA) axis is of crucial importance in the fight-flight response and is part of the stress system in connection with the locus coeruleus and the arousal and alerting system (Posner, 2008; Van Bockstaele, Reyes & Valentino, 2010). The HPA axis and the sympathetic nervous system interact with the immune system through the immune-neuroendocrine network (Correa, Maccioni, Rivero*, et al*, 2007). The stress response and the inflammatory response are important protective mechanisms, but dysfunctions in the immune-neuroendocrine network may result in pathological responses.

Recent development in neuroimaging research has made possible new ways to explore human brain networks (Power, Fair, Schlaggar*, et al*, 2010). Structural connectivity is studied by structural MRI and DTI, and new maps of white matter have been developed from DTI studies (Mori, Oishi & Faria, 2009). Functional MRI (fMRI) gives information about functional connectivity, i.e. correlated activity in neural ensembles, either during cognitive tasks or as the intrinsic cerebral activity during rest (van den Heuvel & Hulshoff Pol, 2010). From studies of fMRI when different cognitive tasks are undertaken, three attentional networks have been described: the alerting, the orienting, and the executive attention networks (Fan, McCandliss, Fossella*, et al*, 2005; Posner & Rothbart, 2007). The orienting and alerting networks begin development in early infancy, whereas the executive attention

network is presumed to develop from the age of one year (Posner, Sheese, Odludas*, et al*, 2006). The executive attention network seems to correspond to the three fronto-subcortico-frontal circuits described above, i.e. the dorsolateral prefrontal, the orbitofrontal and the anterior cingulate networks.

Results from task-independent fMRI (resting state fMRI) describe what is assumed to be intrinsic spontaneous brain activity, and the functional networks activated during rest seem to correspond to those mapped through tasks (Smith, Fox, Miller*, et al*, 2009). Ten years ago the default mode network (DMN) was described as a resting state network that deactivates during attentional demanding tasks (Raichle, MacLeod, Snyder*, et al*, 2001). The DMN, one of the most extensively studied resting state networks, includes the medial prefrontal cortex, the posterior cortex cinguli and the adjacent precuneus and parts of the parietal cortex.

Whereas the correlated activity measured by fMRI reflects functional connectivity, effective connectivity describes the dynamic communication between the various neural systems by means of mathematics (Power, Fair, Schlaggar*, et al*, 2010). The use of graph-theory and Dynamic Causal Modelling to analyze cerebral networks is a rapidly evolving field (Friston, Li, Daunizeau*, et al*, 2010).

Developmental delays or deficits may disturb the maturation of the neural circuits (Rice & Barone, 2000), and defects in the cerebral networks are involved in a variety of neuropsychiatric diseases (Bonelli & Cummings, 2007). Dysfunction of the HPA axis and the stress network may result in different dysfunctions (Charmandari, Kino, Souvatzoglou*, et al*, 2003), including neurodevelopmental disorders (Talge, Neal & Glover, 2007). Disturbances in resting state networks have been reported in disorders like schizophrenia (Woodward, Rogers & Heckers, 2011) and depression (Hamilton, Furman, Chang*, et al*, 2011), and activity in the DMN during task-related activity may interfere with task-specific neural processing and

explain the variability in attentional performance observed in individuals with ADHD (Sonuga-Barke & Castellanos, 2007).

1.5. Perception, attention and cognitive control

1.5.1. Perception; the auditory pathway

The organism receives information about the environment through the senses, and the sensorial input is transferred to the brain for further perceptual processing. The main senses are hearing, sight, taste, smell and touch. The auditory pathway is one of the most studied sensory pathways. Sound input is transferred through the vestibulocochlear nerve to the cochlear nuclei in the brainstem and travels through the lateral lemniscus to the contralateral inferior colliculus of the midbrain. The two lemnisci communicate through commissural fibers. From the inferior colliculus, the auditory stimulus reaches the medial geniculate nucleus in the posterior thalamus for further transfer to the primary auditory cortex located in the posterior, superior temporal lobe. The inferior colliculus, medial geniculate nucleus in the thalamus and the auditory cortex are reciprocally communicating through the colliculo-thalamo-cortico-collicular loop; this circuit is critical in the induction of auditory neuromodulation (Xiong, Zhang & Yan, 2009).

The processing of auditory stimuli is lateralized to the left temporal lobe, and the input from the left ear transferred to the right hemisphere through the lateral lemniscus crosses over to the primary auditory cortex in the left temporal lobe for further processing. The posterior part of the CC and the commissura anterior interconnect the auditory cortices in the two hemispheres. The commissura anterior seems to transfer basic auditory information from less differentiated auditory areas than the CC (Bamiou, Sisodiya, Musiek*, et al*, 2007). Both the frontal and the parietal cortices are involved in the further auditory processing with an antero-ventral pathway linked to the recognition of the sound, and a postero-dorsal stream

responsible for the localization of the sound in space (Rauschecker, 2011). Whereas the left hemisphere is responsible for language processes of phonology and syntax, the right hemisphere mediates higher order language functions essential in the interpretation of the communicative context and in the understanding of abstractions and indirect statements (Mitchell & Crow, 2005).

1.5.2. Attention

Global attention is the ability to allocate necessary awareness to sensory stimuli for further perceptual processing. "When any object of external sense, or of thought, occupies the mind in such a degree that a person does not receive a clear perception from any other one, he is said to attend to it." Sir Alexander Crichton, a Scottish physician, wrote this definition of attention in his book *Inquiry into the Nature and Origin of Mental Derangement,* which was published in 1798. Attention can be divided into voluntary and reflexive attention, the first being a top-down, instruction-driven process, and the second being a bottom-up, stimulus-driven process.

Attention implies consciousness and alertness. Consciousness in medicine is measured by the degree of responsiveness. The terms arousal and alertness are often incorrectly used as though they are synonyms. Arousal is the organism's global preparation state to meet challenges and dangers and is closely linked to the fight-flight response and automatic behavioral responses, which are crucial for survival. Alertness is the mental state of readiness to respond to sensory stimuli, a state of aroused awareness.

In the middle of the 20th century attentional research focused on the distinctions between various hierarchical levels of consciousness, arousal and alertness. Moruzzi and Magoun explored the neural components regulating the brain's sleep-wake mechanisms and suggested thalamic projections as possible mediators of reticular stimulation to the cortex (Moruzzi & Magoun, 1949). Later research confirmed that the ascending reticular activating system

(RAS) is the structure responsible for regulation of arousal and the transition between sleep and waking (Steriade, 1996). RAS originates in the brainstem, including the reticular formation and its excitatory cholinergic connections, and extends through two pathways: one via the medial thalamus and the other via the lateral hypothalamus, basal ganglia and forebrain. Through these pathways the reticular formation regulates the cortical cell excitability and the states of consciousness (Rosenzweig, Watson & Breedlove, 2005). Thalamic nuclei are not only a relay station between the brainstem and the peripherial sensory apparatus, but seem to have an active role in the regulation of cortical activity (Llinas & Steriade, 2006). Disturbance of the thalamocortical activity, referred to as thalamocortical dysrhythmia, may cause symptoms of neuropsychiatric disorders like Parkinson's disease and petit mal epilepsy (Llinas, Ribary, Jeanmonod*, et al*, 1999).

In 1953 the British scientist Edward Colin Cherry described the "cocktail party effect" as the ability to keep focused in a conversation despite much background noise, in other words selective attention ability (Cherry, 1953). Cherry's postulation was the beginning of an era that focused on the regulation of attention and behavior by the executive functions sited in the prefrontal cortex. Donald Eric Broadbent, a British experimental psychologist, published the filter model of selective attention, a gating mechanism that filtered out irrelevant stimuli before processing relevant stimuli into perceptual meaning (Broadbent, 1958). Research on selective attention revealed the influence attention has on perceptions. The brain continuously receives enormous amounts of sensory stimuli, external and internal, and both assessment and filtration of incoming stimuli, as well as coordination of further processing, are necessary to secure goal-directed behaviour. Various theories about information selection have been published, as well as an updated version of Broadbent's theory of selective attention (Lachter, Forster & Ruthruff, 2004).

In the cortical association areas sensory stimuli are processed in order to produce a meaningful perceptual experience (Arnsten, 2006). The inferior temporal cortex is central in the processing of visual stimuli, whereas auditory information is processed in the superior temporal cortex. The parietal association cortex seems to be a key area for directing attention in time and space.

As referred to in section 1.4.3. Neural circuits, three specific networks involved in different aspects of attention are described: the alerting, the orienting and the executive attention (Fan, McCandliss, Fossella*, et al*, 2005; Posner & Rothbart, 2007). The alertness of the organism is mediated through the alerting network and depends on the state of arousal regulated by the RAS. The orienting network is involved in the ability to orient attention in response to sensory input. Through the executive attention network the cognitive processes are coordinated despite disturbances and conflict situations in the aim of reaching internal goals. The executive attention network mediates the executive control functions described in the next section.

