NEUROCOGNITIVE DEVELOPMENT FROM CHILDHOOD TO ADULTHOOD:

Structural brain maturation and its relationships with higher-order cognitive functions

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AMENDMENTS

After the submission of my dissertation to the Faculty of Social Sciences November 30, 2009, paper I has been printed in *Cerebral Cortex*, while paper II has been published online in advance of being printed in *Human Brain Mapping*. The content of the two papers have undergone no changes in the proof process, and the current versions referred to above therefore replace the manuscripts originally included in the dissertation. A revised version of paper III has been accepted for publication in *Neuropsychologia*.

Blindern, Oslo, May 5, 2010

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GENERAL SUMMARY

The overarching goal of this project, *Neurocognitive Development*, has been to contribute to a deeper understanding of normal brain maturation from childhood to adulthood and how this relates to cognition. Although the structural maturation of the brain is beginning to be better characterized by magnetic resonance imaging (MRI) studies, and cognitive development has received much attention for decades, studies on the relationships between different MRI measures and between such indices of neuroanatomy and cognitive functions in development are still scarce. In three papers, the present thesis examines structural brain maturation and its relationships with behavioral performance indices of so-called higher-order cognitive functions, more specifically general intellectual abilities and different selected executive functions. The thesis demonstrates mostly nonlinear age-related cortical thinning, mainly linear white matter (WM) volume increases and decelerating changes in diffusion tensor imaging (DTI) parameters in the age-range 8-30 years. All three classes of measures were sensitive to brain maturation and showed unique associations with age. Furthermore, the results indicate that the apparent cortical thinning in adolescence cannot be explained by WM maturation in subjacent regions as measured by volumetry or DTI. The thesis further demonstrates age-independent relationships between cognitive functions and MRI and DTI indices, respectively, and also indicates associations between brain maturation and cognitive functions. Independently of age, both verbal and performance intellectual abilities were related to DTI indices of WM microstructure, predominantly in the left hemisphere. Further, verbal, but not performance abilities, were associated with WM microstructure maturational differences in widespread regions. This complements previous findings of the significance of cortical maturation for general intellectual abilities. Furthermore, using a battery of six tasks proposed to index the executive functions working memory updating, inhibition and shifting, the thesis demonstrates negative age-independent relationships between cortical thickness and performance on two tasks thought to reflect updating and inhibition function, respectively. Also, individual performance differences on two tasks assumed to index inhibition ability were associated with differences in estimated cortical maturation in posterior brain regions, but no such effects were found in the prefrontal cortices. In sum, this thesis contributes to the description and understanding of brain maturation and how this relates to, and likely is important for, the development of selected higher-order cognitive functions.

LIST OF PAPERS

I. Tamnes, C.K., Østby, Y., Fjell, A.M., Westlye, L.T., Due-Tønnessen, P. & Walhovd, K.B. (2010). Brain maturation in adolescence and young adulthood: Regional age-related changes in cortical thickness and white matter volume and microstructure. *Cerebral Cortex, 20*, 534-548.

II. Tamnes, C.K., Østby, Y., Walhovd, K.B., Westlye, L.T., Due-Tønnessen, P. & Fjell, A.M. (In press). Intellectual abilities and white matter microstructure in development: A Diffusion tensor imaging study. *Human Brain Mapping.*

III. Tamnes, C.K., Østby, Y., Walhovd, K.B., Westlye, L.T., Due-Tønnessen, P. & Fjell, A.M. (In submission). Neuroanatomical correlates of executive functions in children and adolescents: A magnetic resonance imaging (MRI) study of cortical thickness.

INTRODUCTION

It has been argued that the partnership between developmental psychology and neuroscience traditionally has been ambivalent (Segalowitz, 2007). Especially with neuroscience advancements, such as improvements in structural and functional brain imaging methods and genetic studies being more available, we can however now expect a more fruitful blending of the two fields in the future (Segalowitz, 2007). The central topic of the current thesis, namely the delineation of age-related changes in macromorphological brain characteristics and indices of white matter (WM) microstructure, and how these relate to each other and to cognitive functions, reflects one approach to such a blending. Childhood, adolescence and even young adulthood are periods of ongoing structural brain development and concurrent improvements in many cognitive functions. The overarching goal of the current thesis is to improve the characterization of structural brain maturation from childhood to adulthood and how these changes are related to general intellectual abilities and selected executive functions.

WHAT IS KNOWN ABOUT STRUCTURAL BRAIN MATURATION?

In vivo neuroimaging provides a unique window for non-invasively studying the living human brain and has given us new insights into aspects of brain anatomy and function. MRI is likely the most prominent of all brain scanning methods for both structural and functional imaging. With its lack of ionizing radiation, it allows safe scanning of healthy children and adolescents.

Early anatomical brain development is extremely dynamic with robust, but highly differentiated volume increases in different tissue classes (Knickmeyer, et al., 2008). However, there is still a limited amount of imaging data available regarding infancy and early childhood. In infants, the contrast pattern observed with MRI T1 images is typically opposite to what is seen in adults; the cortex is lighter than the underlying WM. After a period in which gray matter (GM) and WM are not well differentiated, this likely switches to the "adult" pattern around 12 months of age (Lenroot & Giedd, 2007). The total volume of the brain rapidly increases throughout the first years of life and then stays relatively stable. By the age of 6 years, the total size of the brain has been estimated to be approximately 90% of its adult size (Giedd, 2004; Reiss, Abrams, Singer, Ross, & Denckla, 1996). Marked maturational changes do however continue in late childhood, adolescence and even into adulthood. GM

volume reductions appear counterweighted by WM increases, thus resulting in a relatively stable total volume (Rivkin, 2000).

Cortical thickness and volume appear to follow an inverted U-shaped maturational course with a period of initial childhood increase until about 7-10 years of age and a subsequent adolescent decline (Giedd, 2004; Gogtay, et al., 2004; Shaw, et al., 2008). Studies so far indicate that the adolescent decline in thickness is followed by a period with slower decline and the more stable cortical dimensions of adulthood (Shaw, et al., 2008; Sowell, et al., 2003). There is also, at least to a certain degree, regional variance, with different areas of the cortex maturing with different trajectories and at different times. It has been suggested that cortical regions with simple laminar architecture, 3-layeres allocortex, tend to show simpler developmental trajectories (linear), whereas regions with complex architecture, 6-layered isocortex, typically have more complex trajectories (cubic). Transition cortex tends to have relatively simple developmental trajectories (mix of linear and quadratic). Interestingly, it seems that cortical maturation not only mirror the cytoarchitecture, but possibly also the evolutionary history of the cerebral cortex (Shaw, et al., 2008). Within isocortex, peak cortical thickness is likely attained in the primary sensory and motor areas before adjacent secondary and associations areas. Shaw et al. (2008) have pointed out that, in general, cortical maturation progress in a posterior-to-anterior and peripheral-to-central fashion.

Subcortical GM structures generally also seem to follow an inverted U-shaped maturational course (Giedd, et al., 1996; Jernigan, Trauner, Hesselink, & Tallal, 1991; Sowell, Trauner, Gamst, & Jernigan, 2002; Toga, Thompson, & Sowell, 2006). Substantial heterogeneity in maturational trajectories between different structures has however also been described. Østby et al. (2009) found volume reductions in most subcortical structures and cerebellar GM in adolescence, while hippocampus and amygdala showed slight volume increases and thalamic volume did not show any age effects. The observed effects of age are however typically weaker for subcortical than for cortical volumes (Sowell, et al., 2002; Østby, et al., 2009).

In contrast to the apparently mostly nonlinear maturational course of cortical and subcortical GM, with reductions in thickness and volume in adolescence, cerebral WM volume has been shown to increase in a more linear manner throughout late childhood and adolescence, with only minor regional differences between the different lobes (Giedd, 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Paus, et al., 2001; Sowell, et al., 2002). This volume

increase seems to extend until approximately middle age and then decline (Allen, Bruss, Brown, & Damasio, 2005; Bartzokis, et al., 2003; Walhovd, et al., 2005; Walhovd, et al., In press).

WM consists largely of myelinated long-distance axonal projections of neurons and is important for integration of activity between different brain areas, which is pivotal to all types of cognitive processing. DTI, a novel type of MRI technique, indirectly provides *in vivo* information about tissue microstructure by utilizing random diffusion of water molecules in the brain (Le Bihan, 2003). Fractional anisotropy (FA) is a frequently used intravoxel metric characterizing directional coherence of water displacement (Pierpaoli & Basser, 1996). Additionally, average magnitude of water diffusion, mean diffusivity (MD), as well as axial diffusivity (AD), defined as the principal diffusion eigenvalue, and radial diffusivity (RD), the mean of the second and third eigenvalues, can be measured. Both WM volume and FA have been suggested to index WM integrity. However, DTI derived indices and WM volume have recently been found to be only weakly to moderately related in a middle-aged sample, thus indicating that these two methods provide us with complementary information about WM (Fjell, et al., 2008). Interestingly, DTI studies suggest that, despite little myelination, the fundamental diffusion hierarchy in the brain's large fiber tracts seems to be established very early in life and even before birth (Kasprian, et al., 2008). However, decelerating age-related increases in FA and decreases in MD during childhood, adolescence, and early adulthood have consistently been found (Cascio, Gerig, & Piven, 2007; Lebel, Walker, et al., 2008). A recent life-span study combining WM volumetry and DTI, supported the notion of protracted WM volume growth into the sixth decade of life, while DTI indices plateaued early in the fourth decade (Westlye, et al., In press-b). This further indicates the complementary nature of these two types of WM measures. Example individual MRI and DTI images at various stages of development from the NIH MRI Study of Normal Brain Development are shown in Figure 1. Note that the major fiber tracts are clearly visible in the FA maps already in infancy.

In summary, *in vivo* structural imaging studies indicate sustained regional cortical thinning, subcortical GM volume reductions in most structures, WM volume increases and changes in DTI indices of WM microstructure in late childhood, throughout adolescence and even into young adulthood. However, there has been a lack of studies that can help delineate the dynamics of development of the brain's constituents in more detail. Although a complex interplay between cortical and WM maturation is assumed, this has rarely been investigated in

a detailed manner, and little is known about the relationships between different structural measures in development. In addition to yielding a more complete description of age-related changes across different indexes, this could provide some indirect information on possible neurobiological processes underpinning structural brain maturation. In order to appreciate how MRI studies may help in this task, we need to consider neurodevelopment at the molecular level.

WHAT ARE THE UNDERLYING CHANGES AT THE NEUROBIOLOGICAL LEVEL IN DEVELOPMENT?

Brain development is a dynamic process of regressive and progressive changes. At a lower level of analysis than possible with structural neuroimaging, human brain development can be characterized by four major stages: (1) neuronal proliferation, (2) migration of neurons, (3) organization of the neuronal circuitry, including for instance synaptogenesis, dentritic and axonal arborization and pruning, and (4) myelination (Goldstein, et al., 2009; Volpe, 2008).

Lenroot and Giedd (2007) have given a good overview of these processes. Following primary neurulation, the formation of the neural tube that is usually complete by 3-4 weeks of gestation, proliferation occurs for neurons primarily in the third and fourth months of gestation and for glia cells through the first year of life. Migration, when neurons move from their origins in the ventricular zone to specific sites in the central nervous system (CNS) along radial glia fibers, occurs during the third through fifth months of gestation. The major events associated with neural circuitry organization include proper alignment, orientation and layering of cortical neurons, dendritic and axonal differentiation, synaptogenesis, synaptic elimination in terms of cell death (apoptosis) and selective synapse elimination, and glial proliferation and differentiation (Goldstein, et al., 2009). Synaptogenesis is thus followed by a period of massive loss of connections referred to as synaptic pruning. Organization of the neural circuitry, as well as myelination of axons begin before birth and likely extend well into postnatal life (Lenroot & Giedd, 2007).

Synaptic elimination has been shown to continue into adolescence in both non-human primates and humans (Bourgeois & Rakic, 1993; Huttenlocher & Dabholkar, 1997), although the scarcity of postmortem tissue has not permitted a detailed exploration of the time course of this process. This reduction in number of synapses is likely accompanied by a reduction in

neuropil as well as number of glial cells (Paus, Keshavan, & Giedd, 2008). Histological studies have also demonstrated that although myelination is most pronounced during the first postnatal year, it likely continues well into the second and even third decade of life (Benes, 1989; Benes, Turtle, Khan, & Farol, 1994; Yakovlev & Lecours, 1967). At a neurobiological level, both pruning and myelination have thus been shown in adolescence.

As discusses below, the relationships between the neurobiological events occurring in development and age-related changes observed with MRI, such as apparent cortical thinning, WM volume increases and diffusivity changes in adolescence, are not well understood. Multi-modal imaging and combination of *in vivo* and *ex vivo* methods might however increase our understanding of the relations between structural and neurobiological brain maturation. Studies of age-related changes in behavioral performance measures indexing various cognitive functions may further increase our understanding of the functional significance of these changes.

WHAT IS CHARACTERISTIC OF COGNITIVE DEVELOPMENT FROM CHILDHOOD TO YOUNG ADULTHOOD?

At the most general level, several of the classical theories of cognitive development (e.g. Piaget's approach) have emphasized discontinuity in development, describing development as progressing through qualitatively distinct stages. In contrast, within the information processing approach that dominates the field of neurocognitive development, the focus has primarily been on the continuity of development, studying cognitive development as a continuous and gradual process in which the same core abilities or functions become quantitatively more efficient or refined over time. The continuity-discontinuity issue is however as discussed by Lerner (2002) more complex than this, as statements or theories about the character of intraindividual development may involve change along three dimensions; descriptive continuity versus discontinuity, explanatory continuity versus discontinuity and the quantitative versus qualitative character of one's description and explanation. Taking a pragmatic and integrative perspective, cognitive development likely involves a range of processes that encompass both continuity and discontinuity (Case, 1987; Gathercole, 1998).

Rudimentary forms of many cognitive abilities are likely present in young children. Most cognitive abilities do however improve steeply in childhood and further, at a slower rate, in adolescence (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Segalowitz & Davies, 2004; Waber, et al., 2007). Such nonlinear age-related trajectories are typically found for raw score performance on a wide variety of neuropsychological tests assessing intellectual level, verbal abilities, visuospatial skills, different aspects of memory and executive functions. Linear performance improvements have however been found for some tasks assessing more basic information processing (Waber, et al., 2007).

Developmental studies suggest that executive functions have a protracted developmental course relative to many other cognitive functions (Huizinga, Dolan, & van der Molen, 2006). Executive functions can be defined as general purpose control mechanisms that modulate the operation of other cognitive processes and thus regulate the dynamics of cognition and action (Miyake, Friedman, et al., 2000). The issue of whether executive functions should be conceptualized as unitary in the sense that they reflect the same core mechanism or abilities, or non-unitary, i.e. including distinct sub-functions or sub-components is still a topic of theoretical discussion, although a common contemporary view is that they show both unity and diversity at a cognitive level (Miyake, Friedman, et al., 2000). Three often-postulated sub-functions are working memory updating, inhibition and shifting. Updating concerns the ability to monitor task-relevant incoming information and revise representations held in working memory to accommodate new input. Inhibition refers to the ability to deliberately inhibit dominant, automatic or prepotent responses when necessary, while shifting can be conceptualized as the ability to flexibly switch back and fourth between multiple tasks, operations or mental sets (Miyake, Friedman, et al., 2000). Performance on tasks thought to index updating, inhibition and shifting have been shown to improve throughout childhood and into adolescence. Different developmental trajectories have also been observed for different executive functions (Huizinga, et al., 2006).