1.5.3. Executive functions, cognitive control and self-regulation

With Cherry's description of the cocktail party phenomenon (Cherry, 1953), the focus changed from the cortical association areas and the neuronal mechanisms behind incoming stimuli perception to research about more complex attentional models and the ability to modulate sensory processing. Executive functions are a theorized concept of the ability to synchronize and modulate cognitive processes like planning, selective attention, decision-making, problem solving, cognitive flexibility, abstract thinking and response inhibition. The term was introduced to explain the role of the "higher" functions of the prefrontal cortex, but it has no precise definition (Jurado & Rosselli, 2007). Theories of the executive system were developed from research on people with damaged frontal lobes (Cummings, 1993). They had great problems organizing daily life, but seemed to perform normally when separate

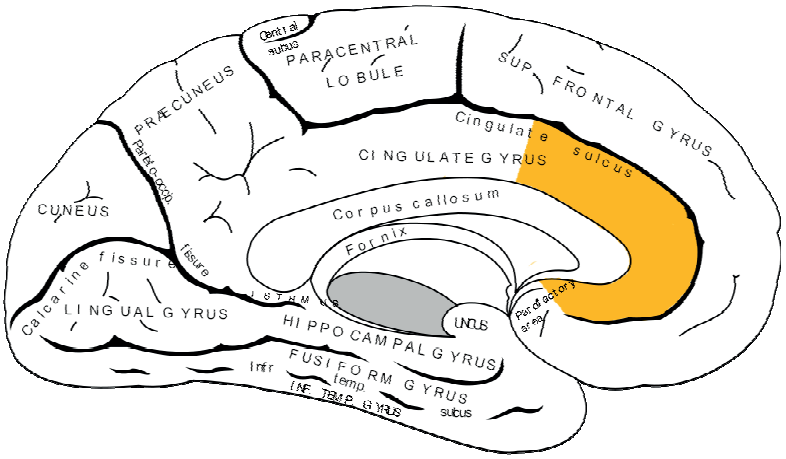
fundamental cognitive functions, like memory, learning, language and reasoning were tested. This phenomenon was called the "dysexecutive syndrome", and led to different theories about the system related to the frontal lobes that coordinate the various cognitive functions necessary for goal-directed and planned actions.

Cognitive control is defined as "the ability to orchestrate thought and action in accordance with internal goals" (Miller & Cohen, 2001), i.e. to cope with disturbances and conflict situations in the aim of reaching internal goals. Cognitive control, to a large extent, has replaced the term executive functions in the literature, even though the term is not an exact synonym as it takes a narrower view of the ability to detect and coordinate conflicting cognitive processes in the aim of goal-directed behaviour. Despite different models of the organisation of cognitive functions, there seems to be consensus that they are organized in a hierarchical manner. This hierarchical organization allows for both top-down, instruction-driven interactions and bottom-up, stimulus-driven interactions.

Self-regulation is another term that is often used though it is without a consistent definition. It can be used in the sense of the ability to modulate behaviour according to societal norms (Heatherton, 2011), depending on empathetic skills and the exertion of cognitive control and response inhibition. When used in relation to emotions, self-regulation is the ability to regulate emotional experiences and the emotional influence on behaviour (Eisenberg, Spinrad & Eggum, 2010). Children are born with different temperaments, and, therefore, demands for emotional control differ. The newborn is totally dependent on the external regulation from parents or other caregivers, but already during the first year of life, the development of internal self-regulation starts and develops parallel to the ability to sustain and orient attention. Emotion-related self-regulation corresponds to the "hot" executive functions (Rubia, 2010).

It has been proposed that executive functions are mediated through the executive attention network, which includes the ACC and lateral prefrontal areas implicated in top-down regulation of cognitive control and emotion-related self-regulation (Posner, Sheese, Odludas*, et al*, 2006). The ACC is a medial frontal region defined by Brodmann's areas 24, 32, 25 and 33, but is not a homogenous structure (Figure 3). The dorsal ACC differs from the ventral ACC according to cytoarchitecture and organization of neurotransmitter receptors (Palomero-Gallagher, Mohlberg, Zilles*, et al*, 2008). This dichotomy is reflected in functional differences with the dorsal part engaged in cognitive conflict situations and the ventral part activated during emotional stimuli (Bush, Luu & Posner, 2000). The ACC may be a regulator of the arousal state of the body through interplay with the autonomic nervous system and seems to play a crucial role in the maintenance of balance between cognitive control, regulation of emotions and autonomic activity (Critchley, Mathias, Josephs*, et al*, 2003).

Figure 3. Medial surface of left cerebral hemisphere with the anterior cingulate cortex (yellow)



Gray, H. (1918) The Anatomy of the Human Body (modified)

Dysfunctional executive functions and other cognitive impairments are common in different neuropsychiatric disorders like schizophrenia (Heinrichs & Zakzanis, 1998), bipolar disorder (Harvey, Wingo, Burdick*, et al*, 2010), autism (O'Hearn, Asato, Ordaz*, et al*, 2008) and ADHD (Seidman, 2006). Some of these deficits may be consequences of the same psychopathological mechanisms. Interdiagnostic research based on trait classification has been recommended (Levy & Ebstein, 2009), and neuropsychologic or neuroimaging investigations of mutual traits across different diagnoses may reveal intermediate components between phenotype and genotype, i.e. endophenotypes (Gottesman & Gould, 2003).

1.6. Attention-Deficit/Hyperactivity Disorder

1.6.1. History

Sir Crichton described in his monograph *Inquiry* (1798) a condition with "the incapacity of attending with a necessary constancy to any one object". This is possibly the first scientific description of an inattentive disorder (Palmer, ED; Finger, S., 2001). Sir Crichton presumed a physiological explanation to this condition with increased sensitivity of the nerves, an astonishing proposal at a time when psychiatric symptoms were explained as defects of morality. One hundred years later in 1902, the English paediatrician Sir George W. Still described cases from his clinical practice to the Royal Society of medicine (Still, 2006), in which the children had impaired sustained attention and behavioural problems from a young age. He described the condition as a "defect of moral control", even though he suggested a biological aetiology. Notably, he observed that these children had close relatives who often had some of the same problems.

After the encephalitis epidemics in 1917-18, a large number of children developed attentional and behavioural problems, a condition classified as Post-Encephalitic Behaviour Disorder. Twenty years later the term Minimal Brain Dysfunction (MBD) was used to refer to

dysfunctional behaviour in children with hyperactivity, impulsivity, problems with attention and concentration, disobedience, general unhappiness and lack of self-esteem (Saunders, 1979). These labels reflected the etiological hypothesis of brain damage.

The term MBD was commonly used to describe this disorder until around 1970. The hypothesis of brain trauma was not confirmed, and in DSM II, the label was changed to Hyperkinetic Reaction of Childhood (American Psychiatric Association, 1968). The classification of Attention Deficit Disorder (ADD), with or without hyperactivity, was included in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition *(*DSM-III) released in 1980 (American Psychiatric Association, 1980). The classification was changed to Attention Deficit/Hyperactivity Disorder in the last revised version of DSM, DSM-IV (American Psychiatric Association, 1995). The 10th edition of the International Classification of Diseases *(*ICD-10) appeared in 1992; it used the term Hyperkinetic Disorders (World Health Organization, 1992).

ADHD was regarded as a disorder restricted to childhood, but since the 1970s, reports have been published describing typical symptoms and functional impairment lasting into adulthood, a condition that was named adult brain dysfunction (Mann & Greenspan, 1976). The persistence of ADHD in adults is now widely accepted, but there is still disagreement concerning diagnostic criteria (Bell, 2011; McGough & Barkley, 2004). It was not until 1997 that the Norwegian authorities allowed stimulants to be prescribed to adults, and in the period 1997-2005, it was necessary to individually apply and be granted permission from a regional expert team. The prescription of stimulants is still strongly regulated. It is required that an application is submitted to the health authorities, and any subsequent prescriptions are restricted to neurologist and psychiatrist and general practitioners who are supervised by a neurologist or psychiatrist.

1.6.2. Symptoms, classification and prevalence

ADHD is a neurodevelopmental disorder with symptoms from preschool age. According to both DSM-IV and ICD-10, the disorder is classified with three subsets of symptoms: inattention, hyperactivity and impulsivity. Both classification systems require the start of some age-inappropriate symptoms before the age of seven that cause dysfunction in two or more settings, such as in school, at home or in test situations. The symptoms must last for more than six months. DSM-IV uses three subclassifications: mainly inattentive, mainly hyperactive/impulsive and the combined subtype. The criteria are fulfilled when at least six inattentive and/or six hyperactive/impulsive symptoms are present. According to the classification of Hyperkinetic disorders in ICD-10, symptoms of both inattention and hyperactivity/impulsivity are required (F90.0 Disturbance of activity and attention). The inattentive symptoms are characterized by impaired sustained attention, an increased level of distractibility and problems organizing and completing activities.

The symptoms are often devastating to social life, and the children may have problems understanding the social codes and more subtle aspects of communication. Many of the adult participants in the present project have told stories of loneliness due to lack of social skills and unpopular behaviour during childhood and adolescence. A major problem is the lack of metacognitive perspective; they do not understand what they do wrong. These problems often continue into adulthood and lead to educational and occupational difficulties. Data from the Bergen ADHD project confirmed international reports of a high incidence of occupational disability (Halmoy, Fasmer, Gillberg*, et al*, 2009).

The estimates of prevalence of ADHD differ depending on the methods of assessment and the population studied, but an estimated worldwide-pooled prevalence in children and adolescents is 5.3% (Polanczyk, de Lima, Horta*, et al*, 2007). In some of the children with ADHD, the symptoms decline and disappear, which can be explained by a delayed cerebral

maturation (Shaw, Eckstrand, Sharp*, et al*, 2007). The majority of affected children, however, continue to have some symptoms and functional impairment into adulthood (Biederman, Mick & Faraone, 2000; Faraone, Biederman & Mick, 2006). Symptoms of inattention seem to persist or even worsen, whereas symptoms of hyperactivity and impulsivity often decline. Ongoing brain development may reflect these changes in symptoms, but compensatory strategies and coping mechanisms may also contribute. Adults with persistence of ADHD may represent a subgroup with neurobiological dysfunctions, such as dysregulation of the dopaminergic or glutamatergic systems, rather than late maturation of the cortex (Carlsson, 2001; Genro, Kieling, Rohde*, et al*, 2010; Staller & Faraone, 2007).

1.6.3. Comorbidity

ADHD is associated with high rates of comorbid disorders in both children and adults. Dyslexia, anxiety disorders, depression, bipolar disorder, personality disorders and substance abuse are common conditions that coexist with ADHD (Cumyn, French & Hechtman, 2009; Germano, Gagliano & Curatolo, 2010; Taurines, Schmitt, Renner*, et al*, 2010). Problems with emotion-related self-regulation, sensation seeking and impulsiveness may increase substance abuse and criminality in people with ADHD. There seems to be a relationship between ADHD and low self-esteem (Dittmann, Wehmeier, Schacht*, et al*, 2009; Edbom, Lichtenstein, Granlund*, et al*, 2006), and negative beliefs about the self and maladaptive coping strategies reduce quality of life (Newark & Stieglitz, 2010). Symptoms of ADHD may be overlapping with other psychiatric disorders, and diagnostic assessment and the distinction between comorbid symptoms and differential diagnoses are a challenge. Affective disorders, anxiety disorders, borderline personality disorder and substance abuse are some of the most common differential diagnoses (Haavik, Halmoy, Lundervold*, et al*, 2010).

1.6.4. Treatment

Medication, psychosocial interventions, and treatment of comorbid disorders are recommended as therapeutic interventions according to the Norwegian guidelines for diagnostic assessment and treatment of ADHD (Norwegian Directorate of Health, IS-1244, 2007). In 1937, Dr. Charles Bradley introduced the use of stimulants in children who demonstrated hyperactivity (Strohl, 2011), and to this date stimulants are still the medication of choice. The effect of medication with methylphenidate or amphetamine is well documented in children (Brown, Amler, Freeman*, et al*, 2005; Jensen, Garcia, Glied*, et al*, 2005). Age does not seem to have any influence on the effect of stimulants, though studies of adults are sparse (Cornforth, Sonuga-Barke & Coghill, 2010; Kooij, Bejerot, Blackwell*, et al*, 2010). Atomoxetine is recommended if treatment with stimulants has had no effect or if contraindications are present. Recent studies showed promising results, even if the variability in treatment response seems to be substantial (Young, Sarkis, Qiao*, et al*, 2011; Marchant, Reimherr, Halls*, et al*, 2011).

Patients are legally entitled to receive information about the disorder, implications and therapeutic interventions. Socioeconomic problems and relationship conflicts with family and friends are common challenges in treatment. Psychosocial interventions have to be individually tailored to be effective (Greene & Ablon, 2001). Counselling of the parents and teachers of children and adolescents with ADHD is important, and specific parenting training interventions such as “The Incredible Years” for the youngest children or “Parent Management Training – Oregon” (PMTO) for children 6-12 years of age should be offered (Norwegian Directorate of Health, IS-1244, 2007). Both programs have documented effects concerning conduct problems (Ogden & Hagen, 2008; Patterson, Forgatch & Degarmo, 2010; Webster-Stratton, Reid & Hammond, 2001), and one study on the Incredible Years program has revealed effect among children with ADHD (Webster-Stratton, Reid & Beauchaine,

2011). The New Forest Parenting Programme (NFPP) is evaluated and seems to be an effective intervention for preschool children with ADHD (Daley, Jones, Hutchings*, et al*, 2009). Multisystemic therapy (MST) (Henggeler, Cunningham, Pickrel*, et al*, 1996) are interventions for adolescents and their families that address social, emotional and behavioural problems, but the evidence of the effectiveness is not conclusive (Littell, Popa & Forsythe, 2005).

Few non-pharmacological treatment studies of ADHD are published. Cognitive behavioural therapy, either in groups or individually, may relieve ADHD symptoms in adult patients (Bramham, Young, Bickerdike*, et al*, 2009; Virta, Salakari, Antila*, et al*, 2010). There are reported some positive results after electroencephalography (EEG)-neurofeedback training in children (Lansbergen, van Dongen-Boomsma, Buitelaar*, et al*, 2011), and promising reports about the therapeutic benefit of computer based training of working memory in children have been published (Beck, Hanson, Puffenberger*, et al*, 2010; Klingberg, Fernell, Olesen*, et al*, 2005). Research on cognitive training in adults with ADHD seems almost completely neglected, even if studies of other adult populations reveal that training the cognitive functions in adult brain is possible (White & Shah, 2006).

Systematic research with different diets is sparse, but some studies have been published regarding zinc (Arnold, Disilvestro, Bozzolo*, et al*, 2011), restricted elimination diet (Pelsser, Frankena, Toorman*, et al*, 2011), artificial food colours (Stevens, Kuczek, Burgess*, et al*, 2010) and fatty acids (Transler, Eilander, Mitchell*, et al*, 2010). Evidence is too limited to draw firm conclusions, and more research on nutritional interventions of ADHD subgroups is necessary.

1.6.5. Neuropsychology in ADHD

Neuropsychological tests are widely used in assessment of cognitive abilities in neurology and psychiatry, and are important tools in rehabilitation of various cerebral disorders. Clinical

neuropsychological tests provide quantifiable data about different cognitive functions like problem-solving, language, memory, attention, abstract thinking and motor speed. The most used test-battery in Norway has been the Halstead-Reitan Neuropsychological Battery (Kane, 1991). Delis-Kaplan Executive Function System (D-KEFS) is a newer test-battery for the assessment of higher-level cognitive functions, i.e. executive functions (Homack, Lee & Riccio, 2005). Clinical neuropsychological evaluation is often part of the diagnostic assessment of ADHD. The neuropsychological tests that most consistently differentiate adults with ADHD from controls are the Continuous Performance Test (CPT), the Stroop Color and Word Test, the Trail Making Test, the Controlled Word Association Test (COWAT) and the Wechsler Adult Intelligence Scale (WAIS) (Seidman, 2006). However, no specific neuropsychological ADHD test profile exists, and neuropsychological tests are not diagnostic tools. Neuropsychological evaluation is perhaps more important during the (re)habilitation, when evaluating treatment response and in identifying particular strengths and weaknesses of cognitive functions, which are valuable assessments when planning education or employment options for an adult with ADHD.

The most commonly administered intelligence scales are the WAIS (Hartman, 2009) and the Wechsler Intelligence Scale for Children (WISC) (Slate, 1995). Wechsler Abbreviated Scale of Intelligence (WASI) is a short version of the WAIS-III battery and provides an estimate of full scale IQ in a shorter amount of time (Axelrod, 2002). The symptoms of ADHD may influence the results from IQ testing, even if the associations are generally modest (Jepsen, Fagerlund & Mortensen, 2009). Matched for IQ with a healthy control group, the ADHD group may represent a subgroup that has reduced symptoms or has acquired enough compensatory strategies to manage IQ tests in a way that equals the healthy subjects, and it is not recommended to match for IQ if a representative group of ADHD is wanted (Dennis, Francis, Cirino*, et al*, 2009).

In experimental neuropsychology of ADHD, a wide variety of tests have been used, mostly in children, and the results confirm the heterogeneity of ADHD (Doyle, 2006). The results of a recent meta-analytic review of adults with ADHD suggest impairments across multiple neuropsychological domains like attention, behavioural inhibition and memory (Hervey, Epstein & Curry, 2004). The "consistent inconsistency" of neuropsychological results is possibly a result of the intra- and inter-individual variability in performance. It has been suggested that deficits in temporal processing that result in intra-individual variability may be an endophenotype of ADHD (Castellanos & Tannock, 2002).