The above description of some gross features of cognitive development is short, but should suffice to make it clear that variability across domains and modalities can not only be found in brain development, it is also characteristic of behavioral and cognitive age-related changes. The question largely remains, however, of to what extent systematic relationships can be identified across brain and behavior changes in development.

HOW IS NEUROANATOMY AND COGNITION RELATED IN DEVELOPMENT?

A reasonable hypothesis is that cognitive development is supported by the ongoing structural maturation of the brain. As described, late childhood and adolescence is characterized by structural cerebral maturation, most pronounced for cortical and WM measures, and development of cognitive functions, perhaps especially functions labeled as higher-order or executive in nature. Brain maturation processes thus overlap with the timing of normal development of cognitive functions. Although these processes at least to a certain degree mirror each other in time, relatively little is known about the specific relationships between them.

Generally, it is thought that brain regions associated with more basic cognitive functions mature first, followed by areas involved in more complex functions and top-down control of cognition and behavior. The sequence in which the cortex matures, typically measured in terms of estimated peak cortical thickness, volume or density, at least to a certain extent seems to parallel cognitive milestones in development; with motor and sensory regions subserving relatively basic functions maturing earliest, followed by parietal and temporal association cortices associated with basic language skill and spatial attention, and prefrontal and lateral temporal cortices thought to be involved in higher-order cognitive control functions maturing last (Casey, Tottenham, Liston, & Durston, 2005; Gogtay, et al., 2004). A roughly similar regional sequence of WM microstructure maturation has also been suggested by DTI studies, with areas with fronto-temporal connections maturing more slowly than other regions (Lebel, Walker, et al., 2008). There are a number of examples from pathological conditions, e.g. fetal alcohol spectrum disorders and cerebral palsy that reduced cognitive function is related to deviant brain development. However, the evidence for direct relationships between brain and cognitive changes in normal development is still scarce. Some correlations between structural indices and behavioral performance measures of cognitive functions in development have been reported (Casey, et al., 2005; Durston & Casey, 2006; Liston, et al., 2006), although few studies have directly explored links between brain maturation trajectories and cognitive functions.

In a seminal paper, Shaw et al. (2006) demonstrated that the structural maturation of cerebral cortex is related to general intellectual abilities. The results suggested that children at different levels of intellectual abilities had different maturational trajectories of cortical thickness, primarily in frontal regions. More specifically, children with high intelligence scores were

characterized by an accelerated and prolonged phase of increase in cortical thickness, as well as a more rapid cortical thinning in adolescence. Sowell et al. (2004) found that gain in verbal intelligence was correlated with cortical thinning in the left hemisphere in lateral dorsofrontal and lateral parietal regions, while a similar expected right hemisphere association with gain in performance intelligence was not found. Intellectual abilities are likely supported by multiple interconnected cortical regions, and a reasonable assumption is thus that the integrity of the connecting fibers is important. Associations between DTI indices of WM microstructure and measures of intelligence have been found in healthy adults and in samples with various neurological abnormalities, genetic disorders and developmental disorders, but there are limited data available on such links in healthy children and adolescents. Schmithorst et al. (2005) have demonstrated age-independent positive associations between FA and intellectual abilities bilaterally in WM association areas in children, but little is known about how WM microstructure maturation is related to intellectual abilities.

Executive functions are also thought to depend on distributed networks, more specifically encompassing both frontal and posterior (mainly parietal) associative cortices, as well as subcortical structures and WM pathways (Collette, Hogge, Salmon, & Van der Linden, 2006). Prefrontal cortex is possibly especially important and it has been proposed that these regions provide a modulatory influence on basic processes subserved by more posterior brain regions (Knight, Staines, Swick, & Chao, 1999). The protracted development of executive functions has thus been tentatively attributed to the assumed relatively late maturation of the prefrontal cortex. Little is however known about the relationships between different executive functions and structural properties of the brain in development. To our knowledge, no studies have directly investigated the relationships between development of different executive functions and structural brain maturation.

MAIN RESEARCH OBJECTIVES

PAPER I

In the first paper, we aimed to characterize age-related changes in cortical thickness, regional WM volume and DTI indices of WM microstructure from childhood to adulthood in terms of trajectory, regional variance, magnitude and timing. The main aim was however to explore

the relationships between different cerebral structural indices in development. Investigating these different measures in the same sample might give a more complete understanding of brain maturation, by allowing direct comparisons of age-related changes in different indices. A principal reason for studying brain development in a multimodal perspective was however that this indirectly can inform us on the neurobiological underpinnings of structural age-related changes and in particular on the events underlying the apparent cortical thinning in adolescence.

PAPER II

The main objective was to test how general cognitive abilities, i.e. verbal abilities and performance abilities, are associated with age-related changes in DTI indices of WM microstructure. Additionally, we investigated age-independent associations between these intellectual abilities and WM microstructure in participants aged 8-30 years. Behavioral measures of general intellectual abilities were explored since these may indicate the cognitive significance of brain maturation at a gross level. General intellectual abilities have previously been studied in relation to development of cortical thickness, whereas the relation with age-related changes in DTI indices of microstructural WM characteristics is still unknown. Given the proposed distributed nature of the neural networks underlying general intellectual abilities, we expected that age-related changes in DTI indices of the integrity of the connections between the different regions in these widespread networks would be associated with and important for gross intellectual abilities.

PAPER III

The general aim was to directly investigate relationships between behavioral performance indices of different selected executive functions and cortical thickness in development. In addition to exploring age-independent relationships, a central objective was to investigate whether cortical maturation, and more specifically maturation of the prefrontal cortex, was associated with levels of executive functioning. As opposed to general intellectual abilities, the relationship between different executive functions and development of cortical thickness has to our knowledge never before been thoroughly investigated. Furthermore, executive functions are conceptualized as more specific processes that those involved in general

intellectual functions, so it appeared reasonable to investigate possible specific relationships with different areas of the cortex (e.g. “the frontal hypothesis”).

METHODS

DESIGN

In the present thesis, we used a cross-sectional research design, comparing participants at different ages at roughly the same point in time. Generally, the main problem associated with this kind of design is that one can not be certain whether differences between the different age groups (cohorts) are reflections of age-related changes or of the groups not being identical to begin with. That is, different cohorts may originally differ on other characteristics than age as a result of growing up in different historical periods. Such differences might for instance be related to nutrition, medical care, school reforms or degree of stimulation from the environment. To ensure some degree of comparability, one might match the participants on important variables other than age, although one can never fully avoid the confounding of age and cohort (Lerner, 2002). The cohort effect problem with cross-sectional designs is however probably not a major problem in the present thesis, since the age-span of the participants was relatively limited in this context. A more serious concern is the possible loss of sensitivity due to large individual variation in brain anatomy and cognitive performance. Importantly, inferences regarding developmental trajectories do not necessarily follow from the current studies, as there are many serious challenges involved in drawing inferences about longitudinal processes from cross-sectional studies (Kraemer, Yesavage, Taylor, & Kupfer, 2000). Thus, the results from the present thesis need to be verified with longitudinal data.

A longitudinal research design can avoid the fundamental cohort problem of cross-sectional designs and increase sensitivity, by repeatedly testing the same participants at more than one point in time and mapping individual maturational and developmental trajectories. However, unique characteristics of willing participants, selective drop out and participants getting accustomed to testing are serious challenges with such an approach (Lerner, 2002). Some of the problems involved in the cross-sectional and longitudinal designs can possibly be resolved through the use of a sequential design that combines features of both the other approaches.

Follow-up assessments of the included participants in the present studies, as well as inclusion of new participants, are underway.

PARTICIPANTS

The data material included in the different papers in this thesis consisted of the same or highly overlapping samples. In papers I and II, the sample was drawn from the first wave of two ongoing research projects at the Center for the Study of Human Cognition, University of Oslo; *Neurocognitive Development* (participants 8-19 years old) and *Cognition and Plasticity through the Life-Span* (participants 20-30 years old). In paper III only participants in *Neurocognitive Development* with complete datasets on a battery of executive function tasks were included as there were variations in the tasks employed in the two projects. In papers I and II, 168 participants were included, while in paper III, the dataset consisted of 98 participants. The participants were evenly distributed with regards to age and sex.

Volunteers were recruited by newspaper advertisements and through local schools and work places. Screening interviews were conduced with parent/guardian of participants aged 8-19 years and with all participants aged 16-30 years. Participants were required to be in the age range 8-30 years, right-handed, speak Norwegian fluently, have normal or corrected-to-normal vision and hearing, not be under psychiatric treatment, not use medicines known to affect CNS functioning, including psychoactive drugs, and not have injury or disease known to affect CNS function, including neurological or psychiatric illness, or serious head injury. All subjects' MR scans were examined by a specialist in neuroradiology and required to be deemed free of significant anomalies. Detailed descriptions of the samples are given in the papers.

The samples in the present studies showed relatively high general cognitive function and may not be seen as representative of the full range of individual differences in development. This is a caveat of most studies of this type aiming to describe healthy development. Further, in the present samples, there were also some minor differences between different age-groups in general intellectual abilities, with the youngest participants on average having slightly lower estimated full scale IQ and larger variability than older participants. One might speculate that this was caused by an age-related recruitment bias and more specifically by different

motivation factors to participate for children and adolescents. However, given the relatively small magnitude of these differences, it is unlikely that they had large effects on the results.

MRI imaging, cognitive testing and electrophysiological recordings took place in three separate sessions. In addition, in *Neurocognitive Development*, hand x-rays for determination of biological age and blood samples for hormone analysis were conducted. In the present thesis, only imaging data and behavioral tests of general intellectual abilities and selected executive functions were used and are described below.

MRI

MRI is an imaging technique based on the principles of nuclear magnetic resonance that detects proton signals from water molecules and is used to produce high quality images of the internal structure and function of the body and obtain information about contrast between different anatomical structures (Bjørnerud & Nordlid, 2002; Westbrook, Roth, & Talbot, 2005). MRI is based on the absorption and emission of energy in the radio frequency range of the electromagnetic spectrum. The key to MRI is the structure and vast amount of water in the human body, including the brain. About 70% of the body is made up of water and most types of tissue contain between 60 and 80% water, with the exception of bone (20-25%). The most abundant atom in the body is hydrogen, which is most commonly found in molecules of water containing two hydrogen atoms and one oxygen atom and fat where hydrogen atoms are arranged with carbon and oxygen atoms. The principles of MRI rely on the spinning motion of specific nuclei present in biological tissue, which creates a magnetic field, called magnetic moment. So called MR active nuclei are characterized by their tendency to align their axis of rotation to an applied magnetic field. The hydrogen nucleus is the MR active nucleus most commonly used. Normally, the protons' magnetic moments are randomly oriented, which yields a net magnetization of zero. In short, first, MRI creates a steady state of magnetism by placing the body in a steady magnetic field. This induction of an external magnetic field aligns the magnetic moments of the protons either parallel or anti-parallel to this field. Second, the body is stimulated with electromagnetic radiation to change the steady-state orientation of protons. The electromagnetic radiation is sent in short pulses, often called a radio frequency pulse. The term resonance is used because the radio frequency pulse must be of a certain frequency to be able to affect the protons. Third, the electromagnetic radiation is stopped and emission of energy is detected and registered by a coil placed over the head of the

participant. This oscillating signal voltage over time is the MR signal. Lastly, the MR signals are used to construct images.

A relatively novel MRI modality/method, called DTI, has emerged, allowing a new *in vivo* technique for studying the large WM fiber bundles containing the neuronal projections connecting the different functional regions of the brain (Johansen-Berg & Behrens, 2009; Mori, 2007). DTI is a technique in which diffusion of water molecules is measured in a series of different spatial directions, from which the shape and orientation of the diffusion ellipsoid is determined at each image pixel by fitting the measurement results to the ellipsoid describing the average local cytoarchitecture. The diffusion process is a reflection of thermal Brownian motion. Diffusion is affected and limited by the local tissue microstructure that the water molecules are surrounded by. If there are no constrains on the diffusion, it is said to be Gaussian (normally distributed) and isotropic. If there are structures present, these will limit the diffusion of water molecules in certain directions and the diffusion is said to be anisotropic. The six parameters required to mathematically describe an ellipsoid are three eigenvalues that define the shape and three eigenvectors that define the orientation. DTI produces images of biological tissue weighted with the local microstructural characteristics of water diffusion.

MRI ACQUISITION AND ANALYSIS

All imaging data were acquired using a 12-channel head coil on the same 1.5-T Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany) at Rikshospitalet University Hospital. The pulse sequences used for morphometric analyses were two repeated 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequences. For diffusion-weighted imaging (DWI), a single-shot twice-refocused spin echo echo planar imaging pulse sequence with 30 diffusion sensitized gradient directions was used. Additionally, a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence and a T2 space sequence were used to aid neurological examination. For detailed descriptions of the sequences and analysis, it is referred to the method sections in the papers. Example individual MRI and DTI images from two representative participants from the current project are shown in Figure 2.

For morphometric analyses in papers I and III, we used the software package FreeSurfer, developed at the A. Martinos Center for Biomedical Imaging at Harvard Medical School. The cortical surface was reconstructed to measure thickness at each surface location, or vertex, using a semiautomated approach described elsewhere (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Salat, et al., 2004; Segonne, et al., 2004; Segonne, Grimson, & Fischl, 2005). In short, thickness measurements were obtained by reconstructing representations of the GM-WM boundary and the cortical surface and then calculating the distance between those surfaces at each point across the cortical mantle. This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortion, resulting in a measure of cortical thickness for each person at each point on the reconstructed surface. Additionally, in paper I the cortical surface was parcellated according to procedures described by Fischl et al. (2004). The cortical surface was divided into 33 different gyral-based areas in each hemisphere, and mean thickness was calculated for each label.

Based on the cortical parcellation, regional WM volume was calculated by a newly developed algorithm (Fjell, et al., 2008; Salat, et al., 2009). Each gyral WM voxel was labeled according to the surface label of the nearest cortical voxel, with a 5-mm distance limit. This yielded 33 WM volumes in each hemisphere, corresponding to the 33 cortical areas, as well as the volume of deep WM, consisting of all WM voxels not assigned a cortical label.

The surface reconstruction and segmentation procedures are run automatically, but require supervision of the accuracy of the spatial registration and tissue segmentations. The types of errors that most often prompted user intervention in the current datasets were insufficient removal of non-brain tissue (typically vessels adjacent to the cortex, especially in the orbitofrontal cortices). Also, in presence of local artifacts, small parts of WM may rarely be mistakenly segmented as GM, thus obscuring the GM/WM boundary. All volumes were visually checked for accuracy, and the types of segmentation errors mentioned were manually corrected by trained operators. Minor manual edits were performed on most subjects, usually restricted to removal of vessels orbitofrontally included within the cortical boundary. However, it has been shown that user interventions are not necessary to obtain reliable segmentations across field strength, scanner upgrade and manufacturer (Han, et al., 2006). For both cortical thickness and regional WM volume measures, one might discuss whether

individual differences in intracranial volume (ICV) should be corrected for or not. This was not done in the present thesis, since the main aim was to analyze the regional relationship between cortical thickness and WM volume measures in development and correcting for ICV would likely take out some of the effects of age on these measures.