Despite neuropsychological heterogeneity, executive functions are usually disturbed in individuals with ADHD, and much focus has been on behavioural inhibition. Several models have been proposed, and one of the first unifying theories suggested response inhibition as the main problem in ADHD (Barkley, 1997). Barkley emphasized the impact of impaired behavioural inhibition on executive functions, including self-regulation of affect, motivation and arousal. Later multifactorial models have included problems with arousal and activation, as in the cognitive-energetic model (Sergeant, 2005) and the dynamic developmental behavioural theory (Sagvolden, Johansen, Aase*, et al*, 2005).

1.6.6. Neuroimaging in ADHD

Nearly 20 years ago, more than 200 neuroimaging studies of neurodevelopmental disorders were reviewed (Peterson, 1995). Despite the many neuroimaging studies published after this review, the conclusions are inconsistent and the neurobiological substrate of ADHD is still not known. One of the most striking observations is the diversity of reported findings across the various neuroimaging modalities (Bush, Valera & Seidman, 2005; Castellanos, Kelly & Milham, 2009; Cubillo & Rubia, 2010; Valera, Faraone, Murray*, et al*, 2007). Perhaps this reflects the heterogeneity of ADHD and the methodological variations and limitations.

Magnetic resonance imaging is the neuroimaging method most used because it is noninvasive and does not involve ionizing radiation exposure. In proton MRI, the magnetic properties of the highly abundant ^{1}H atom in organic tissues are exploited using magnetic fields and radio frequency waves. In the strong external magnetic field in the MRI scanner, the electrons change their small magnetic fields, and most of the protons are oriented parallel to the magnetic force. When radio frequency waves are turned on as excitation pulses, the direction of the protons are influenced, and energy is absorbed by the protons. The absorbed energy is released when the radio frequency waves are turned off, and the protons reorient according to the magnetic force. The sensors that surround the body pick up the MR signals from synchronously dissipated energy and images are constructed from the distribution of protons. Because the density of protons in grey matter is much higher than in white matter, the images give sharp distinction between grey and white matter. Different MRI modalities are available in addition to structural MRI: DTI, task-dependent and task-independent (resting state) fMRI, and MRS.

Most of the structural MRI research of ADHD includes cross-sectional studies of children or adolescents (Krain & Castellanos, 2006; Shaw & Rabin, 2009; Valera, Faraone, Murray*, et al*, 2007). The only published meta-analysis from structural brain imaging research (Valera, Faraone, Murray*, et al*, 2007) concluded with decrease of total and right cerebral volume, various frontal regions, the right nucleus caudatus, the posterior part of the CC and regions in the cerebellum as the most consistent results in children with ADHD relative to controls. These findings may reflect disturbances in frontostriatal circuits in adult ADHD, as well as involvement of the cerebellum. The few structural brain imaging studies of adults with ADHD reveal abnormalities in prefrontal and temporoparietal regions (Cubillo & Rubia, 2010), but the research of adults is too sparse to draw firm conclusions.

Reduced size of the CC may represent impaired interhemispheric connectivity, and decreased volume of the posterior part of the CC is one of the most replicated findings in the research of children with ADHD. The only published structural MRI study of the CC in adults with ADHD reported the same finding (Rusch, Luders, Lieb*, et al*, 2007). In this adult study, it is not possible to draw conclusions about the impact of ADHD itself, however, since the ADHD participants included had a comorbid borderline personality disorder. A longitudinal study of the CC reports disruption of the anterior callosal growth, which may reflect an abnormal prefrontal lateralization (Gilliam, Stockman, Malek*, et al*, 2011).

Thalamus is an important modulator in the fronto-subcortico-frontal loops, but few ADHD studies have explored the thalamic nuclei. A recent study reported reduced volumes in the pulvinar and associations between reduced volumes of the lateral thalamus and symptoms of hyperactivity and increased volumes of the medial thalamus and inattentive symptoms (Ivanov, Bansal, Hao*, et al*, 2010).

In the recent years, longitudinal ADHD studies have been published in which a fully automated technique estimated cortical thickness at > 40 000 cerebral points (Shaw, Eckstrand, Sharp*, et al*, 2007; Shaw, Gilliam, Liverpool*, et al*, 2011; Shaw, Lerch, Greenstein*, et al*, 2006). This research revealed a delay of the maturation of the cerebral cortex in children with ADHD with an average of three years compared to controls (Shaw, Eckstrand, Sharp*, et al*, 2007) and a disruption of the normal developmental increase in the dimension of the right prefrontal region (Shaw, Lalonde, Lepage*, et al*, 2009). The delay of the cortical development in the ADHD cohort is most obvious in prefrontal regions. Children who improve clinically, however, have been shown to have partial normalization of cortical thickness (Shaw, Lerch, Greenstein*, et al*, 2006).

Structural MRI projects images of the brain's macroscopic anatomy, whereas data from DTI reflect the microstructure of the fibre bundles. In white matter, the lipid rich membrane

of the myelin sheath wraps the axons, restricts the diffusion of water, and forces the water molecules to move along the axons. This direction of water diffusion, and thus the microstructural property of white matter, is studied with measures of fractional anisotropy (FA) and mean diffusivity (MD). FA expresses the preference of water to diffuse in an isotropic or anisotropic manner, and is bounded by 0 and 1. In isotropic matter diffusion is similar in all directions and the FA value is 0. Tractography is another DTI modality in which white matter tracts are 3D reconstructed. It is important to be aware that, despite the beauty of such reconstructions, they are not photographs of the white matter bundles, but indirect reconstructions with many potential pitfalls and challenges (Jones & Cercignani, 2010).

Results from the DTI research of ADHD are sparse and replications of the findings are necessary. Studies of adults have reported microstructural changes in the right anterior cingulate bundle, the right superior longitudinal fasciculus and the orbitofrontal white matter (Konrad, Dielentheis, El Masri*, et al*, 2010; Makris, Buka, Biederman*, et al*, 2008). Just one combined structural MRI and DTI study of the CC in children with ADHD has been published. It reported both macro- and microscopic reduction of the isthmus in the ADHD group compared to controls (Cao, Sun, Gong*, et al*, 2010).

Magnetic Resonance Spectroscopy can be used to detect and quantify chemical compounds using the chemical shifts of metabolites separated in a spectrum. MRS is one of the newest imaging tools and comes with methodological challenges. Results from a meta-analysis of 16 spectroscopic studies that included children and adults with ADHD revealed inconsistent findings (Perlov, Philipsen, Matthies*, et al*, 2009). Most of the studies measure metabolite ratios, with the concentration of total creatine (Cre) used as an internal concentration reference. Altered ratios of choline compounds, *N*-acetyl aspartate, glutamate (Glu), glutamine (Gln) and the sum of Glu and Gln (Glx) are the most often reported findings in ADHD patients relative to controls (Perlov, Philipsen, Matthies*, et al*, 2009). The prefrontal

cortex and the basal ganglia are the regions of interest most studied. A total of seven MRS studies of adults with ADHD have, so far, been published (Colla, Ende, Alm*, et al*, 2008; Ferreira, Palmini, Bau*, et al*, 2009; Hesslinger, Thiel, Tebartz van Elst*, et al*, 2001; Kronenberg, Ende, Alm*, et al*, 2008; Perlov, Philipsen, Hesslinger*, et al*, 2007; Perlov, Tebarzt van Elst, Buechert*, et al*, 2010; Rusch, Boeker, Buchert*, et al*, 2010). In four of these studies the ACC has been examined, and a significantly reduced Glx/Cre ratio in ACC was reported in one study (Perlov, Philipsen, Hesslinger*, et al*, 2007). The inconsistent findings across the studies may be a result of sample heterogeneity and the use of different spectroscopic methodologies.

In fMRI the difference of magnetic properties between oxygenated and deoxygenated haemoglobin is used to measure the blood oxygen level-dependent (BOLD) signal. The BOLD signal varies depending on neural activity, and the method indirectly visualizes regions of altered neural activity. The spatial resolution is good in fMRI, whereas temporal resolution is poor. During task-positive fMRI, the participant performs cognitive tasks and the associated cerebral regions are identified. Tests of response inhibition are often used in fMRI studies of ADHD. Functional neuroimaging ADHD literature reveals dysfunctions in widely distributed regions, with disturbed activity in fronto-striatal and fronto-parietal circuits as the most consistent findings (Bush, Valera & Seidman, 2005; Dickstein, Bannon, Castellanos*, et al*, 2006).

Task-negative or resting state fMRI identifies correlation patterns of spontaneous brain activity during rest, the resting state functional connectivity. In ADHD the connectivity within the DMN (see section 1.3.3.) seems reduced (Fox & Greicius, 2010), which may be related to the increase of intrasubject variability in ADHD reported in neuropsychological research (Castellanos, Kelly & Milham, 2009; Sonuga-Barke & Castellanos, 2007).

Results from the different modalities of brain imaging ADHD studies confirm abnormalities in the areas and networks important in attention, response inhibition, cognitive control and emotion-related self-regulation (Bush, 2010). The three fronto-subcortico-frontal loops arising from the prefrontal cortex (the dorsolateral prefrontal, the orbitofrontal and the anterior cingulate circuits), as well as parietal and temporal regions and the cerebellum, seem to be involved in the pathophysiology of ADHD (Cherkasova & Hechtman, 2009; Vaidya & Stollstorff, 2008). The diversity of findings may reflect the intra- and interindividual variations of symptoms observed in ADHD patients.

1.6.7. Brain lateralization in ADHD

Lateralization processes may be of importance in the pathophysiology of ADHD (Roessner, Banaschewski, Uebel*, et al*, 2004). Inattention, defective response inhibition and impersistence are more commonly seen in adults with right hemisphere dysfunction than with left hemisphere dysfunction (Heilman, Voeller & Nadeau, 1991). Different studies have supported the suggestion of a right-sided fronto-striatal dysfunction in ADHD (Casey, Castellanos, Giedd*, et al*, 1997; Castellanos, Giedd, Marsh*, et al*, 1996; Depue, Burgess, Willcutt*, et al*, 2010). Two DTI studies of adults have concluded that there were microstructural changes in the right anterior cingulate bundle and the right superior longitudinal fasciculus (Konrad, Dielentheis, El Masri*, et al*, 2010; Makris, Buka, Biederman*, et al*, 2008). In subjects with ADHD, the normal asymmetrical development with a torque seems to be disturbed concerning the prefrontal anatomic lateralization, with lack of the normal increase in the right-sided prefrontal cortex (Shaw, Lalonde, Lepage*, et al*, 2009). A recent publication confirms reduced right frontal cortical thickness in children, adolescents and adults with ADHD compared to healthy controls (Almeida, Ricardo-Garcell, Prado*, et al*, 2010). The combination of an ADHD disorder and atypical right-hemisphere morphology seems to be associated with poor social comprehension in children (Miller, Miller, Bloom*, et*

al, 2006). Problems with response inhibition, inattention and impaired social comprehension in people with ADHD may be a reflection of developmental deviance and a dysfunction of the right hemisphere, but firm conclusions are not possible to draw.

1.6.8. Etiology and neurobiological models

ADHD is regarded as a neurodevelopmental disorder in which the normal cerebral development is disturbed either in utero or after birth. The causes of the developmental deviation in ADHD are still unknown, but for childhood ADHD a heritability of 76% has been found, based on a meta-analysis of many twin studies (Faraone, Perlis, Doyle*, et al*, 2005). Although the hereditability of ADHD in adults has been much less investigated, it appears to be substantially lower, with an estimation of 30% in one study (Boomsma, Saviouk, Hottenga*, et al*, 2010). The apparent difference in hereditability between childhood and adult ADHD is not explained, but methodological differences and larger variation in environmental factors in adulthood have been suggested (Franke et al., submitted).

Many candidate gene-based association studies have identified several genes of potential etiological importance, like DRD4, DRD5, SLC6A3, SNAP-25 and HTR1B (Faraone & Mick, 2010), but they seem to have modest contributions to the overall hereditability. A few genome-wide linkage and association ADHD studies have been performed, but with few firm conclusions (Franke, Neale & Faraone, 2009).

In genetic research two main models have been proposed regarding the frequency of specific sequence variations of DNA (Hoffman & State, 2010). According to the "common disease-common variant" hypothesis, common genetic polymorphisms in the population (> 5%) account for most of the risk for neurodevelopmental disorders, and risk alleles may also be present in healthy relatives. The "rare variant-common disease" hypothesis presumes that an accumulation of many different rare mutations and copy number variants (CNVs) results in neurodevelopmental disorders. Such rare, inherited CNVs may constitute the genetic

mechanisms of ADHD, possibly mediated by genes with influence on cerebral development and neuromodulation (Elia, Gai, Xie*, et al*, 2010). Recently, regulatory RNAs, including microRNAs have been identified as key modulators of brain development and gene expression, and they may also be of huge importance in the pathophysiology of neurodevelopmental disorders (Forero, van der Ven, Callaerts*, et al*, 2010).

Cerebral development is influenced by a complex interplay of genes and environmental factors, and gene-by-environment interactions are likely to be of etiologic importance in ADHD (Nigg, Nikolas & Burt, 2010; Thapar, Langley, Asherson*, et al*, 2007). The influence of different pre- and perinatal environmental factors on genetic expression may increase the susceptibility for ADHD (Mill & Petronis, 2008), and epigenetic processes may explain the development of different phenotypes from identical CNVs.

Endophenotypes, which are intermediate components between phenotype and genotype (Gottesman & Gould, 2003), may be based on neuropsychological, neuroimaging or biochemical measures. Different models of ADHD have been proposed with the description of various endophenotypes. The earliest theories developed within a neuropsychological framework. One of the first models stressed the impact of impaired behavioural inhibition on executive functions, including self-regulation of affect, motivation and arousal (Barkley, 1997). ADHD is, however, a neuropsychologically heterogeneous disorder (Seidman, 2006; Sonuga-Barke, Wiersema, van der Meere*, et al*, 2010; Willcutt, Doyle, Nigg*, et al*, 2005), which is reflected by the suggestion of multiple pathway models. The cognitive-energetic model includes problems with arousal and activation (Sergeant, 2005). From neuroimaging research and use of task-independent resting state methods, increased intrasubject variability has been suggested as an endophenotype of ADHD (Castellanos, Kelly & Milham, 2009). Other models relate to biochemical mechanisms such as the glutamatergic theory that proposes hypoactive glutamatergic cortical neurons as the main problem (Carlsson, 2001) or

the dynamic developmental behavioural theory that describes dopaminergic hypofunction as the core deficit increasing individual vulnerability to environmental factors (Sagvolden, Johansen, Aase*, et al*, 2005).

2. AIMS OF THE PROJECT

The overall aim of the project was to investigate brain lateralization, attention and cognitive control in adults with ADHD by combining behavioural measures with various MRI measures. Specific aims were to explore auditory lateralization and the ability to direct attention and exert cognitive control during DL tasks when given different types of instructions, i.e. to map the micro- and macrostructure of the CC and to measure glutamate levels in the left and right midfrontal brain regions, including the ACC.

In the three studies we predicted the following:

a. Impaired cognitive control during the FL condition in the ADHD group compared to the controls.
b. Reduction of CC size and reduction of callosal FA values in the ADHD group compared to the controls.
c. Reduction of Glu/Cre in the midfrontal region, including the ACC, in the ADHD group compared to the controls.

3. MATERIALS AND METHODS

3.1. Participants

Three separate articles constitute this thesis, where the results are from the same sample of 29 adults with ADHD and a corresponding control group. Both the adults with ADHD and the controls in study II and III were recruited from the Norwegian ADHD database (Johansson, Halleland, Halmoy*, et al*, 2008). The participants, except for the control group in study I, went through DL tests and MRI scanning. The MRI protocol consisted of structural MRI, fMRI, resting state fMRI, DTI and MRS. The actual studies used results from structural MRI, DTI and MRS. The fMRI data are not reported in this thesis.

In study I, results from DL in the 29 participants with ADHD were compared with data from 58 healthy controls that were randomly drawn from the Bergen Dichotic Listening Database to match the ADHD subjects for sex, handedness, and age (Paper I: Dramsdahl, Westerhausen, Haavik*, et al*, 2011). The Bergen Dichotic Listening Database (Hugdahl, Westerhausen, Alho*, et al*, 2009) consists of more than 1500 subjects from the age of 7 to 89, including males and females, right- and left-handers. Thus, the size of the database allows for random samplings of subjects while at the same time keeping matching on factors such as age, sex and handedness. In study II, results from structural MRI and DTI of the CC were analyzed, and the 29 adults with ADHD were compared with the results from 38 healthy controls recruited from the Medical Birth Registry of Norway matched to the ADHD sample (Paper II: Dramsdahl, Westerhausen, Haavik, *et al,* submitted). In study III, we used the results from MRS and compared measures of Glu/Cre in the midfrontal region from the 29 ADHD participants with measures from 37 of the healthy controls that participated in study II (Paper III: Dramsdahl, Ersland, Plessen, *et al,* submitted). Table 1 gives an overview of the distribution concerning sex, age, IQ and handedness.