DTI processing and analyses were done using two different approaches. In paper I, we used a combination of FreeSurfer and FSL, while in paper II we used FSL and TBSS, which are developed by the FMRIB analysis group at the University of Oxford. In paper I, a novel approach was employed, which in the same way as the WM volume segmentation, allowed us to compare cortical thickness and WM properties in anatomically adjacent areas, minimizing inaccuracies and measurements biases due to intermodal and intersubject registration. The procedure has previously been described and validated by Fjell et al. (2008). For details, it is referred to this reference and paper I. In short, diffusion metrics are sampled from overlapping voxels from probabilistically defined major WM tracts (Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005) and FreeSurfer WM regions. The approach thus yields average DTI measures from 34 regions in each hemisphere, corresponding to the WM regions, but restricted to areas within these regions presumably containing major WM tracts. In addition to FA, MD was computed as the mean of all three eigenvalues, RD as the mean of the second and third eigenvalues and AD was defined as the principal diffusion eigenvalue. Note that this nomenclature pertains to the eigenvalues of the diffusion tensor and not necessarily to the underlying brain tissue (Wheeler-Kingshott & Cercignani, 2009).

In the other approach, used in paper II, DTI analyses and tensor calculations were done using FSL (Smith, et al., 2004) and TBSS (Smith, et al., 2006). Briefly, after preprocessing, all individuals' FA volumes were skeletonised and transformed into a common space. Next, a mean FA volume of all participants was generated and thinned to create a mean FA skeleton representing the centers of all common tracts. The mean skeleton was thresholded at FA > .25. Individual FA values were then warped onto this mean skeleton mask by searching perpendicular from the skeleton for maximum FA values. Similar warping and analyses were employed on MD, RD and AD skeletons sampled from voxels with FA > .25. The resulting tract invariant skeletons for each participant were fed into voxel-wise analyses. Additionally, binary masks were created based on the probabilistic JHU WM tractography atlas (Mori, et al., 2005). We chose seven major WM tracts in each hemisphere and two commissural tracts as tracts of interest (TOIs). Voxels intersecting both the skeleton and the TOIs were used in

regional analyses. The TBSS method likely to a certain degree solves the issues of cross-subject data alignment and the arbitrariness of the choice of spatial smoothing extent by employing a carefully tuned non-linear registration followed by a projection onto the alignment-invariant skeleton (Smith, et al., 2006). However, as discussed below, in using this method, diffusion data are only sampled from the center of each pathway, excluding more peripheral and possibly very interesting regions. Illustrations of some of the neuroimaging data from the different analysis approaches used in the present thesis are shown in Figure 3.

COGNITIVE ASSESSMENT

In the present thesis, data are reported from cognitive tasks measuring general intellectual abilities and six tasks hypothesized to index primarily one of the three target executive functions of working memory updating, inhibition or shifting.

General intellectual abilities were assessed by Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). WASI was chosen specifically in this study because it enabled use of the same test measures across the entire age range included. Verbal IQ was estimated from the subtests Vocabulary and Similarities, and performance IQ was estimated from the subtests Matrix reasoning and Block design. Full scale IQ was estimated from all four subtests. In short, in the Vocabulary task words are presented that the participant defines or explains and this is thought to mainly be a measure of expressive vocabulary, verbal knowledge and information. In Similarities, pairs of words are presented and the participant explains the similarity between the objects or concepts. The resulting measure is thought to reflect mainly verbal concept formation and abstract verbal reasoning ability. Matrix reasoning consists of incomplete patterns that the participant completes by selecting from different possible options and this task is thought to be a measure of nonverbal fluid reasoning. In Block design, the participant is asked to quickly replicate geometrical patterns using two-colored cubes and this subtest likely taps abilities related to spatial visualization, visual-motor coordination, abstract conceptualization and perceptual organization. All four tasks are also thought to be good measures of general intellectual abilities (Wechsler, 1999). Age-related changes in performance on all four sub-tests are shown in Figure 4. As there are no Norwegian norms available for WASI, the original U.S. material was used when describing the general cognitive abilities of the samples. However, for the analyses on the associations between intellectual abilities and WM microstructure and WM microstructure maturation in paper II,

z-transformed raw scores not adjusted for age were used. Here, general verbal and performance abilities were investigated separately.

Executive functions were assessed by a battery consisting of four tasks adopted from Miyake et al. (2000), namely Keep track, Letter memory, Antisaccade and Plus minus, and two tasks from the D-KEFS battery (Delis, Kaplan, & Kramer, 2001), namely Stroop and Trail making. Some modifications to the tasks adopted from Miyake et al. were done to make them more appropriate for the age-range of the participants in the present project. Further adjustments were made after pilot testing of the tasks. The D-KEFS tasks were administered in the standardized way. Detailed descriptions of the tasks are given in paper III. These six tasks are considered to predominantly index three frequently postulated executive functions; working memory updating (Keep track and Letter memory), inhibition (Antisaccade and Stroop) and shifting (Plus minus and Trail making). Z-transformed raw or ratio scores were used when investigating the associations between task performance and cortical thickness in paper III.

STATISTICAL ANALYSES

For descriptions of the statistical analyses performed, it is referred to the methods sections in the papers. Generally, statistical comparisons of surface maps were generated by computing general linear models (GLMs) within the FreeSurfer software package of the effects of each variable on thickness at each vertex. Voxel-based global DTI analyses were carried out using permutation based inference (Nichols & Holmes, 2002) as implemented in the randomize tool within FSL. Regional cortical, WM volume and DTI analyses were generally carried out using multiple regressions in SPSS.

In papers I and II, exponential fitting equations of the form $x = b_1 + b_2 \times e^{(-age/t)}$, where b_1 is the estimated value at the asymptote, b_2 is the difference between the b_1 value and the estimated value at age zero, and t is a time constant indicating rate of development, were employed in order to describe estimated age-trajectories. Further, in papers II and III, interaction effects between age and cognitive measures on DTI indices and cortical thickness, respectively, were tested using interaction terms of the form behavioral measure × age.

Corrections for multiple comparisons were performed as described in the papers by different methods, including Bonferroni corrections, using a p-value threshold corresponding to a

commonly used criterion of false discovery rate (FDR), and by means of cluster analyses as implemented with Z Monte Carlo simulations within the FreeSurfer software package (Hagler, Saygin, & Sereno, 2006) and Threshold Free Cluster Enhancement (TFCE) in FSL (Smith & Nichols, 2009).

ETHICAL CONSIDERATIONS

The studies were carried out in accordance with the Declaration of Helsinki (1964). Both *Neurocognitive Development* and *Cognition and Plasticity through the Life-Span (under the name "Biologiske Prediktorer for Hukommelse")* were approved by a Norwegian regional committee for research ethics (REK-Sør) and the Norwegian Social Science Data Services (NSD). The studies were undertaken after written informed consent was obtained from all participants older than 12 years of age and from the parents/guardians of volunteers under 18 years of age. Oral informed consent was given by participants under 12 years of age.

SUMMARY OF PAPERS

PAPER I: BRAIN MATURATION IN ADOLESCENCE AND YOUNG ADULTHOOD: REGIONAL AGE-RELATED CHANGES IN CORTICAL THICKNESS AND WHITE MATTER VOLUME AND MICROSTRUCTURE

The development of cortical gray matter, white matter (WM) volume and WM microstructure in adolescence is beginning to be fairly well characterized by structural magnetic resonance imaging (sMRI) and diffusion tensor imaging (DTI) studies. However, these aspects of brain development have rarely been investigated concurrently in the same sample and hence the relations between them are not understood. We delineated the age-related changes in cortical thickness, regional WM volume and diffusion characteristics and investigated the relationships between these properties of brain development. One hundred and sixty-eight healthy participants aged 8-30 years underwent sMRI and DTI. The results showed regional age-related cortical thinning, WM volume increases and changes in diffusion parameters. Cortical thickness was the most strongly age-related parameter. All classes of measures showed unique associations with age. The results indicate that cortical thinning in adolescence cannot be explained by WM maturation in underlying regions as measured by volumetry or DTI. Moderate associations between cortical thickness and both volume and diffusion parameters in underlying WM regions were also found, although the relationships were not strong. It is concluded that none of the measures are redundant, and that the integration of the 3 will yield a more complete understanding of brain maturation.

PAPER II: INTELLECTUAL ABILITIES AND WHITE MATTER MICROSTRUCTURE IN DEVELOPMENT: A DIFFUSION TENSOR IMAGING STUDY

Higher-order cognitive functions are supported by distributed networks of multiple interconnected cortical and subcortical regions. Efficient cognitive processing depends on fast communication between these regions, so the integrity of the connections between them is of great importance. It is known that white matter (WM) development is a slow process, continuing into adulthood. While the significance of cortical maturation for intellectual development is described, less is known about the relationships between cognitive functions and maturation of WM connectivity. In this cross-sectional study, we investigated the associations between intellectual abilities and development of diffusion tensor imaging (DTI) derived measures of WM microstructure in 168 right-handed participants aged 8-30 years. Independently of age and sex, both verbal and performance abilities were positively related to fractional anisotropy (FA) and negatively related to mean diffusivity (MD) and radial diffusivity (RD), predominantly in the left hemisphere. Further, verbal, but not performance abilities, were associated with developmental differences in DTI indices in widespread regions in both hemispheres. Regional analyses showed relations with both FA and RD bilaterally in the anterior thalamic radiation and the cortico-spinal tract and in the right superior longitudinal fasciculus. In these regions, our results suggest that participants with high verbal abilities may show accelerated WM development in late childhood and a subsequent earlier developmental plateau, in contrast to a steadier and prolonged development in participants with average verbal abilities. Longitudinal data are needed to validate these interpretations. The results provide insight into the neurobiological underpinnings of intellectual development.

PAPER III: NEUROANATOMICAL CORRELATES OF EXECUTIVE FUNCTIONS IN CHILDREN AND ADOLESCENTS: A MAGNETIC RESONANCE IMAGING (MRI) STUDY OF CORTICAL THICKNESS

A range of cognitive abilities improves in childhood and adolescence. It has been proposed that the protracted development of executive functions is related to the relatively late maturation of the prefrontal cortex. However, this has rarely been directly investigated. In this cross-sectional study, 98 healthy children and adolescents (8-19 years old) were tested with six tasks considered to index three frequently postulated executive functions; updating (Keep track and Letter memory), inhibition (Antisaccade and Stroop) and shifting (Plus minus and Trail making). Task performance was then related to magnetic resonance imaging (MRI) measures of cortical thickness. The correlations between performance on the different tasks did not indicate any clear organization of the measures in the domains updating, inhibition and shifting. Performance on the tasks Keep track, Letter memory and Antisaccade correlated negatively with cortical thickness, probably related to the common influence by age. Independently of the effects of age, performance on the Keep track task was associated with thinner cortex bilaterally in clusters encompassing parietal and frontal regions, including areas in the left inferior frontal gyrus, while performance on the Antisaccade task was associated with thinner cortex bilaterally in occipital and parietal regions. Levels of performance on the Antisaccade and Stroop tasks were related to estimated rates of cortical maturation in posterior brain regions, but not in the prefrontal cortex. Thus, the results did not directly support the notion that individual differences in maturation of prefrontal cortex are associated with individual differences in levels of executive functioning.

GENERAL DISCUSSION

Developmental psychology aims to describe changes that occur as we age and explore what causes or drives these changes. The field of neurocognitive development is still a young endeavor, and most of the research is concerned with delineating developmental trajectories and describing relationships between different variables in development. It is however generally assumed that both typical and atypical development are products of an interaction between both nature and nurture (Lerner, 2002), although relatively little is know about the specifics of how they interact. Brain maturation and the development of cognitive functions represent central areas of research for cognitive neuroscience and developmental psychology. Studying children and adolescents are motivated both by an interest in these age groups per se, as well as by interest in the developmental processes and the nature of the end products of development (Schaffer, 1996). Investigations of relationships between different structural indices may for instance give indirect information on neurobiological processes involved in brain maturation, while studies on links between neuroanatomy and cognitive functions in development might inform us about the functional organization of the brain.

DISCUSSION OF MAIN FINDINGS

In paper I, a cross-sectional investigation of structural brain maturation in 168 healthy participants aged 8-30 years, the results showed sustained regional age-related cortical thinning, WM volume increases and changes in diffusion parameters in WM. Consistent with previous research (Cascio, et al., 2007), the relatively novel DTI approach employed showed anisotropy increase and overall diffusion decrease with age in major tracts in most WM regions. Analyses of the eigenvalues suggested that the observed FA increase and MD decrease were mainly driven by a decrease in RD, but that reduction in AD also contributes to the MD decrease to some extent. This is largely consistent with previous research showing overall diffusion decrease with age, although the degree of age-related reduction in AD varies somewhat across studies, and increases in AD have also infrequently been reported (Ashtari, et al., 2007). In general, cortical thickness and DTI indices showed nonlinear age-related changes, with the greatest change occurring in late childhood and adolescence, while linear WM volume increases with age were found in the majority of the regions.

Further, the magnitude of regional age-related changes in cortical thickness, WM volume and DTI indices were characterized in terms of absolute and percentage change from 8 to 30 years, while regional timing of developmental changes were estimated in terms of age at 90 % of peak. Comparing the timing estimates with previous research (Shaw, et al., 2008), we found some indications of a regional relationship between timing of peak cortical thickness in late childhood and timing of cortical thinning in late adolescence and early adulthood, although this needs to be investigated directly. The monotonous trajectory of cortical thinning beginning in late childhood is not particularly well suited for timing estimates. Ongoing work indicates that intracortical T1 signal intensity can be used as a measure to shed light on the question of when cortical maturation ends (Westlye, et al., In press-a). The estimates of developmental timing also suggested that FA and MD in major tracts in the frontal and temporal lobes reach their developmental plateau later than in other regions. This supports previous findings on the maturation of WM microstructure (Lebel, Walker, et al., 2008), and further show this pattern with a more differentiated regional approach. A recent report estimating age at maximum FA on a voxel-by-voxel basis in the tract skeleton (Westlye, et al., In press-b), does however suggest that concluding that WM microstructure in frontal and temporal regions mature relatively late compared to other regions might be too simplistic. Here, no clear regional pattern was observed, although central areas seemed to peak earlier than areas closer to the surface. This pattern of a central-to-peripheral age-gradient in FA mirrors what is known about the sequence of early myelogenesis starting in central areas in fetal life, with more peripheral and intracortical connections being the last to become myelinated (Barkovich, Kjos, Jackson, & Norman, 1988; de Graaf-Peters & Hadders-Algra, 2006). The changes observed here in later childhood, adolescence and young adulthood suggest that FA possibly is a sensitive measure to additional and protracted development of myelin in later years.

The main novelty of the study reported in paper I was however the investigation of the relationships between different MRI derived indices of neuroanatomy in development. This has never before been thoroughly investigated, and our analysis approach allowed us to explore the relationships between cortical thickness and subjacent WM volume and DTI parameters in a regional manner. The results from regional multiple regression with age predicted from cortical thickness, WM volume and FA as simultaneous independent variables, summarized and illustrated in Figure 5, indicated that all three classes of measures were sensitive to brain maturation, and had unique associations with age. Cortical thickness was

however the most strongly age-related parameter. This observation indicates that different maturational processes are at play in different tissue classes simultaneously. Importantly, the results also indicated that cortical thinning in adolescence cannot be well explained by WM maturation in subjacent areas as measured by volumetry or DTI in major tracts. Although, as discussed below, *in vivo* neuroimaging studies are unable to directly inform on the neurobiological processes underpinning structural brain maturation, this finding may implicate that proliferation of myelin into the periphery of the neuropil is not the main factor accounting for the observed cortical thinning during adolescence. Furthermore, in short, moderate associations between cortical thickness and both volume and diffusion parameters in underlying regions in development were also found, as illustrated in Figure 6. The results did however not indicate a regionally tightly linked pattern of age-related changes in different measures.