Table 1. Distribution of sex, age, IQ and handedness

	Adults with ADHD	**Control groups**		
		Paper I (DL)	**Paper II (DTI)**	**Paper III (spectro)**
Number	29	58	37	38
Sex	15 males 14 females	30 males 28 females	14 males 23 females	15 males 23 females
Age	Mean 32.9 SD = 7.1 Range 21 – 48	16 – 30 years: 34 31 – 49 years: 24	Mean age 30.0 SD = 6.4 Range 21 – 41	Mean age 29.8 SD = 6.5 Range 21 – 41
IQ	Mean 110.6 SD = 14.3 Range 78 - 128	No information	Mean 116.7 SD = 9.2 Range 96 – 136	Mean 116.3 SD = 9.4 Range 96 – 136
Handed-ness	23 right-handed 6 left-handed	46 right-handed 12 left-handed	32 right-handed 5 left-handed	33 right-handed 5 left-handed

The Norwegian ADHD database in Bergen consists of data and materials from approximately 600 adults with ADHD and 900 healthy controls. Before inclusion in the database, all patients had been diagnosed according to ICD-10 or DSM-IV criteria for hyperkinetic disorder/ADHD by psychiatrists or psychologists. The controls in the ADHD database are recruited from the Medical Birth Registry of Norway. All participants in the three studies, with the exception of the control group in study I, were interviewed with the ADHD module of K-SADS (Kaufman, Birmaher, Brent*, et al*, 1997), which was adjusted for adults and administered by the doctoral candidate According to the symptoms reported from childhood, 19 participants had combined type, 7 had inattentive type, and 3 had hyperactive/impulsive type. Based on present symptoms, the subgroups were as follows: 19 participants with combined type, 9 with inattentive type, and 1 with hyperactive/impulsive type. The Adult ADHD Self-Report Scale (ASRS-18) (Kessler, Adler, Ames*, et al*, 2005) was used to determine current ADHD symptoms in both groups. It has two subscales: one measures inattentive symptoms and one measures hyperactive/impulsive symptoms. Audiometry was performed for the frequencies 500, 1000, 2000 and 3000 Hz prior to the DL task. The doctoral candidate interviewed the participants according to exclusion criteria, which were as follows:

- Current serious psychiatric disturbance or substance abuse
- Epilepsy or other neurological or physical disease with cognitive impairment
- A lifetime history of developmental delay
- Premature birth (before 34 weeks of gestational age)
- IQ below 70 (measured by WASI)
- Hearing deficit

Both medication naïve and medicated ADHD participants were included. Thirteen of the patients had not taken stimulants or atomoxetine during the past six months. Sixteen patients

currently took medication with stimulants (n = 15) or atomoxetine (n = 1). They were asked to discontinue their medication 48 hours prior to testing. Nine patients followed this instruction, whereas seven patients continued their medication, five of which reduced the dosage the last 48 hours.

3.2. The Dichotic Listening paradigm

In study I, the 29 adults with ADHD went through a DL paradigm consisting of the consonant-vowel (CV) stimuli /ba/, /da/, /ga/, /pa/, /ta/ and /ka/ presented in dichotic stimuli pairs (Hugdahl, Westerhausen, Alho*, et al*, 2009). Details of the testing procedure are described in paper I.

Lateralization of auditory processing is tested with DL procedure during non-forced (NF) condition. Due to the lateralization of the auditory processing to the left hemisphere, a right-ear advantage (REA) is a normal group effect, i.e. correct reports from right ear are superior to those from the left ear. The REA can be modulated by instructing the participants to focus their attention on the input to only one ear (Bryden, Munhall & Allard, 1983; Hugdahl & Andersson, 1986). In the forced-right (FR) condition, the CV syllables that are presented to the right ear are reported, and normally the number of correct reports from the right ear increase due to synergy between the top-down effect of orienting attention to the right side and the bottom-up effect favouring the right ear stimulus, caused by lateralization of speech perception. During the forced-left (FL) condition, there is a conflict between the top-down and bottom-up processes, which will call for executive, cognitive control, processes. In healthy adults, the number of correct reports from the left ear normally exceeds those of the right ear because the ability to exert cognitive control overrules the stimuli-driven, bottom-up effect (left-ear advantage; LEA). The DL procedure with the NF, FR and FL conditions tap three separate cognitive processes, viz. speech perception, orientation of attention and executive, or cognitive control (Hugdahl, Westerhausen, Alho*, et al*, 2009). Thus, the DL

forced-attention paradigm has the advantage that separate cognitive processes can be investigated within the same experimental paradigm, with minimal differences between conditions, yielding maximal experimental control.

3.3. MR scanning procedures

In study II and III, results from the MRI scanning were analyzed. ^{1}H-MR scanning was performed on a 3.0 Tesla GE Signa HDx system (General Electric Medical Systems, Milwaukee, WI) using an eight-channel head coil. T_1-weighted images were acquired using a Fast Spoiled Gradient Recall sequence (FSPGR) with the following parameters: TE = 14 ms, TR = 400 ms, inversion time = 500 ms, collecting 188 sagittal slices of 1 mm thickness (no interslice gap, scan matrix: 256 x 256, field of view of 256 x 256 mm²) to achieve a reconstructed voxel size of 1 x 1 x 1 mm.

DTI was obtained with a diffusion-weighted sequence based on a single-shot echo-planar imaging (EPI) sequence (TE = 89 ms, flip angle = 90º). Sensitizing gradients were applied in 30 directions with a weighting factor of b = 1000 s/mm² and six (unweighted) b0 images were acquired. The measurement consisted of 45 axial slices of 2.4 mm thickness (no interslice gap, scan matrix: 128 x 128, field of view of 220 x 220 mm²) and reconstructed to a voxel size of 1.72 x 1.72 x 2.4 mm.

Single-voxel point-resolved spectroscopy (PROBE-PRESS sequence) was performed with the following parameters: TE = 35 ms and TR = 1500 ms. Voxel size was 20 x 20 x 20 mm^3 localized in the left and the right midfrontal region including the dorsal ACC in each participant. A high-resolution T_1-weighted image was acquired to position the slices parallel to the line connecting the lowest edge of the splenium and the rostrum of the CC.

Further details of the scanning procedures and the pre and post-processing sequences are described in the method sections of papers I-III. The different MRI modalities are described in section 1.6.6. Neuroimaging in ADHD.

3.4. Statistical analyses

Statistical analyses were made by General Linear Model using the Statistica 8 software (http://www.statsoft.com/). The data in all three studies were analysed with an analysis of variance (ANOVA) with group (two levels: ADHD, control) as between-subject factor. In paper I and II, we also included sex (two levels: males, females) as between-subject factor. Within-subject factors were in paper I as condition (three levels: NF, FR, FL) and ear (two levels: left and right ear), in paper II as callosal subregion (four levels: genu, truncus, isthmus, splenium) and in paper III as side (two levels: left and right ACC). Significant main effects and interactions were followed-up by lower-order ANOVA, analyses of covariance (ANCOVA) or appropriate t-tests. For main and interaction effects, the effect size was determined as the proportion of explained variance (η^2), whereas for pair-wise comparisons, the effect-size was measured with Cohen's d and d' for independent or dependent measures, respectively.

In paper II, the ANOVA was repeated twice: first with uncorrected size of the CC and the second time with the CC size adjusted for brain size. The CC areas were corrected using estimates of the forebrain volume. The threshold-free cluster enhancement procedure (TFCE) (implemented in FSL; http://www.fmrib.ox.ac.uk/fsl/) was used for multiple comparisons in separate voxel-based main and interaction effect analyses of group differences in FA.

In paper III, the ratio of Glu/Cre were estimated by LCModel software version 6.2-1A (http://s-provencher.com/pages/lcmodel.shtml). For all participants, the standard deviation of the Glu/Cre was below 20%. The ratio of Glu to Cre were estimated by LCModel software

version 6.2-1A (Provencher, 2001) using a simulated basis-set for a TE of 35 ms. LCModel automatically quantifies in vivo spectra, avoiding analyses of individual peaks or use of any subjective influenced model. Estimated standard deviations (Cramér-Rao lower bounds) below 20% were accepted, which is a rough criterion for estimates of acceptable reliability (Provencher, 2011).

3.5. Ethical considerations

The participants had been included in the Norwegian ADHD biobank and had agreed to re-contact. They were contacted by telephone and received written information either per email or during the interview before the experimental situation. Written informed consents were obtained from all the participants. The study was approved by the Norwegian Regional Medical Research Ethics Committee West.

The main ethical consideration was the risk of revealing symptoms or discovering unknown pathological processes that would require follow-up. The Bergen fMRI Group has established routines for information and follow-up of any incidental clinical finding during an MR scanning session which is implemented into all studies that are run under the responsibility of the Bergen fMRI Group. All structural MRI images are therefore examined for eventual pathology by an experienced neuroradiologist, and findings are reported to the Haukeland University Hospital for eventual further MR investigation and following treatment. All participants were informed that the MRI scanning was part of a research project, and not suitable for clinical MRI assessment.

4. SUMMARY OF PAPERS

Paper I

The ability of adults with ADHD to direct their attention and exert cognitive control was tested in a forced instruction DL task. The performance of 29 adults with ADHD was compared with 58 matched controls from the Bergen DL Database. There was an overall significant right ear advantage during the NF and FR conditions with no significant group differences in these conditions, i.e. for perception lateralization and focus of attention. An expected absence of significant right ear advantage in the FL condition was revealed. However, the adults with ADHD were impaired in their ability to report the left-ear syllable during the FL instruction condition, whereas the control group showed the expected LEA in this condition. This supports the hypothesis of a deficit in cognitive control in the ADHD group.