In the other two papers, we investigated relationships between structural brain indices and higher-order cognitive functions in development. More specifically, in paper II we explored the relationships between general intellectual abilities and DTI indices of WM microstructure in the tract skeleton, and in paper III we investigated the associations between behavioral performance indices of different selected executive functions and cortical thickness. In both papers, we analyzed age-independent associations and associations between performance levels and maturational rates.

One general hypothesis about the relationship between brain maturation and cognitive development is that cognitive functions become more fine-tuned and efficient with development with the elimination of an overabundance of synapses and the strengthening of relevant connections (Casey, et al., 2005). This widely accepted hypothesis for normal developmental changes is also referred to as progressive specialization, focalization or the focal network model (Berl, Vaidya, & Gaillard, 2006). The fine-tuning of cognitive functions is likely a result of both largely genetically determined maturational processes and experience-driven changes. Neuronal and synaptic pruning and strengthening of connections through myelination, increases in axonal diameter and other processes, such as in the case of long-term potentiation (LTP), may thus result in more efficient cognitive processing by increasing signal to noise in the system (Durston, et al., 2006). Indirectly supporting the idea of fine-tuning of cognitive functions, a combined longitudinal and cross-sectional functional MRI (fMRI) study, found evidence for a developmental shift from diffuse to more focal

recruitment of cortical regions during performance of a cognitive control task (Durston, et al., 2006). Interestingly, several functional imaging studies on aging indicate an association between increasing age and a dedifferentiation of and more widespread brain activation during various cognitive tasks. These changes in aging are also typically associated poorer performance (Reuter-Lorenz & Lustig, 2005).

Despite several observations in support of the focal network model, results from other studies, for instance observed increases in fMRI signal extent in development during verbal fluency or working memory tasks, are not explained by this model. An alternative hypothesis, the regionally weighted model, proposes that the same areas of a distributed network are involved across age, but that the degree of engagement of each region changes during development (Berl, et al., 2006). For instance, a positive association between children's response inhibition ability and posterior activation has been observed, in contrast to adults that consistently activated a network comprising both posterior and prefrontal regions (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). Further, Rubia et al. (2000) have proposed that maturation of the frontal cortex may be achieved either by a continuous enhancement of physiological and cognitive function or alternatively by a discontinuous transition from a functionally adequate but immature system to the more efficient adult network. In the latter, the transition is described as discontinuous because the immature network may have only a few regions in common with the mature network. In sum, the relationship between brain maturation and cognitive development is likely a complex one, involving a range of different maturational processes in different tissue classes simultaneously, and both continuous and discontinuous developmental changes.

In order to increase our understanding of brain-cognition relationships in development, more studies directly testing such associations are needed. In paper II, the same 168 participants aged 8-30 years as in paper I were included. The results showed that, independently of age, both general verbal and performance abilities, as assessed by raw scores from the four WASI tests, were related to DTI indices in tract skeleton voxels, indicating a relationship between WM microstructure and general cognitive functions in late childhood, adolescence and young adulthood. As expected, positive relations with FA and negative relations with MD and RD were found across age. A striking hemisphere asymmetry was however notable, with stronger and more widespread associations seen in the left hemisphere, surprisingly not only for verbal, but also performance abilities. As discussed in more detail in paper II, the results for

general verbal abilities expand on previous studies showing associations between more specific verbal abilities and DTI indices in the left hemisphere, while the results for performance abilities were unexpected since common tests used to measure these abilities are assumed to particularly rely upon the right parietal region.

Further, the results suggested that children and adolescents with different levels of verbal abilities, but not with different performance abilities, may have different maturational trajectories of WM microstructure in widespread areas in both hemispheres. Here, regional analyses showed relations between verbal abilities and age-related changes in both FA and RD bilaterally in the anterior thalamic radiation and the cortico-spinal tract and in the right superior longitudinal fasciculus. The results suggested that children with high verbal abilities show an initial accelerated WM microstructure maturation, before reaching a plateau, indicating earlier development of neuroanatomical connectivity. In contrast, participants with average verbal abilities may show a steadier and more protracted developmental pattern, with longer time used to reach the plateau or continued development in early adulthood. Importantly, these results implies that intellectual development is related to WM microstructure maturation, which complements previous findings on the significance of cortical maturation for general intellectual abilities (Shaw, et al., 2006). The extensive nature of both the age-independent associations and the associations between verbal abilities and WM maturation are also consistent with distributed models of higher-order cognitive functions like the Parieto-Frontal Integration Theory (Colom, et al., 2009; Jung & Haier, 2007). This model proposes a neural network that underpins individual differences in intellectual abilities that includes association cortices within parietal and frontal regions and WM structures linking these areas.

In paper III we investigated the relationships between behavioral performance indices of different executive functions and cortical thickness in development. 98 healthy children and adolescents aged 8-19 years completed a battery of six neuropsychological tasks considered to predominantly index three frequently postulated executive functions; updating (Keep track and Letter memory), inhibition (Antisaccade and Stroop) and shifting (Plus minus and Trail making). Thus, we aimed to explore relationships between structural properties of the brain and more specific cognitive functions than in the previous paper. However, the pattern of moderate correlations between the different tasks did not yield any empirical support in favor of structuring the tasks according to the updating, inhibition and shifting categories or

pursuing further statistical analysis for this purpose. Instead, individual task measures from Keep track, Letter memory, Antisaccade and Stroop were used for further analyses. Plus minus and Trail making were not subjected to further analyses since these measures were not related to age. These results indicate that more research focused on developing a set of reliable (and valid) executive function tasks suited for both children and adolescents and on the organization of executive functions at different ages is needed.

Concerning the relationships between the executive functions indices and cortical thickness, first, the results showed concurrent age-related performance improvements on Keep track, Letter memory and Antisaccade and age-related cortical thinning in widespread regions. This indicates that development of these cognitive functions is mirrored by the cortical maturation occurring in the same period. However, these associations cannot be used to infer a direct causal relationship since the common influence of age likely explains most of these associations. Second, independently of age, performance on the Keep track task was negatively associated with cortical thickness bilaterally in parietal and frontal areas around the central sulcus, but also encompassing areas in the left inferior frontal gyrus and superior medial parietal (paracentral) areas in the right hemisphere. Independently of age, performance on the Antisaccade task was negatively associated with cortical thickness bilaterally in occipital and parietal regions, including the parieto-occipital cortices, cuneus, pericalcarine and the lingual cortices. Third, individual differences in task performance on Antisaccade and Stroop were associated with differences in cortical maturation in posterior brain regions. For unknown reasons, these effects were however in opposite directions for the two task measures.

Importantly, and somewhat surprisingly, no effects of the interaction terms executive function measures × age were observed in the frontal lobes. No direct evidence was thus found supporting the notion that individual differences in the structural maturation of the prefrontal cortex is related to individual differences in levels of executive functioning. This is discussed further in paper III and below.

REGIONAL SPECIFICITY OF ASSOCIATIONS

An important general question pertains to what degree associations between behavioral performance indices of different cognitive functions and MRI indices of brain structure and

microstructure in development are global, as in encompassing large areas of the brain, or regionally specific. Likely, some of the neurobiological processes underlying structural brain maturation are fairly undifferentiated across the brain. However, although large complex neural networks likely are important for so-called higher-order cognitive functions such as intellectual abilities and executive functions, some cortical regions and fiber tracts are nonetheless thought to be especially involved in such cognitive processes.

In paper II, our results suggested relatively widespread associations between intellectual abilities and DTI indices of WM microstructure and between general verbal abilities and WM microstructure maturation. The fairly extensive and regionally unspecific nature of these associations are likely a function of both the sensitivity benefits of the cluster enhancement method employed coupled with high statistical sensitivity from a quite large sample of 168 participants, and a reflection of neuroanatomically unspecific and distributed relationships between general cognitive abilities and neural connectivity. Note however that a striking hemisphere asymmetry for the age-independent associations and some regional specificity in the relationships were also found.

In contrast, in paper III, we found fewer and more regionally confined associations between performance indices of executive functions and cortical thickness independently of age and estimated cortical maturation, respectively. This could be due to a range of factors, including possibly lower reliability of the tasks employed for assessment of executive functions than the WASI tasks used to assess intellectual abilities, fewer participants included (98 vs. 168) and thus lower statistical power, a different cluster method employed, and possibly more specific and/or weaker relationships between executive functions and neuroanatomy. Importantly, DTI indices and cortical thickness are also very different types of indexes of neuroanatomy and could possibly be very differently associated with cognitive functions. Comparisons of the results from papers II and III should therefore be done with great caution, particularly since different numbers of participants were included and different methods were employed. Furthermore, threshold levels used for determination of statistical significance are sensitive to statistical power and should therefore be complemented with descriptions of uncorrected results and effect sizes.

NEUROBIOLOGICAL MEANING OF IMAGING PARAMETERS

The neurobiological events causing cortical thickness, WM volumetric and diffusivity changes in brain tissue in development are not fully understood. As discussed in more detail in paper I, two central neurobiological events that may be underlying cortical thinning in adolescence are (1) pruning in the form of use-dependent selective synapse elimination together with associated changes, and (2) events occurring at the interface between cortex and WM, such as proliferation of myelin into the periphery of the cortical neuropil, causing an apparent cortical thinning (Shaw, et al., 2008). This thesis indicates that cortical thinning in adolescence cannot be explained by WM maturation in underlying regions as measured by volumetry or DTI in major fiber tracts, and thus in our opinion indirectly gives some information relevant for this discussion. However, no simple unitary neurobiological explanation of the apparent pronounced cortical thinning in adolescence can be expected.

A number of neurobiological factors also influence DTI indices (Beaulieu, 2009) and the relative roles of these factors are possibly also age-dependent. In the present thesis, relatively small or no age-related changes and associations with intellectual abilities were observed for AD. RD likely therefore account for most of the effects on both FA and MD. As discussed in paper II, a tentative link between RD and myelin has previously been proposed. However, DTI parameters are sensitive to general diffusion properties and are not selective markers of specific neurobiological properties. Factors other than myelin, such as the within-voxel directional coherence, the local density of fibers, size of axons and partial voluming, are also important. It has thus been argued that hypothesized differences in myelination are perhaps too hastily considered as an explanation for age-related differences in DTI parameters, and likely also associations between these indices and cognitive abilities, to the exclusion of other possible factors (Paus, 2010). In sum, it should thus be stressed that the specific neurobiological meaning of both morphometric and DTI parameters is unclear.

ESTABLISHING BRAIN-COGNITION RELATIONSHIPS IN DEVELOPMENT

Beyond the specificity limitations associated with imaging indices of neuroanatomy, as well as questions regarding the construct validity of tasks used to index cognitive functions, characterization of brain-cognition relationships in developing populations poses severe challenges related to analysis and interpretation. Specific associations are not straightforward to establish, since simple associations between two such moving targets are likely explained

by the common influence of age. Such associations therefore simply demonstrate concurrent age-related changes, but cannot be used to infer a direct relationship. For instance, using such an approach, age-related improvements in intellectual abilities in childhood and adolescence would in all likelihood be correlated with the participant's height, although no one would claim a causal relationship between the two.

This simplest way of testing more specific associations between imaging indices of neuroanatomy and measures of cognitive functions in developmental populations is to statistically control for the effects of age. This is however not optimal in samples with wide age-ranges, as age is really the main variable of interest. Although this approach is best suited for relatively age-homogeneous samples, it does give indications of brain-cognition relationships across the age-span studied. A third analysis approach is to explore brain-cognition associations separately for different age-groups either with little age-variance within each group or with controlling for the effects of age within each group. Such an approach can be used in order to explore for instance differences in the relationships between neuroanatomy and cognitive abilities between children, adolescents and young adults (Shaw, et al., 2006). This strategy was however not employed in any of the main analyses in the present thesis, as it substantially reduces statistical power as well as the possibility of describing the dynamics of development. Forth, interaction terms of the type behavioral measure × age (or alternatively; indices of neuroanatomy × age) can be employed in order to explore relationships between individual differences in cognitive abilities and brain maturational differences. Here, the associations between the interaction terms and the indices of neuroanatomy are tested, while controlling for the main effects of age on the latter. In the current thesis, this approach was employed in papers II and III. A challenge with this type of analysis is however that the interpretation of the results is more complicated than in the case of for instance age-independent associations. Furthermore, the relationships between age and cognitive abilities and neuroanatomy, respectively, are often nonlinear. This could possibly be dealt with by additionally controlling for the effects of age^2 and possibly age^3, although this would further complicate the interpretation of the results.

Longitudinal data additionally yields the possibility of estimating individual change in both structural MRI indices and cognitive performance (Sowell, et al., 2004). This can likely greatly increase sensitivity to developmental processes, as well as specific associations

between brain maturation and cognitive development, although it is still problematic to infer causal relationships between the two.

Besides structural brain imaging, links between brain maturation and development of cognitive functions should also be explored with functional imaging such as fMRI and electrophysiological measures. Interestingly, studies suggest that event-related potentials (ERPs) associated with frontal brain regions and executive functions, such as error-related negativity (ERN), show developmental amplitude changes well into adolescence (Davies, Segalowitz, & Gavin, 2004; Segalowitz & Davies, 2004; Wiersema, van der Meere, & Roeyers, 2007). Such measures could therefore for instance be explored as possible mediating factors between neuroanatomical maturation and development of complex behaviors. Electrophysiological data, including data on ERN, have been collected in the first wave of the current project and analyses are underway.

APPLIED RELEVANCE

The issues of the current thesis are important beyond scientific curiosity and theoretical interest pertaining to children, development and neuroanatomy-cognition relationships per se. For instance, the neurobiological maturation of the brain will influence functional imaging results (Berl, et al., 2006), and techniques such as fMRI are increasingly popular within both basal and applied developmental neuroscience. Enhanced understanding of normal brain maturation and cognitive development may also improve our understanding of abnormal or atypical patterns of development, such as in childhood neurological injury, various neurodevelopmental disorders and childhood onset psychiatric disorders (Marsh, Gerber, & Peterson, 2008; Paus, et al., 2008). At the most fundamental level, large studies of normal brain maturation and cognitive development are needed for comparison of results from studies involving more specific samples. Indeed, data from the present project will serve as comparison data in projects on developmental risk factors. A clear understanding of the normal developmental processes is also required, if one is to be able to interpret the impact of any interruption or deviation to these processes.

For instance, it is known that prenatal exposure to different teratogenic agents, such as alcohol or various drugs, can lead to a variety of cognitive, behavioral and neurological impairments and likely also deviations to various developmental processes. Diffusion abnormalities have

recently been demonstrated in children with fetal alcohol spectrum disorder (FASD) in a DTI study (Lebel, Rasmussen, et al., 2008). Here, tracts with significant FA reductions also showed elevation of radial diffusivity, suggesting decreased barriers to diffusion across the axons, such as reduced myelination and/or axonal density. Similarly, morphometric abnormalities, in terms of a number of smaller neuroanatomical volumes, have been demonstrated in children prenatally exposed to opiates and other substances (Walhovd, et al., 2007). Further studies examining both healthy and exposed children are however needed for a better understanding of the specific neurobiological meanings of these deviations, delineation of the maturational trajectories in exposed children as compared to normal maturation and how these abnormalities relate to functional deficits. Lebel et al. (2008) did for instance not find any significant correlations between cognitive measures and DTI parameters in children with FASD.

Another important applied area is research on developing reliable cognitive tasks suited for developmental populations and the validation of these, including criterion validity in terms of for instance relationships with other tasks and structural and functional neuroimaging indices. This is of great importance for clinical pediatric neuropsychological practice; because such tasks are used in the assessment of cognitive functions and the results in turn affect what interventions are planned and what kind of resources that are made available to the child and the family. Research focused on developing suitable tasks is perhaps especially important with regards to the domain of executive functions, as the common practice of relying mainly on complex neuropsychological tests, such as the Wisconsin Card Sorting Test and the Tower of Hanoi/London, have some serious problems including the so-called task impurity problem, generally low reliability and questionable construct validity (Miyake, Emerson, & Friedman, 2000). In the present thesis, we used a battery of six relatively simple tasks hypothesized to index predominantly one of three target executive functions. Although results from previous studies have demonstrated a certain predictive and criterion validity of similar tasks, both the behavioral results and the results on the relationships between task measures and cortical thickness in the current sample spanning from childhood to early adulthood were mixed and indicated need for further improvements of these tasks for use on children.

LIMITATIONS AND FUTURE DIRECTIONS

Besides the aspects already discussed above, the present thesis also have other possible limitations. First, studying children, adolescents and adults in the same sample raises some methodological problems in relation to MRI acquisition and analysis. For instance, the scans of younger children are likely more prone to movement artifacts, which could necessitate a larger degree of user intervention during processing and/or lead to inaccurate estimations of brain measures. Primarily due to subject motion, some of the youngest individuals had only one usable MP-RAGE sequence. However, the number of acquisitions (single vs. multiple averaged) have been found to have negligible effects on reliability (Han, et al., 2006). Children may also have smaller neuroanatomical volumes, and hence biases may be introduced when comparing morphometric measures across children and adults. Child scan parcellations and segmentations may also suffer from greater partial voluming effects. However, the total volume of the brain of 8 year olds is comparable to that of adults (Reiss, et al., 1996), and the software packages used are well suited to account for varying anatomies. Another challenge in imaging studies comparing participants with widely different ages and possibly different macrostructural brain characteristics is registration. For instance, it is expected that amount of warping needed to align each individual FA volume to a common template is associated with age (Westlye, et al., In press-b). All scans were however visually inspected by trained operators (C.K.T. and L.T.W.), and in our experience the methods and registrations used were deemed to yield accurate results in children of the present age. These issues are likely more challenging in even younger children.

Second, concerning cognitive testing, the choice of tasks employed, especially to index different executive functions, is not given or exhaustive. There is no current consensus on how best to measure executive functions. The most serious challenge with cognitive testing is perhaps the question of measurement invariance, i.e. whether we are actually measuring the same construct across age (Huizinga, et al., 2006). This is a considerable challenge for developmental studies in general. For instance, inhibition as measured in the Stroop task is likely influenced by the degree to which reading is automated. Although all the children participating were capable readers, it is safe to assume that the average level of reading skills was lower in 8 year olds than in 10 year olds. Also, the ability to sustain focused attention for longer periods of time such as during the relatively long testing sessions in the present project (up to three hours including breaks), likely varies with age. Thus, other processes than those one is trying to measure likely influence task performance and these factors may interact with

age. For some of the cognitive measures, we used ratio scores in order to control for some of these confounding factors. Still, it is likely impossible to ensure that other abilities than those one is aiming to measure do not have different influences at different ages. However, the main alternative option, using different tasks or different tasks versions for different age-groups, would introduce other serious challenges in terms of both analysis and interpretation.

Third, the choice of age-range sampled is an important issue as this will obviously affect the results in different ways. This is for instance demonstrated by our results on age-related changes in cortical thickness. In paper I, including participant up to 30 years, we found widespread nonlinear age-related decreases in cortical thickness, with thinning being most pronounced in young age and then decelerating in late adolescence and young adulthood. In paper III, including only participants up to 19 years, no significant quadratic effects of age on cortical thickness were found. As demonstrated by Shaw et al. (2006), the magnitude and even direction of correlations between cognitive functions and cortical thickness, and presumably also other MRI indices of neuroanatomy, is also dependent of the age period studied. Moreover, since exact age-trajectories from global fit models, such as quadratic models, are substantially affected by the age-range sampled (Fjell, et al., 2010), we used exponential models in both papers I and II when interpreting brain maturation trajectories as well as when calculating magnitude and timing estimates of age-related changes. The choice of models to be used and the interpretations of these are however challenging, since many brain structures show complex, nonlinear patterns of maturation. More complex models than those investigated, perhaps especially the linear associations between behavioral indices of cognitive functions and MRI measures, could have been investigated.

Forth, another possible limitation of the present thesis is that diffusion data were derived only from areas presumably included in major fiber tracts in WM regions (paper I) and from the center of each pathway (paper II). It might be that thin myelinated fibers more proximal to the GM-WM boundary or in the periphery of the tracts are more interesting with respect to age-related changes in late development and possibly also more strongly related to individual differences in cognitive abilities in healthy well-functioning participants. Due to constraints on imaging resolution in DTI and more crossing fibers close to the cortical mantle, DTI measures from more peripheral regions is however currently challenging and data is lacking. Furthermore, different studies (such as paper I and paper II, respectively) sample diffusion

data with different methods and from different regions, making direct comparisons of results across studies more difficult.

Lastly, a more detailed investigation of possible sex differences in structural and microstructual brain maturation and its relationships with cognitive functions could have been conducted as several previous studies have reported such differences in development (Giedd, et al., 1999; Lenroot, et al., 2007; Schmithorst & Yuan, 2010; Schneiderman, et al., 2007; Sowell, et al., 2007). When controlling for brain size, findings of sex differences in cortical GM in both adults and children have been inconsistent, with some studies reporting no differences, and some showing enlargements in females (Sowell, et al., 2007). Findings have also been inconsistent with respect to interactions between age and sex in measures of regional brain volumes. In the current studies, we found few and small effects of sex, and females and males were combined in most analyses in order to ensure high statistical power, simplify interpretations and improve curve fits. The lack of clear sex differences in our developmental studies is consistent with a recent large multisample study showing minute effects of sex on the aging brain (Fjell, et al., 2009). Future studies could however investigate sex differences in development in greater detail, for instance by exploring the effects of steroid hormones on sexual dimorphisms in brain maturation (Neufang, et al., 2009).

CONCLUSIONS

In conclusion, this thesis demonstrates age-related changes in cortical thickness, regional WM volumes and DTI indices of WM microstructure from childhood to early adulthood. Further, these different indices of neuroanatomy showed unique associations with age and the results also indicate that the apparent cortical tinning in adolescence cannot be explained by WM maturation in subjacent regions. Moreover, the thesis demonstrates moderate, albeit significant age-independent relationships between behavioral performance indices of so-called higher-order cognitive functions and both DTI indices of WM microstructure and cortical thickness. The cognitive functions investigated were general intellectual abilities, i.e. verbal and performance abilities, and different selected executive functions, i.e. working memory updating, inhibition and shifting. Furthermore, associations between estimated brain maturation and both general verbal abilities and behavioral indices thought to reflect the executive function inhibition were shown. This suggests that individual differences in rates of

both microstructural and structural brain maturation are associated with individual differences in cognitive abilities.

Since the nervous system contains a vast number of neurons (more than 100 billions) and a complex architecture of neuronal connectivity (a single neuron may communicate with a large number of other neurons), no single neuroimaging technique can likely more than scratch the surface of the brain's neuronal network (Mori, et al., 2005). Future research, preferably using sequential designs, should therefore take advantage of multimodal imaging and also combine this with other types of data, e.g. genetic, electrophysiological, hormonal or histological. Two important but challenging questions are what specific neurobiological processes underpin structural brain maturation and cognitive development, and how direct causal mechanisms can be established between coincidental changes in brain and cognition.

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FIGURES

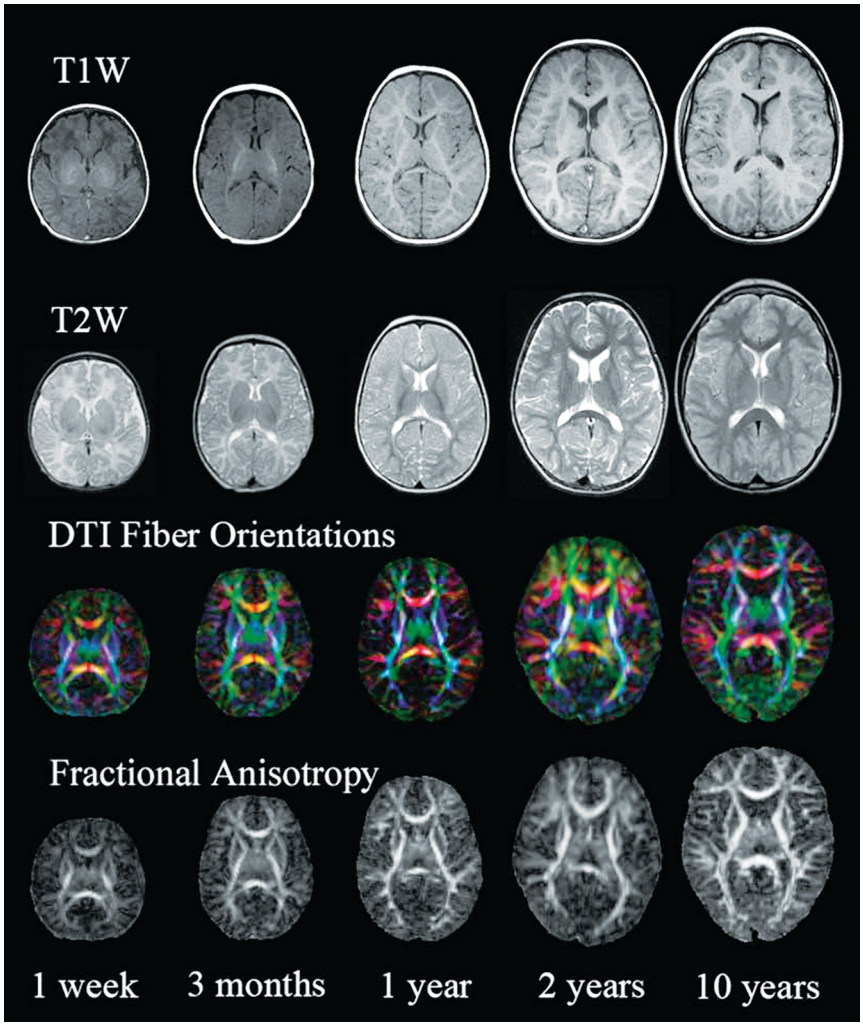

Figure 1. Example individual MRI and DTI images at various stages of development. Shown from the top are transversal slices from: T1 weighted images, T2 weigthed images, DTI fiber orientation maps, and fractional anisotropy maps. The images are from the NIH MRI Study of Normal Brain Development (http://www.bic.mni.mcgill.ca/nihpd/info/image_gallery.html). Reprinted with permission.

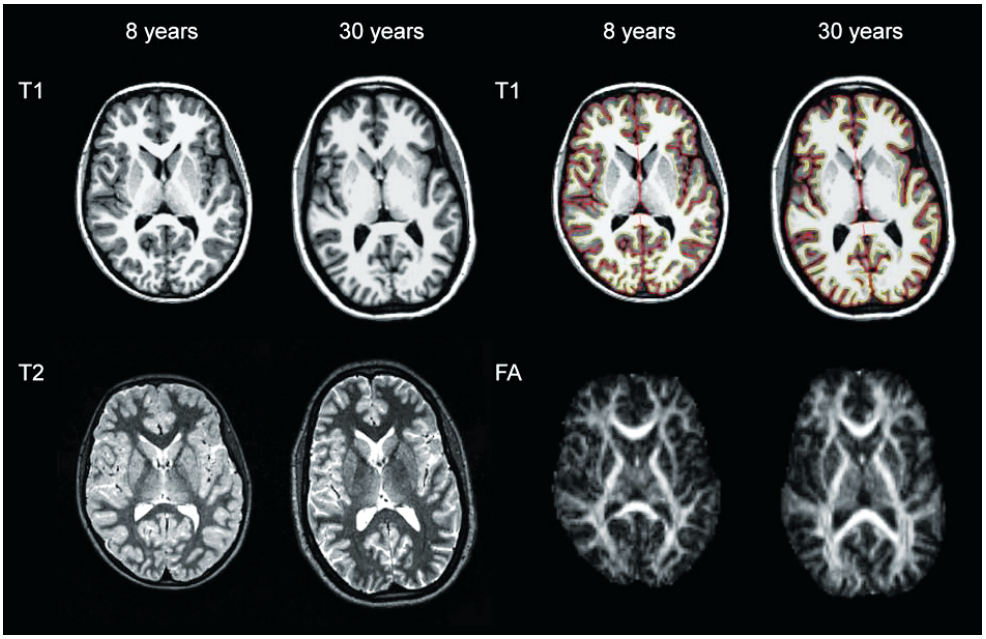

Figure 2 Example individual MRI and DTI images from two participants in the current project. The two participants were representative female participants 8 and 30 years old, respectively. The top row shows transversal slices of TI weighted images and T1 weighted images with reconstructed representations of the cortical - white matter boundary and the cortical surface. The bottom row shows T2 weigthed images and fractional anisotropy (FA) maps. All images are resampled to 1×1×1 mm.

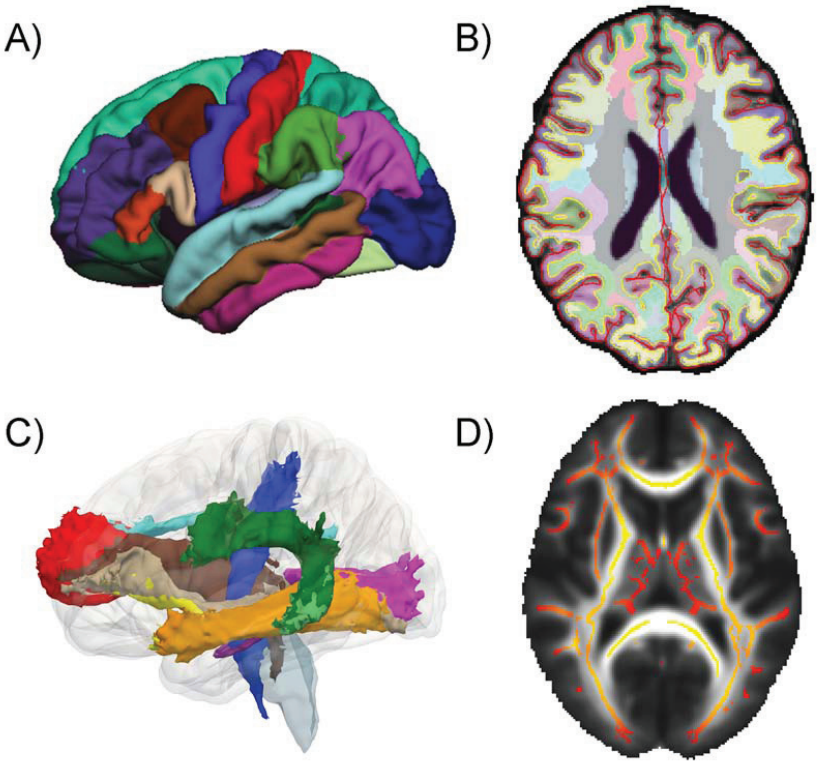

Figure 3 Illustrations of some of the neuroimaging data used in the present thesis. (A) Left lateral view of the average cortical surface for 168 participants aged 8-30 years from FreeSurfer. The surface was parcellated into 33 different gyral-based areas for each hemisphere and the different areas are shown in different colors. (B) Transversal slice of T1 image from a representative participant (15-year-old female). Both the cortical parcellation and the gyral WM segmentation from FreeSurfer are shown, with different areas in different colors. (C) Left lateral view of a 3D rendering of probabilistic tracts from the Mori atlas displayed on a semitransparent template brain, with different tracts shown in different colors. The figure was made by use of 3D slicer software (http://www.slicer.org/). (D) Transversal slice of the TBSS mean FA skeleton for 168 participants aged 8-30 years overlaid on the mean FA map.