Paper II

Reduced size of the posterior part of the CC is one of the most consistent findings in children with ADHD, while studies of adults are few. The micro- and macrostructure of the CC in adults with ADHD was investigated by means of structural MRI and DTI. The size of different subdivisions of the CC and the values of FA were compared between the 29 participants with ADHD and the 37 controls. FA values were reduced in the isthmus/splenium part of the CC in the ADHD group compared to the control group, though the size of the CC did not differ between the two groups. Our findings thus demonstrate a divergence between micro- and macrostructural measures in the CC of adults with ADHD. This contrasts with findings demonstrating callosal abnormalities in both micro- and macrostructure in children with ADHD. Our results may indicate that adults with ADHD in part have succeeded in catching-up a developmental delay of the CC, which resulted in a normalization of callosal

macrostructure in adulthood. However, microstructural differences were still present in the adults, which may reflect impaired interhemispheric connectivity in the posterior part of the CC.

Paper III

Impaired cognitive control in ADHD may be related to a prefrontal cortical glutamatergic deficit. Proton MRI with single-voxel point-resolved spectroscopy was used to measure Glu/Cre in the medial prefrontal regions in two groups: 29 adults with ADHD and 38 healthy controls. The ADHD group showed a significant reduction of Glu/Cre in the left midfrontal region including the ACC compared to the controls. A side effect with reduced Glu/Cre in the left compared to the right midfrontal region was revealed in both groups. The reduction of Glu/Cre in the left midfrontal region in the ADHD group may reflect a glutamatergic deficit in prefrontal neuronal circuitry in adults with ADHD, resulting in problems with cognitive control. Side differences showing reduced Glu/Cre in the left compared to the right midfrontal region in both groups may indicate a functional and morphological lateralization.

5. DISCUSSION AND CONSIDERATIONS

5.1. Bottom-up versus top-down regulation

Adults with ADHD performed as well as the controls during NF and FR conditions of the DL task, which reflects normal auditory lateralization and normal ability to direct attention in both groups. However, when they were given an instruction in conflict with the perceptual bottom-up process during the FL condition, they were not able to override the preference to report from the right ear. Thus, the results from the DL experiment may reflect a normal bottom-up regulation in the ADHD group, but a deficit in top-down regulation with impaired cognitive control, and failure of executive regulation. The results correspond to clinical ADHD reports of the main problems occurring in situations with distractions and the compensatory strategies that are developed to avoid conditions of cognitive conflict. The combination of a normal ability to direct attention and an impaired cognitive control may explain the confusing experiences in relation to people with ADHD. They are apparently listening to what you say, but the next moment they seem to have forgotten your instruction and, therefore, not able to carry out the task.

5.2. Auditory lateralization and interhemispheric transfer

Except for our study, there is no combined structural MRI and DTI study of the CC in adults with ADHD. The discrepancy between micro- and macrostructure of the posterior CC in adults with ADHD contrasts with findings in children demonstrating callosal abnormalities in both micro and macrostructure (Cao, Sun, Gong*, et al*, 2010). Adults with ADHD may have a partial normalization of developmental delay of interhemispheric connections.

Reduced FA values in the posterior part of the CC may reflect an abnormal lateralization, possibly with an increase of lateralization in the auditory and parietal cortices in adults with ADHD, according to the finding that there is an inverse relationship between callosal

connectivity and brain lateralization (Aboitiz & Montiel, 2003). Impaired interhemispheric transfer in the posterior part of the CC is expected to reduce the processing of left ear input and favour right ear input. This could explain the problems in the ADHD group during FL condition. It would, however, be expected to also influence the results during NF and FR conditions. Our study, with indifferences between the two groups during these conditions, does not support a theory of increased lateralization of auditory processing in people with ADHD.

5.3. Glutamate, cognitive control and thalamic filter-function

The reduced Glu/Cre in the midfrontal region measured in MRS may reflect a disturbance of glutamatergic activity. A deficit in cognitive control could be a result of a prefrontal cortical dysfunction mediated by a glutamatergic deficit. Glutamate exerts a regulatory influence on thalamus through the two striatothalamic pathways: the direct, activating pathway and the indirect, inhibitory pathway: A glutamatergic deficit in prefrontal cortex may cause a defect thalamic filter-function in addition to dysfunctions in cognitive control. The modulatory influence on thalamus regulates the sensory input to the cortex, and a defect thalamic filter-function may result in overload of stimuli to cortex and cause psychotic symptoms (Carlsson, Waters, Holm-Waters*, et al*, 2001). However, a hypoglutamatergic condition in prefrontal cortices with imbalance in the regulation of the thalamocortical transfer may explain symptoms of other psychiatric disorders. A defect thalamic filter and overwhelming sensory input to cortex could result in the ADHD symptoms of inattention, hyperactivity and impulsivity.

Tonic dopamine modulates the phasic dopamine activity through inhibitory autoreceptors, and an increase of tonic dopamine level causes a down-regulation of the phasic dopamine level (Grace, 2000). Psychostimulants immediately cause an increase of the phasic dopamine

release, but with repeated administration the steady-state level of tonic dopamine concentration increases and the release of phasic dopamine is reduced through activation of the inhibitory autoreceptors. In ADHD, low tonic extracellular dopamine may up-regulate the phasic spike-dependent dopamine. Moderate white noise seems to exert a positive effect on the cognitive performance in children with ADHD (Soderlund, Sikstrom & Smart, 2007). This phenomenon is explained with the Moderate Brain Arousal model and the induction of stochastic resonance in the dopaminergic system necessary for optimal cognitive performance (Sikstrom & Soderlund, 2007). A dopaminergic imbalance causes hypersensitivity to environmental stimuli, but also increased threshhold for induction of stochastic resonance. In the daily environment of our modern society, the auditory input is likely to exceed the moderate level of beneficial noise. The Moderate Brain Arousal model fits with the theory of a defect thalamic filter, and both mechanisms may have a synergetic influence on vulnerability to excess of sensory input in ADHD.

5.4. Neuromodulation and compensatory mechanisms

Visual input can be regulated by closing the eyes, but we are not able to physically shut our ears. We are almost constantly exposed to auditory stimuli, and the thalamic filter function may be of particular importance as a modulator regarding auditory stimuli. Increased callosal transfer of auditory stimuli due to impaired filtering of auditory input to the left ear, may trigger compensatory mechanisms. Research on neural reorganization after sensory deprivation has revealed striking neuroplastic changes (Merabet & Pascual-Leone, 2010), and it is likely that increased sensory input triggers adaptive structural and functional mechanisms, as well. Increased callosal transfer of auditory stimuli due to defective thalamic filter function may cause reduced posterior callosal microstructure. Impaired interhemispheric transfer of auditory stimuli protects the primary auditory cortex in the left temporal lobe from

overwhelming auditory input, at least from the left ear. Other compensatory mechanisms may have developed to protect input from the right ear, and thus explain a normal behavioural response during NF and FR conditions.

5.5. Research and assessment of persistent ADHD

Research on persistent ADHD has many challenges. Results from research of children and adolescents have to be interpreted in light of knowledge we have about normal cerebral maturation and individual differences in brain developmental trajectories. In an adult group these possible biases are eliminated, but the differentiation between pathophysiological processes and compensatory mechanisms due to neuromodulation may be a larger challenge in research on adults with ADHD.

The lack of standardized diagnostic assessment of adults with ADHD is another problem. The classification of ADHD was conceptualized as a disorder of children, and ADHD has just recently been accepted as a disorder in adults, which is reflected in the scant number of diagnostic assessments developed for adults. K-SADS is a validated semi-structured diagnostic interview for children, but in research of adults the ADHD module in an adapted version is often used in the assessment. There is, however, no standardized adult version of the ADHD-module of K-SADS, and the interview is validated in children, not in adults. Recently, the first structured diagnostic interview for adult ADHD, DIVA (Kooij & Francken, 2010), was translated to Norwegian (http://www.divacenter.eu/DIVA.aspx). There are no validation studies of DIVA yet.

Many adults with ADHD symptoms had not been diagnosed in childhood, and a retrospective diagnosis has several challenges. It is difficult to remember one's behaviour from before the age of 7 and nearly impossible to report an objective description of behaviour

at that time. Information from parents or others is often difficult to obtain, in particular information about preschool age.

Even though ADHD has become accepted as a credible adult diagnosis, there are controversies about the criteria. First, the age of onset criterion according to DSM-IV and ICD-10 has been debated. Impairments due to symptoms are often reported later than the age of seven, even if the symptoms were present earlier (Applegate, Lahey, Hart*, et al*, 1997). In particular, the inattentive symptoms are easily masked. Adults with late-onset ADHD seem to report similar degrees of impairment as those with onset before the age of 7 (Faraone, Biederman, Spencer*, et al*, 2006). Second, the question about residual categories and subthreshold diagnoses has been discussed (Bell, 2011; McGough & Barkley, 2004). Third, conceptualizing ADHD through a categorical framework as in the diagnostic manuals has drawbacks, so the use of a dimensional or continuum model has been suggested with emphasis on impairments and need for treatment (Haslam, Williams, Prior*, et al*, 2006). The age and situation inappropriate aspects of the symptoms are emphasized in the diagnostic manuals, but represent challenges. There is no exact division between immature behaviour and symptoms of ADHD; normal behaviour in younger ages may be defined as symptoms of ADHD later on depending on demands and tolerability in the environment. The symptoms in adults often differ from those in children. Though the hyperactive and impulsive symptoms seem to decline, the inattentive symptoms persist or worsen (Faraone, Biederman & Mick, 2006). The expression of symptoms may change because of environmental conditions, and secondary problems and symptoms may represent confounding factors. These diagnostic challenges have consequences both in clinical practice and in research.