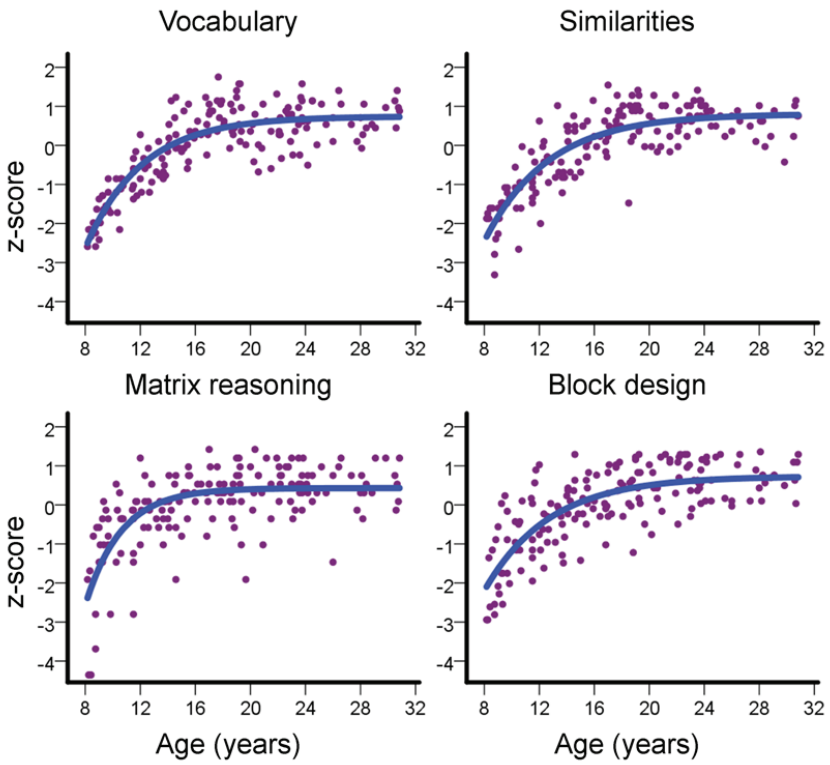

Figure 4 Age-related changes in performance on all four WASI sub-tests measuring general intellectual abilities. The scatter-plots show z-transformed task performance plotted as a function of age. Exponential models are fitted for illustration purposes. N =168.

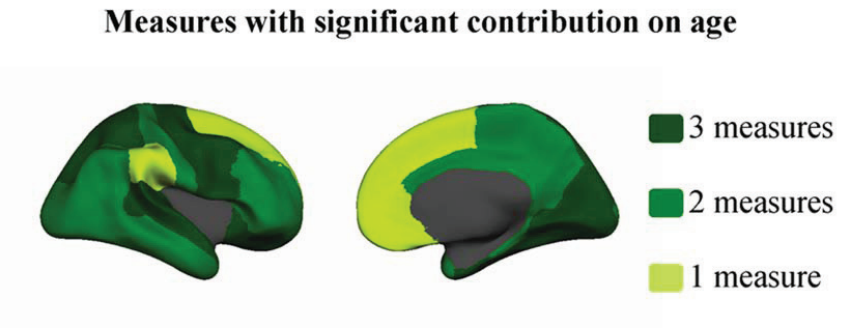

Figure 5 Results from multiple regressions where age is predicted from regional cortical thickness, WM volume and FA simultaneously. The results are summarized as the number of measures showing unique significant assoiciations with age in each region. This number is color-coded in each cortical parcellation and shown on the surface of a semi-inflated average template brain. All measures are averages between both hemispheres. The medial wall and corpus callosum are masked. N =168. All three classes of measures gave unique contributions ($p < .05$) to age in 14 of 33 regions, while at least two of the measures gave significant contributions in 28 of the regions. The results are described in more detail in paper I.

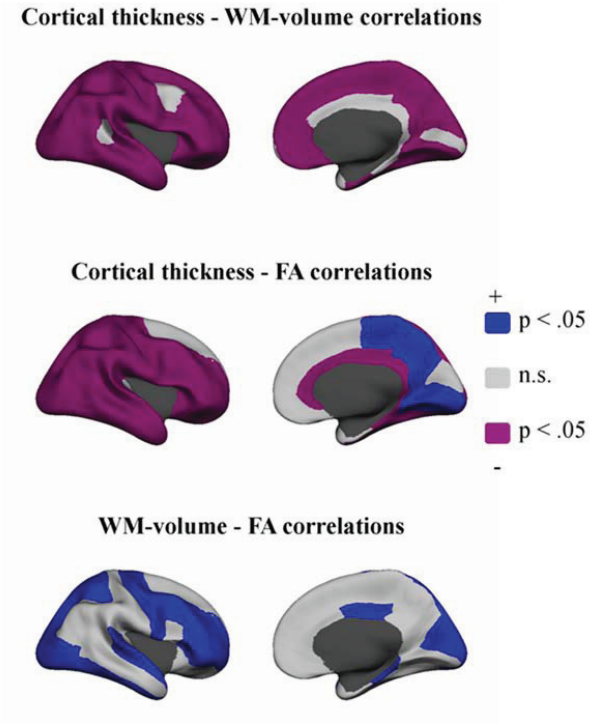

Figure 6 Correlations between cortical thickness, WM volume and FA in adjacent regions in development. Regional significant correlations are color-coded in each cortical parcellation as purple for negative correlations and blue for positive correlations and shown on the surface of a semi-inflated average template brain. All measures are averages between both hemispheres. The medial wall and corpus callosum are masked. N =168. The results are described in more detail in paper I.

PAPERS I-III

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II

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III

Neuroanatomical correlates of executive functions in children and adolescents: A magnetic resonance imaging (MRI) study of cortical thickness

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Shortened title: Neuroanatomical correlates of executive functions

Abstract

A range of cognitive abilities improves in childhood and adolescence. It has been proposed that the protracted development of executive functions is related to the relatively late maturation of the prefrontal cortex. However, this has rarely been directly investigated. In this cross-sectional study, 98 healthy children and adolescents (8-19 years old) were tested with six tasks considered to index three frequently postulated executive functions; updating (Keep track and Letter memory), inhibition (Antisaccade and Stroop) and shifting (Plus minus and Trail making). Task performance was then related to magnetic resonance imaging (MRI) measures of cortical thickness. The correlations between performance on the different tasks did not indicate any clear organization of the measures in the domains updating, inhibition and shifting. Performance on the tasks Keep track, Letter memory and Antisaccade correlated negatively with cortical thickness, probably related to the common influence by age. Independently of the effects of age, performance on the Keep track task was associated with thinner cortex bilaterally in clusters encompassing parietal and frontal regions, including areas in the left inferior frontal gyrus, while performance on the Antisaccade task was associated with thinner cortex bilaterally in occipital and parietal regions. Levels of performance on the Antisaccade and Stroop tasks were related to estimated rates of cortical maturation in posterior brain regions, but not in the prefrontal cortex. Thus, the results did not directly support the notion that individual differences in maturation of prefrontal cortex are associated with individual differences in levels of executive functioning.

Keywords: Cerebral cortex; Cognitive control; Development; Inhibition; Shifting; Updating

1. Introduction

A range of cognitive abilities improves steeply in late childhood and further, at a slower rate, in adolescence (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Segalowitz & Davies, 2004; Waber, et al., 2007). Developmental studies have shown that executive functions have a protracted developmental course relative to many other cognitive functions (V. Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Brocki & Bohlin, 2004; Garon, Bryson, & Smith, 2008; Huizinga, Dolan, & van der Molen, 2006; Romine & Reynolds, 2005; Welsh, 2002). Executive functions are control mechanisms that modulate the operation of other cognitive processes and thus regulate the dynamics of cognition and action (Miyake, et al., 2000). Concurrently with the development of executive functions, the brain shows rapid structural maturation. Neuroimaging studies show sustained regional development of the cerebral cortex, subcortical structures and white matter (WM) volume and microstructure from early childhood, throughout adolescence and even into adulthood (Giedd, 2004; Giorgio, et al., 2010; Gogtay, et al., 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Shaw, et al., 2008; Sowell, et al., 2003; Tamnes, Østby, Fjell, et al., In press; Østby, et al., 2009). A reasonable hypothesis is that cognitive development is caused partly by the ongoing maturation of the brain. More specifically, the protracted development of executive functions has been tentatively attributed to the relatively late maturation of the prefrontal cortex (V. Anderson, 2001; Blakemore & Choudhury, 2006; Diamond, 2002; Luna, et al., 2004). To our knowledge, no studies have directly investigated the relationships between development of executive functions and structural cortical maturation. This was the purpose of the present study.

An important theoretical issue concerns whether executive functions should be conceptualized as unitary in the sense that they reflect the same core mechanism or ability, or non-unitary, i.e.

including distinct sub-functions or sub-components. Three often-postulated sub-functions are updating, inhibition and shifting. Updating concerns the ability to monitor task-relevant incoming information and revise representations held in working memory to accommodate new input (Miyake, et al., 2000; Morris & Jones, 1990). Inhibition refers to the ability to deliberately inhibit dominant, automatic or prepotent responses when necessary (Logan & Cowan, 1984; Miyake, et al., 2000). Shifting is conceptualized as the ability to flexibly switch back and forth between multiple tasks, operations or mental sets (Miyake, et al., 2000; Rogers & Monsell, 1995). Using confirmatory factor analysis, Miyake et al. (2000) found that these executive functions were moderately correlated, but also clearly separable. A contemporary view is hence that executive functions show both unity and diversity at a cognitive level. A recent twin study indicates a combination of common and specific genetic influences on updating, inhibition and shifting and places executive functions among the most heritable psychological traits (Friedman, et al., 2008). Further, a range of studies illustrates the predictive validity of these executive function constructs for other cognitive abilities and real-world performance and problems (Friedman, et al., 2007; Friedman, et al., 2006; Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; St Clair-Thompson & Gathercole, 2006; van der Sluis, de Jong, & van der Leij, 2007; Willcutt, et al., 2001; Young, et al., 2009).

Working memory updating and inhibitory control have both been shown to improve throughout childhood and into adolescence, while the cost of shifting between tasks decrease as children grow older (Huizinga, et al., 2006). Differential developmental trajectories have been observed for different executive functions, and adult levels of performance are attained at different ages on different tasks (P. Anderson, 2002; V. Anderson, et al., 2001; Diamond, 2002; Huizinga, et al., 2006; Welsh, 2002). Examining the developmental trends in task performance, Huizinga et al. (2006) found that working memory updating, inhibition and

shifting reached adult levels of performance between 11 and 15 years. When analyzing latent variables extracted from confirmatory factor analysis, working memory updating was found to develop into young adulthood whereas shifting attained mature levels during adolescence.

The neural substrates of executive functions were originally assumed to be located in the frontal lobes, since patients with lesions in the anterior part of the brain frequently demonstrated impaired performance on a range of tasks assessing executive functions (Alvarez & Emory, 2006; Collette, Hogge, Salmon, & Van der Linden, 2006). Progress has been made regarding the fractionation of functions within frontal regions, but clear consensus has not yet been reached (Collette, et al., 2005; Stuss, et al., 2002). Although the importance of the frontal lobes to executive functions is established, neuroimaging and lesion studies suggest that executive functions depend on distributed networks encompassing both frontal and posterior (mainly parietal) associative cortices, as well as subcortical structures and thalamic pathways (Collette, et al., 2006; Collette & Van der Linden, 2002; Heyder, Suchan, & Daum, 2004; Jurado & Rosselli, 2007; Sylvester, et al., 2003). Knight et al. (1999) have proposed that prefrontal cortex provides a modulatory influence on basic processes subserved by posterior brain regions, so that performance on executive function tasks depend on both frontal and posterior regions, as well as their coordination. Consistent with this view, a recent diffusion tensor imaging (DTI) study suggests that age-related degradation of cortical association fiber tracts that connect regions of the frontal lobe and posterior association areas are important contributors to the decrease in set-shifting ability observed in aging (Perry, et al., 2009).

Little is known about the relationships between executive functions and structural properties of the brain in development. Maturation of both the cerebral cortex (Shaw, et al., 2006) and

DTI derived measures of WM microstructure (Tamnes, Østby, Walhovd, et al., In press) have been related to intellectual abilities. A recent multimodal imaging study showed that associations between WM microstructure maturation and functional connectivity measures were related to performance on an inhibition task (Stevens, Skudlarski, Pearlson, & Calhoun, 2009). These studies demonstrate associations between structural brain maturation and higher-order cognitive functions. However, the relationships between different executive functions and structural cortical properties in development have not been thoroughly investigated. The aim of the present cross-sectional study was to explore the relationships between different executive functions and cortical thickness in development. 98 healthy participants aged 8-19 years completed a battery of neuropsychological tests considered to predominantly tap the executive functions updating, inhibition and shifting, and performance was related to MRI-derived cortical thickness measures. The main objective was to investigate whether cortical maturation, and more specifically maturation of the prefrontal cortex, was associated with levels of executive functioning. Since cortical maturation in adolescence is associated with thinning, we expected negative relationships between executive functions and cortical thickness, and participants with higher levels of performance to show stronger negative associations between age and cortical thickness.

2. Methods

2.1. Participants

The sample was drawn from the first wave of an ongoing longitudinal research project at the Center for the Study of Human Cognition, University of Oslo ("Neurocognitive Development"). The study was approved by the Regional Ethical Committee of South Norway (REK-Sør). Volunteers were recruited by newspaper advertisements and through local schools and work places. Screening interviews were conducted with parent/guardian and

with participants aged 16-19 years. Participants were required to be right handed native Norwegian speakers in the age range 8 to 19 years, have normal or corrected to normal vision and hearing, not be under psychiatric treatment, not use medicines known to affect central nervous system (CNS) functioning, including psychoactive drugs, and not have injury or disease known to affect CNS function, including neurological or psychiatric illness, or serious head injury. 116 participants satisfied these criteria. Written informed consent was obtained from all participants older than 12 years of age and from parent/guardian of volunteers under 18 years of age. Oral informed consent was given by participants under 12 years of age. For the present study, 4 participants were excluded due to lacking MRI data and 13 participants due to incomplete behavioral data. All subjects' MR scans were examined by a specialist in neuroradiology (P. D.-T.) and required to be deemed free of significant anomalies. One participant was excluded on this basis. For the remaining 98 participants (50 males/48 females), mean age was 14.3 years (SD = 3.4, range = 8.2-19.7). Mean age for males and females were 13.9 (SD = 3.4) and 14.7 (SD = 3.3) years respectively, not significantly different ($t(96) = -1.19$, $p = .237$). Mean full-scale IQ for the entire sample, as assessed by the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), was 109.8 (SD = 10.6) and no participants scored below 87. As there are no Norwegian norms available for WASI, the original U.S. norms were used. Demographic and intellectual characteristics of the total sample and classified in subgroups according to age are reported in Table 1.

[Insert Table 1 about here]

2.2. Assessment of executive functions

Cognitive testing and MRI acquisition took place in two sessions. During cognitive testing, participants completed six tasks hypothesized to index one of the three target executive

functions updating, inhibition, or shifting. Four of the tasks were adapted from Miyake et al. (2000), namely Keep track (updating), Letter memory (updating), Antisaccade (inhibition) and Plus minus (shifting). Some modifications to these tasks were done to make them more appropriate for the age-range of the participants in the present study (see descriptions below). Two tasks were from the D-KEFS battery (Delis, Kaplan, & Kramer, 2001), namely Stroop (inhibition) and Trail making (shifting). Task administration was computerized or paper-and-pencil. Computerized procedures were administered using E-prime software (Schneider, Eschman, & Zuccolotto, 2002). Task characteristics were as follows:

Updating:

The Keep track task was originally adapted by Miyake et al. (2000) from Yntema (1963). Participants were first shown several target categories on the lower-half of the computer screen. Sixteen words, including 2 or 3 exemplars from each of six possible categories (animals, clothing, colors, countries, fruit, and relatives), were then presented serially in a pseudorandomized order for a duration of 2000 ms per word. The target categories remained on the screen during the trial. The task was to recall the last word presented in each of the target categories. Thus, participants had to continuously update their working memory representations for the target categories. After each trial, participants were asked to recall these words and the task administrator wrote down their responses and encouraged the participant to guess if an insufficient number of words were recalled. Before the task, participants practiced on two trials with two and three target categories respectively. The task itself consisted of four trials with three target categories, four trials with four target categories and one trial with five target categories, for a total of 33 words to be recalled. The percentage of words recalled correctly was the measure of interest. For further analyses, percentage of words recalled correctly was transformed to z-scores.

The Letter memory task was adapted by Miyake et al. (2000) from Morris and Jones (1990). Letters were presented serially for 2000 ms per letter on the computer screen and the task was to recall either the last 3 or 4 letters presented in the list. Only consonants were used and the number of letters presented in each list varied between 5, 7, 9 and 11 across trials in a pseudorandomized manner to ensure that participants would have to continuously update their working memory representations until the end of each trial. To further ensure that the task required working memory updating, the participants were instructed to continuously rehearse the last 3 or 4 letters. The task consisted of 4 trials in which the participants were instructed to recall the last 3 letters presented and 8 trials in which they were instructed to recall the last 4 letter presented, for a total of 44 letters to be recalled. After each trial, participants wrote down their responses on a sheet of paper and were encouraged to guess if an insufficient number of letters were recalled. Before each set of trials, participants practiced on a single trial. The percentage of letters recalled correctly was the measure of interest. For further analyses, percentage of letters recalled correctly was transformed to z-scores.

Inhibition:

The Antisaccade task was adapted by Miyake et al. (2000) from Roberts et al. (1994). Here, a fixation point was first presented in the middle of the computer screen for a variable duration (randomly selected from a list of nine values in 250 ms intervals between 100 and 2100 ms). A visual cue, a small black square, was then presented on one side of the screen (left or right) for 225 ms, followed by the presentation of a small black target arrow on the opposite side of the screen for 140 ms. The target arrow was then masked by gray cross-hatching for 200 ms. The task was to indicate the direction of the arrow (left, up, or right) with a button press. A PST Serial Response Box with millisecond accuracy was used. Since the target arrow was

presented only briefly before being masked, participants were required to inhibit the reflexive response of looking at the initial cue because doing so would make it more difficult to correctly identify the direction of the target arrow. The task consisted of 18 practice trials and two blocks of 60 target trials each, for a total of 120 target trials. The percentage of target trials answered correctly was the measure of interest. For further analyses, percentage of correct target trials was transformed to z-scores.

The Stroop task (Stroop, 1935) employed was the D-KEFS Color-Word Interference Test (Delis, et al., 2001). For the present study, only data from conditions one (Color naming) and three (Inhibition) were used. In the Color naming condition, participants were presented with a sheet of paper with five rows of ten squares, printed in one of three colors (red, blue or green), and were instructed to name the colors one-by-one and row-by-row as fast as possible until finished. In the Inhibition condition, participants were presented with five rows of ten color words (“red”, “blue” and “green”), printed in incongruent colors (red, blue or green), and were asked to name the print colors one-by-one and row-by-row as fast as possible until finished. Participants were thus required to inhibit an overlearned verbal response, i.e., reading the printed words, in order to generate a conflicting response of naming the incongruent ink colors in which the words were printed. Completion time for each condition was measured with a stopwatch. Before each condition, participants practiced on a small number of items. The interference effect was calculated as the ratio between the times to complete the Inhibition condition and Color naming condition. For further analyses, this ratio was transformed to z-scores and inverted to yield a measure of inhibition. In addition, the combined number of both corrected and uncorrected errors on each condition was counted.

Shifting:

The plus-minus task was adapted by Miyake et al. (2000) from Jersild (1927) and Spector and Biederman (1976). Our abbreviated version consisted of three lists of 20 two-digit numbers on a single sheet of paper. The numbers ranged from 10 to 69 and were prerandomized without replacement. On the first list, participants were instructed to add 3 to each number and write down their answers next to the numbers. On the second list, participants were instructed to subtract 3 from each number. Finally, on the third list, participants were instructed to alternate between adding 3 and subtracting 3 from the numbers. Both accuracy and speed were emphasized in the instructions. List completion times were measured by use of a stopwatch. In addition, number of errors on each list was counted. The shift cost was calculated as the ratio between the time to complete the alternating list and the average of the times to complete the addition and the subtraction lists. For further analyses, this ratio was transformed to z-scores and inverted to yield a measure of shifting ability.

The Trail making task employed was the D-KEFS Trail-Making Test (Delis, et al., 2001). Three conditions were administered: Number sequencing, Letter sequencing and Number-Letter switching. All three conditions consist of consecutively numbered circles from 1 to 16 and circled letters from A to P arranged randomly on a sheet of paper. In the Number sequencing condition, the task is to as fast as possible draw a line between the numbered circles in ascending order. In the Letter sequencing conditions, the task is to draw a line between the circles containing letters in alphabetic order as fast as possible. Finally, in the Number-Letter switching condition, the task consists of connecting each number with a letter and each letter with a number (1-A-2-B-3-C, etc.). Before each condition, participants practiced on shorter versions. Completion times were measured by use of a stopwatch. The shift cost was calculated as the ratio between the time to complete the Number-Letter switching condition and the average of the times to complete the Number sequencing and

Letter sequencing conditions. For further analyses, this ratio was transformed to z-scores and inverted to yield a measure of shifting ability.

2.3. MRI data acquisition

Imaging data were acquired using a 12 channel head coil on a 1.5-Tesla Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany) at Rikshospitalet University Hospital, Oslo. The pulse sequences used for morphometric analysis were two repeated 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE), with the following parameters: TR/TE/TI/FA = 2400 ms/3.61 ms/1000 ms/8˚, matrix 192 × 192, field of view = 192. Each volume consisted of 160 sagittal slices with voxel sizes 1.25 × 1.25 × 1.2 mm. Scanning time for each of these sequences was 7 min, 42 sec. The two MP-RAGEs were averaged during post-processing to increase the signal-to-noise-ratio. Primarily due to motion distortion, only one MP-RAGE was available for 18 of the participants (18.4 %). The protocol also included a 25 slices coronal T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE = 7000-9000/109 ms) to aid the neuroradiological examination.

2.4. Image analysis

All datasets were processed and analyzed at the Neuroimaging Analysis Lab, Center for the Study of Human Cognition, University of Oslo, with the additional use of computing resources from the Titan Grid cluster (http://hpc.uio.no/index.php/Titan) run by the Research Computing Services Group at USIT, University of Oslo. Cortical thickness was estimated using FreeSurfer 4.05 and cluster-wise correction for multiple comparisons was performed with FreeSurfer 4.50 (http://surfer.nmr.mgh.harvard.edu). The cortical surface was reconstructed to measure thickness at each surface location, or vertex, using a semi-automated approach described elsewhere (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Fischl &

Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Salat, et al., 2004; Segonne, et al., 2004; Segonne, Grimson, & Fischl, 2005). In short, thickness measurements were obtained by reconstructing representations of the gray matter/WM boundary and the cortical surface and then calculating the distance between those surfaces at each point across the cortical mantle (Dale, et al., 1999; Dale & Sereno, 1993). This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness. The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data and are thus capable of detecting submillimeter differences between groups (Fischl & Dale, 2000). The measurement technique has been validated via histological (Rosas, et al., 2002) as well as manual measurements (Kuperberg, et al., 2003). Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum of 30 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl, Sereno, Tootell, et al., 1999). This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortion, resulting in a measure of cortical thickness for each person at each point on the reconstructed surface. Statistical comparisons of surface maps were generated by computing a general linear model (GLM) of the effects of each variable on thickness at each vertex, which were mapped on the semi-inflated surface of the average brain of the sample (Dale, et al., 1999; Fischl, Sereno, & Dale, 1999).

2.5. Statistical analysis

Initial analyses of the behavioral data from the three completion time based tasks were performed with descriptive statistics for separate conditions. Paired samples t-tests were used to test for significant differences in completion times. Descriptive statistics were then performed for the six raw executive function measures. Analyses of the relationships between the z-transformed executive function measures, sex and age were done using Pearson's bivariate correlations. Executive function measures were plotted as a function of age and both linear and quadratic models were fitted. Partial correlations among the six executive function measures, controlling for the effects of age and sex, were then performed. Next, unique linear and quadratic effects of age on cortical thickness, while controlling for the effects of sex, were calculated for both hemispheres by GLMs at each vertex.

In order to investigate the relationships between executive functions and cortical thickness in development, we first performed GLMs testing the effects of executive function measures on cortical thickness at each vertex, controlling only for the effects of sex. Second, the GLMs were repeated where both the effects of age and sex on cortical thickness were statistically controlled for. Third, in order to test if individual differences in executive functions were related to differences in the development of cortical thickness, we performed GLMs testing the effects of interaction terms of executive function measures × age on cortical thickness, while including age, sex and the respective executive function measure as covariates. A similar approach has previously been described in a seminal paper by Shaw et al. (2006).

The p statistics maps from the vertex-wise GLMs testing the associations between age and cortical thickness and executive function measures and cortical thickness (without adjusting for age) respectively, were thresholded corresponding to a commonly used criterion of false discovery rate (FDR) at 5 % level (Genovese, Lazar, & Nichols, 2002). Note that this criterion

will yield different p-value thresholds for different analyses. For the age-independent analyses and the analyses involving interaction terms of executive function measures × age, corrections for multiple comparisons were performed by means of cluster size inference as implemented in FreeSurfer (Hagler, Saygin, & Sereno, 2006; Hayasaka & Nichols, 2003). Here, only clustered vertices are retained, the underlying idea being that true effects tend to extend over contiguous vertices, whereas noise has much less of a tendency to form clusters. Cluster size limits were estimated with synthesized Z Monte Carlo simulations using a method similar to that used in AFNI's AlphaSim (Ward, 2000) with 5000 iterations per analysis with an initial cluster-forming threshold of $p < .05$. The simulations are a way to get a measure of the distribution of the maximum cluster size under the null hypothesis and thus determine the probability of a certain cluster size under the empirical null. A cluster-wise corrected $p < .05$ was regarded significant. In addition, uncorrected results are provided as supplementary material.

Finally, in order to visualize the results from the surface-based analyses, mean cortical thickness was calculated for the clusters showing significant effects. For the analyses testing the effects of executive function measures independently of age, mean cortical thickness from the significant clusters were plotted against the respective executive function measures both before and after correcting for the effects of age and sex on thickness. For the analyses testing the effects of the interaction terms, mean cortical thickness from the significant clusters were plotted against age after splitting the sample in two equally large groups based on the respective z-transformed executive function measures. Group assignment was done separately for approximately every two years and by splitting by the median within these age brackets. Thus, for each of these age brackets, the sample was split into equally sized groups with no overlap in z-transformed executive function scores. This procedure was performed separately

for each relevant executive function measure. Across all ages, each group consisted of 49 participants. For convenience, the groups are described as low and high score groups, respectively, although no norms were available for the current measures and it is likely that the sample investigated scored above population mean. Note that these plots were included only to visualize the significant effects observed in cluster-wise analyses where continuous variables were explored in the sample as a whole.

3. Results

3.1. Behavioral results

Descriptive statistics for separate conditions in the completion time based tasks are shown in Table 2. For the Stroop task, paired-samples t-tests showed significantly longer mean completion time in the Inhibition condition than in the Color naming condition ($t(97) = 17.48$, $p < .001$). For the Plus minus task, significantly longer completion time was observed in the Shifting condition, than in both the Plus condition ($t(97) = 12.38$, $p < .001$) and the Minus condition ($t(97) = 8.54$, $p < .001$). For the Trail making task, significantly longer completion time was found in the Shifting condition, than in both the Numbers condition ($t(97) = 18.15$, $p < .001$) and the Letters condition ($t(97) = 19.33$, $p < .001$). These results indicate that the different test conditions yielded the expected behavioral effects.

[Insert Table 2 about here]

Descriptive statistics for the executive function measures are shown in Table 3. For Keep track, Letter memory and Antisaccade, percentage correct responses are shown, while for Stroop, Plus minus and Trail making, ratio scores based on completion time measures are

shown. For all further analyses, z-transformed measures were used to facilitate comparisons across tasks.

[Insert Table 3 about here]

Pearson's bivariate correlations among the six z-transformed executive function measures, sex and age are shown in Table 4. Note that the z-transformed ratio scores for Stroop, Plus minus and Trail making were inverted, so that higher scores on all measures reflect better performance. Moderate significant positive correlations were observed between four of the executive function measures, namely Keep track, Letter memory, Antisaccade and Stroop, while Plus minus and Trail making were not associated with any other executive function measures, including each other. Only Stroop correlated with sex, with girls performing better than boys ($r = .22$, $p = .027$). Further, Keep track, Letter memory and Antisaccade showed strong positive correlations with age, while Stroop showed a moderate positive correlation. Plus minus and Trail making were not correlated with age. Scatter plots of the executive function measures by age are shown in Figure 1. For Keep track and Antisaccade, age^2 added significantly to the amount of explained variance. The quadratic models indicated most pronounced age-related improvement on Keep track and Antisaccade in late childhood and early adolescence; although, overall the quadratic models did not diverge dramatically from the linear models.

Partial correlations among the six executive function measures, controlling for the effects of age and sex, are shown in Table 5. Moderate significant positive correlations were observed between Keep track and Letter memory, Keep track and Stroop, and Letter memory and

Antisaccade, respectively. Plus minus and Trail making were still not associated with any of the other measures when controlling for the effects of age and sex.

[Insert Tables 4 and 5 about here]

[Insert Figure 1 about here]

Since the correlation analyses did not indicate any clear organization of the measures according to the proposed executive sub-functions updating, inhibition and shifting, individual task measures from Keep track, Letter memory, Antisaccade and Stroop were used for further analyses. Plus minus and Trail making were not subjected to further analyses since the purpose of the study was to explore the relationships between executive functions and brain morphometry in development, and these measures were not related to age.