5.6. Synthesis

Neurochemical disturbances in ADHD may be a result of genetic and environmental factors and may cause dysfunctions in the cerebral development. Some developmental disturbances may result in delay of maturation, whereas others may cause deviance from normal development. For instance, imbalance in neurotransmitter systems, such as the glutamatergic-catecholaminergic networks may result in a spectrum of various endophenotypes, being observed as different structural, functional and neuropsychological abnormalities or impairments. Developmental disturbances may explain the diversity of findings in different modalities of ADHD research. Glutamatergic dysfunction may affect top-down regulation of cognitive control and emotion-related self-regulation, as well as the bottom-up perceptual influence of both physiological and external stimuli. The thalamus and the subthalamic nuclei have been considered relay stations, but research has revealed that both nuclei are modulators and have a regulatory influence on cognitive, affective, motivational and motor functions (Llinas & Steriade, 2006; Temel, Blokland, Steinbusch*, et al*, 2005). A combination of impaired regulation from prefrontal cortex and a dysfunctional thalamic and/or subthalamic modulation of sensory input to the brain may explain the symptoms of inattention, hyperactivity and impulsivity. Late cerebral maturation and partial normalization may give relief of symptoms during adolescence. Compensatory strategies and benefit of the brain's neuroplasticity may also contribute to improved function in adulthood.

A glutamatergic dysfunction may be a result of epigenetic factors and disturbances in the gene-by-environment interactions, which can have serious consequences. Impairments of the glutamatergic functions as neurotransmitter and neuromodulator during development of the brain may have a strong impact on cerebral maturation. It is perhaps this that results in the diversity of brain abnormalities revealed in ADHD research. A hypoglutamatergic condition is also likely to cause imbalance in other transmitter systems like the dopaminergic circuitry.

Disturbances in the neurochemical homeostasis in the fronto-striato-thalamo-frontal loops could result in a variety of phenotypes classified in different neurodevelopmental disorders.

5.7. Clinical implications

Our finding of impaired cognitive control in ADHD was restricted to an adult group. It is, however, likely that the examined participants had similar cognitive control dysfunctions in childhood. Our finding, thus, emphasizes the importance of intervening as soon as inattention or hyperactivity/impulsivity starts interfering with function. Currently, an ADHD diagnosis is required before necessary supportive interventions in school are started. Some of the pedagogical approaches in Norwegian schools during the last decades may have had a negative influence on children who need structure and external support because they have reduced ability in cognitive control and self-regulation. In addition, the environment at the higher educational level or at work may not be optimal for people with ADHD. Society in general, and the social security system in particular, may have unrealistic expectations. Our society is well regulated and depends on disciplined and reliable people who are able to follow instructions, finish tasks and cooperate with colleagues. The information we have about the devastating consequences of impaired cognitive control and self-regulation and/or excess of cortical sensorial input emphasizes the need for individually tailored treatment and early and adjusted interventions.

6. CONCLUSIONS

In summary, our results show that adults with ADHD have a normal lateralization of auditory processing and ability to direct attention in a non-conflicting situation, whereas they showed less ability to exert cognitive control in a conflict situation between a perceptual bottom-up process and a top-down driven instruction. The combination of normal ability to direct attention, together with impaired ability to exert cognitive control, may explain how children and adults with ADHD are able to be highly focused and concentrated in tasks of low effort demand, or high in interest, or in one-to-one conversations, but lose focus in classroom settings or in social settings with many people. They seem to have the ability to concentrate, so it may seem as though it is a question of willpower if they do not focus or finish their tasks. In reality, they may have a handicap when exposed to multiple sensory stimuli, in that they lack both the ability to maintain focus and a normal filter mechanism that relays the most urgent sensorial input.

An altered microstructure in the posterior part of the CC may reflect a delayed and only partial maturation of the CC in adults with ADHD, or it may be interpreted as a compensatory mechanism with reduced interhemispheric transfer due to a defective thalamic filter.

Glutamate uptake seems to be modulated through a diversity of mechanisms, and a glutamatergic dysfunction may be present in various neuropsychiatric disorders as a result of different genetic, epigenetic, or environmental factors (Danbolt, 2001). The consequences of a glutamatergic disturbance may be:

- Imbalance in the dopaminergic circuits
- Impaired cognitive control
- Impaired thalamic filter and excess of sensory input to cortex
- Widespread morphological and functional brain abnormalities

Like other neurodevelopmental disorders ADHD may have a glutamatergic dysfunction with impact on cerebral maturation.

7. LIMITATIONS

Clinical research can be subject to recruitment biases, and participation in a study like ours could indicate special motivation or resources. Some of the included ADHD patients described effective compensatory strategies developed during adolescence, like rigorous structure of daily life or adapted learning styles. These coping mechanisms may be rooted in neurobiological modulation due to adaptive neuroplasticity, and abnormal findings are thus not necessarily a result of the disorder. On the other hand, our sample may be a subgroup with a more "pure" ADHD without comorbidities, although this would mean that they may not be representative for the whole group of adults with ADHD.

Another limitation is the inclusion of individuals from all the three ADHD subgroups, which was the result of each group being too small to be analyzed separately. This implicates that our ADHD sample is phenotypic heterogeneous.

Our objective was to compare behavioural results with different MRI measures. The ADHD participants and the healthy controls each underwent DL tests and a common MRI protocol. The results from DL during forced instructions have been replicated in many studies, and LEA during the FL condition in healthy adults has been repeatedly reported, as well as failure of LEA in several clinical groups (see Westerhausen & Hugdahl, 2010). Although representative for other variables, most of the men in the control group did not show an expected LEA during the FL condition, whereas the women showed a more expected pattern. As we had access to DL data from the Bergen DL Database, we were able to compare the DL results from the ADHD group with the results from matched individuals from the latter database, to increase our statistical power (one participant with ADHD was matched with two participants from the database). In an attempt to explain why the men in the control group had REA during FL condition, we recruited additional male students, checked all

equipment including the DL programme, and controlled our data. Yet, we did not find any obvious explanation why the male controls were not representative concerning DL. In papers II and III, the control group recruited through the Medical Birth Registry of Norway was used. These conditions represent a potential weakness of the study and may restrict the interpretation of our results.

8. FUTURE PERSPECTIVES

The importance of longitudinal studies of psychiatric disorders is often emphasized, and comparison between various clinical groups is necessary. The diagnostic classifications according to DSM-IV or ICD-10 are commonly used in research, but this is a coarse differentiation of groups, even when the ADHD subgroup classifications are used. One challenge is to identify ADHD specific endophenotypes, since none of the symptoms are pathognomonic for this condition. More interdisiplinary ADHD research on the glutamatergic pathways and their interaction with other transmitter systems may be a key to better understanding ADHD.

Patients with ADHD often struggle with a reduced quality of life and problems that are out of therapeutic range. Increased knowledge about the neurobiological basis of ADHD and susceptibility factors could contribute to the development of preventive interventions and more individually tailored treatments. Although we still do not know the causes of ADHD, we know that many children and adults suffer from symptoms of inattention, excessive impulsiveness and hyperactivity. Research has confirmed what we know from observation and experience: too much stimuli and an unquiet environment places people with ADHD at a disadvantage, possibly because of the combination of deficits in cognitive control and a defective thalamic filter function. Nonetheless, our western society increasingly demands that we handle multiple simultaneous perceptions. We know that both children and adults benefit from quiet surroundings, and there are promising results regarding cognitive training. If this knowledge is taken into account, it could be helpful to many of those who suffer from ADHD, although we still have limited knowledge of its neurobiological underpinnings.

9. ERRATA

Page 21: 4th sentence:

"… divides the CC into five subregions: rostrum, genu, truncus or body, isthmus and splenium (Witelson, 1989)."

should be

"…divides the CC into seven subregions: rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus and splenium (Witelson, 1989)."

Page 48: 1st paragraph; 5th sentence:

"… instructions, i.e. to map the micro- and macrostructure of the CC…"

should be

"…instructions, to map the micro- and macrostructure of the CC…".

Page 49: 1st paragraph; 9th sentence:

"…results from 38 healthy controls…"

should be

"…results from 37 healthy controls…".

Page 49: 1st paragraph; 13th sentence:

"…with measures from 37 of the healthy controls that participated in study II…"

should be

"…with measures from 38 healthy controls of whom 37 participated in study II…".

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