3.2. Cortical thickness

The effects of age on cortical thickness across the surface were computed by GLMs with the effects of sex regressed out. The results are shown in Figure 2. When a commonly used approach to correct for multiple comparisons was employed (FDR 5 %, corresponding to $p < .046$), negative linear associations between cortical thickness and age were observed across almost the entire cortical surface (Figure 2A). When a more conservative threshold was used ($p < 10^{-6}$), strong negative associations with age were observed bilaterally in large areas in the parietal and occipital lobes (Figure 2B). Strong associations were also evident in the superior medial frontal lobes and in the ventrolateral prefrontal, insular and right cingulate cortices. There were no significant unique effects of age^2 on cortical thickness.

[Insert Figure 2 about here]

3.3. Relationships between executive functions and cortical thickness

As an initial examination of the relationships between executive functions and cortical thickness in development, we performed GLMs testing the effects of executive function measures on thickness on a vertex-by-vertex basis, controlling only for the effects of sex. The results are shown in Figure 3. A statistical threshold taking multiple comparisons into account was used (FDR 5 %, corresponding approximately to $p < .04$ for Keep track, Letter memory and Antisaccade and $p < .0002$ for Stroop). Widespread negative associations with cortical thickness were observed for Keep track, Letter memory and Antisaccade. The associations were generally more pronounced in the posterior parts of the brain. No associations were observed between Stroop and cortical thickness.

[Insert Figure 3 about here]

3.4. Age-independent relationships between executive functions and cortical thickness

The above analyses were repeated with age and sex included as covariates. In order to increase sensitivity to regional effects, permutation based cluster-wise correction for multiple comparisons was employed. The results are shown in Figure 4. For Keep track, one cluster in each hemisphere was found, both showing negative associations with cortical thickness. In the left hemisphere, the cluster was centered on the pre- and postcentral gyri, but also encompassed substantial parts of the inferior frontal gyrus and the superior parietal cortex. In the right hemisphere, the cluster encompassed the pre- and postcentral gyri and superior medial areas in the parietal lobe (paracentral areas). For Antisaccade, negative associations were found in bilateral clusters located around the parieto-occipital cortices, cuneus, pericalcarine and the lingual cortices. No significant clusters were found showing age-

independent relationships between cortical thickness and Letter memory or Stroop, respectively. Details on the clusters showing significant associations are given in Table 6. Uncorrected results are shown in Supplementary Figure 1.

Figure 5 shows mean cortical thickness from the significant clusters in the left and right hemispheres, respectively, plotted against Keep track and Antisaccade performance. Strong negative associations between thickness and the behavioral measures are seen (top panel). After controlling for the effects of age and sex on cortical thickness (lower panel), as was done in the cluster-wise analyses above, smaller but still significant negative associations were found, with correlations ranging from -.23 to -.30.

[Insert Figures 4 and 5 about here]

3.5. Relationships between executive functions and cortical maturation

In order to explore the associations between executive functions and estimated cortical maturation, interaction terms of executive function measures × age were added to the GLMs. Figure 6 shows the results from GLMs testing unique linear effects of the interaction terms on cortical thickness, while regressing out the effects of age, sex and the respective executive function measures. Permutation based cluster-wise correction was employed to increase sensitivity to regional effects. The interaction term Antisaccade × age was negatively associated with cortical thickness in both hemispheres in clusters encompassing mainly the parieto-occipital cortices, with effects extending into the inferior, superior and medial parietal cortices. One cluster in the right hemisphere was found showing a positive association between Stroop × age and cortical thickness. This cluster was located mainly around the posterior lingual and fusiform cortices, but also extended up to the inferior parietal cortex. No

significant clusters were found showing associations between cortical thickness and either Keep track × age or Letter memory × age, respectively. Details on the clusters showing significant associations between executive function measures × age and cortical thickness are given in the lower half of Table 6. Uncorrected results are shown in Supplementary Figure 2.

In order to visualize the interactions, mean thickness from the significant clusters were plotted against age after splitting the sample in two equally large groups based on Antisaccade and Stroop performance, respectively (Figure 7). The negative association between the interaction term Antisaccade × age and cortical thickness in the bilateral posterior clusters indicates that a higher level of performance on this task was associated with more pronounced cortical thinning in this region in adolescence. The positive association between the interaction term Stroop × age and cortical thickness in the posterior right hemisphere suggests an opposite pattern, with higher level of performance on this task being associated with less cortical thinning in adolescence.

[Insert Figures 6 and 7 about here]

[Insert Table 6 about here]

4. Discussion

The main findings from the present study were that (1) independently of age, performance on the Keep track and Antisaccade tasks were negatively associated with cortical thickness bilaterally in parietal and frontal (Keep track) and occipital and parietal (Antisaccade) regions, and that (2) the strength of the relationships between age and cortical thickness in posterior brain regions was associated with performance levels on the Antisaccade and Stroop tasks. The other behavioral measures did not show any associations with cortical thickness

independently of age or with rate of cortical maturation. Thus, no direct evidence was found supporting the notion that maturation of the prefrontal cortex is related to levels of executive functioning. The results are discussed in more detail below.

4.1. Development of executive functions

The behavioral tasks used in the present study were primarily adopted from Miyake et al. (2000), who demonstrated that updating, inhibition and shifting were moderately correlated with one another, but also clearly separable. Similar, although not identical, organization of executive functions have since been found in young adults (Friedman, et al., 2006), older adults (Fisk & Sharp, 2004; Hedden & Yoon, 2006; Hull, Martin, Beier, Lane, & Hamilton, 2008) and children (Huizinga, et al., 2006; Lehto, Juujärvi, Kooistra, & Pulkinnen, 2003; St Clair-Thompson & Gathercole, 2006; van der Sluis, et al., 2007; Willcutt, et al., 2001). In a study of children aged 8-13 years, Lehto et al. (2003) observed a factor structure including all three factors updating, inhibition and shifting. Others have identified two factors in children, either updating and shifting (Huizinga, et al., 2006; van der Sluis, et al., 2007) or updating and inhibition (St Clair-Thompson & Gathercole, 2006). We found moderate correlations between the updating and inhibition measures, but no empirical support in favor of structuring the tests according to the updating, inhibition and shifting categories. Disparity across studies may reflect fundamental differences in the organization of executive functions between children, adolescents and adults and variations in or limitations associated with the specific behavioral tasks used. The lack of a clear organization likely reflects multiple factors, including the wide age-range of the sample, the limited number of tasks used and possibly age-related differences in subjective task demands. Our results indicate that more research focused on developing a set of reliable executive function tasks suited for both children and adolescents and on the organization of executive functions at different ages is needed.

Marked age-related improvements on Keep track, Letter memory, Antisaccade and Stroop were found, with slightly accelerated improvements in childhood compared to late adolescence on two of the measures (Keep track and Antisaccade). Age-related differences were not found for the Plus minus and Trail making measures and they were neither associated with each other nor with any other behavioral measures. The two proposed shifting measures were therefore excluded from further analyses. The resulting focus on updating and inhibition is consistent with reports regarding these as the central cognitive processes within the domain of executive functions in children (Brocki & Bohlin, 2004; Welsh, 2002). The scoring procedure used for the shifting tasks might however partly explain why we did not observe any age-related improvements on these measures. In order to control for the known motor and processing speed improvements in late childhood and adolescence (Gasser, Rousson, Caflisch, & Jenni, In press; Kail & Ferrer, 2007), we used ratio scores based on completion times in different conditions. The same type of measure was computed from the Stroop task, which also showed less pronounced age-related improvement compared to the accuracy based measures from the Keep track, Letter memory and Antisaccade tasks. Given a reasonable assumption that shifting ability does improve beyond childhood, our results indicate limitations associated with the use of speed-based scores derived from the Plus minus and Trail making tasks as measures of shifting ability in developmental samples with wide age-ranges. These limitations are also indicated by a study showing that a global speed mechanism may account for large proportions of age-related variance in the speed of responding on executive function tasks in development (Span, Ridderinkhof, & van der Molen, 2004).

4.2. Age-related cortical thinning

As expected, we observed age-related decreases in cortical thickness. Cortical maturation has been fairly well delineated in a number of MRI studies, showing that both cortical thickness and volume follow an inverted U-shaped developmental course with a period of initial childhood increase and a subsequent adolescent decline (Giedd, 2004; Gogtay, et al., 2004; Shaw, et al., 2008; Tamnes, Østby, Fjell, et al., In press). The adolescent decline in thickness is followed by a period with slower decline in early adulthood (Shaw, et al., 2008; Sowell, et al., 2003; Tamnes, Østby, Fjell, et al., In press). In the present study with participants ranging from 8 to 19 years old, linear cortical thinning was observed across almost the entire cortical mantle. We did not observe any childhood cortical thickening in contrast to what has been reported in other samples (Giedd, 2004; Shaw, et al., 2008); likely because the starting age of our sample was too high to detect this, at least with a cross-sectional design. Further, no significant quadratic effects of age on cortical thickness were observed. This is also likely a reflection of the age-range of the sample, as we have previously found decelerating cortical thinning in adolescence and early adulthood (Tamnes, Østby, Fjell, et al., In press). Interestingly, the strongest effects of age on cortical thickness were observed primarily in the parietal and occipital lobes, not in the frontal and temporal lobes which are presumed to mature later.

Relatively little is known about the neurobiological processes underlying structural brain maturation as delineated by the use of MRI. Cortical thinning in adolescence may reflect pruning and reorganization in the form of use-dependent selective synapse elimination (Bourgeois & Rakic, 1993; Huttenlocher & Dabholkar, 1997) which could play a key role in shaping neural circuits and thus provide a biological basis for development of cognitive functions (Hensch, 2004; Knudsen, 2004). In addition, neurobiological changes at the interface between the cortex and the subjacent WM might partly explain the apparent cortical

thinning. Proliferation of myelin into the periphery of the cortical neuropil is one such possible biological event (Shaw, et al., 2008; Sowell, et al., 2004; Yakovlev & Lecours, 1967).

4.3. Relationships between executive functions and cortical thickness

When age was not included as a covariate, widespread negative associations were found between cortical thickness and both the updating measures (Keep track and Letter memory) and one of the inhibition measures (Antisaccade). The common influence of age likely explains most of these relationships, caused by concurrent age-related performance improvements on executive function tasks and age-related cortical thinning. This indicates that development of these cognitive functions are mirrored by the cortical maturation occurring in the same period, but cannot be used to infer a direct causal relationship between brain maturation and cognitive development.

Specific associations between different behavioral measures and cortical thickness were tested by including age as an additional covariate. Keep track performance, which is considered to index updating, was negatively associated with cortical thickness bilaterally in parietal and frontal regions. Performance on the Antisaccade task, which is considered to predominantly index inhibition, was negatively related to cortical thickness bilaterally in occipital and parietal regions. Letter memory and Stroop performance did not show any age-independent associations with cortical thickness. To our knowledge, this is the first study to explore the relationships between different behavioral indices of executive functioning and cortical morphometry in children and adolescents.

Thinner cortices in bilateral parietal and frontal areas around the central sulcus, and also encompassing areas in the left inferior frontal gyrus and superior medial parietal areas in the right hemisphere, were associated with better working memory updating performance as measured by the Keep track task. This is largely consistent with functional imaging evidence from adults showing that working memory is associated with activations in the prefrontal cortex, anterior cingulate, parietal and occipital regions, but that the main components seem to include lateral prefrontal cortex and parietal regions (Cabeza & Nyberg, 2000a, 2000b; D'Esposito, Postle, & Rypma, 2000; Glabus, et al., 2003; Honey, Bullmore, & Sharma, 2000; Smith & Jonides, 1999). Working memory has also been related to DTI indices of WM microstructure in children and adolescents in the left frontal lobe (Nagy, Westerberg, & Klingberg, 2004) and in older adults (Charlton, et al., 2008). Further, a study combining fMRI and DTI suggests that working memory in children and adolescents rely on the integrity of a fronto-parietal network (Olesen, Nagy, Westerberg, & Klingberg, 2003). A distributed nature of the neural substrates of working memory is also supported by human lesion studies (Muller & Knight, 2006; Muller, Machado, & Knight, 2002). Our morphological results from the Keep track task are mainly in line with these fMRI and lesion studies. However, to a larger degree than expected, this association encompassed primary somatosensory and motor areas in addition to associative cortices. The other updating task employed, Letter memory, did not show any age-independent associations with cortical thickness in our sample.

Our results also showed age-independent neuroanatomical correlates of one of the two tasks predominantly considered to index inhibition, namely Antisaccade. However, thinner cortices bilaterally in occipital and parietal areas, not in prefrontal regions, were associated with better performance. Thus, although the Antisaccade task is considered mainly to index inhibition ability, these results suggest that areas engaged in visual detection and attention processes are

also involved. Functional imaging studies from adults have shown that the Antisaccade task activates an extensive network including frontal and supplementary eye fields, occipital visual areas, parietal cortex, striatum and the lateral prefrontal cortex (Brown, Goltz, Vilis, Ford, & Everling, 2006; Ettinger, et al., 2008; Matsuda, et al., 2004; Raemaekers, et al., 2007; Tu, Yang, Kuo, Hsieh, & Su, 2006). Similar areas are also activated in children and adolescents (Velanova, Wheeler, & Luna, 2008). The present results indicate that performance on the Antisaccade task in childhood and adolescence is more related to structural properties of the visual cortex than the prefrontal cortex. Thus, although inferences of localization of cognitive functions from relationships between structural properties and task performance should be drawn with caution, the present results suggest that Antisaccade may be more sensitive to development of the visual processing system than networks presumably related to cognitive control. The other inhibition task employed, Stroop, did not show any age-independent associations with cortical thickness in our sample.

The present study also demonstrated that individual differences in task performance assumed to index inhibition (Antisaccade and Stroop) were related to differences in cortical maturation in posterior brain regions. A negative association between the interaction term Antisaccade × age and cortical thickness in occipital and parietal regions was found, while a positive association between Stroop × age and cortical thickness in posterior regions in the right hemisphere was observed. Interestingly, these results suggest that performance on the Antisaccade task is associated not only with cortical thickness independently of age, but also with estimated rate of cortical maturation in overlapping and adjacent areas in parieto-occipital cortex. Although both Antisaccade and Stroop performance were related to maturational differences in posterior brain regions, it is unclear why these effects were in opposite directions. One might speculate that this relates to different associations with age for

the two cognitive measures and regional differences in cortical maturation. As emphasized by Shaw et al. (2006), the direction of correlations between cognitive functions and cortical thickness is dependent of the age period studied.

Importantly, no effects of the interaction terms executive function measures × age were observed in the frontal lobes. No direct evidence was thus found supporting the notion that individual differences in maturation of the prefrontal cortex is associated with individual differences in levels of executive functioning. Using a similar approach, previous studies have found that general intellectual abilities are related to both cortical (Shaw, et al., 2006) and WM microstructure maturation (Tamnes, Østby, Walhovd, et al., In press). In these studies, high-functioning children showed a different pattern of structural brain maturation than average or lower functioning children. In a study of elderly participants, high-functioning participants showed thicker cortices in specific areas, but only when selected based on general cognitive functions, not when the selection was based on a number of tests related to executive function (Fjell, et al., 2006). Thus, it is possible that developmental changes in macro-structural brain properties are more closely related to development of general intellectual functioning than performance on specific behavioral indices of executive functions.

Although general functions may be more closely related to brain structure than specific behavioral indices of executive functions, the question remains why such indices appeared more strongly related to cortical thickness and cortical maturation in parietal and occipital areas than in prefrontal regions. One reason could be that cognitive processes primarily supported by prefrontal circuits are more strategic and thus more variable across participants, while parietal and occipital areas are involved in more basic cognitive processes that vary less

between subjects (Collette et al., 2005). Strategy usage is likely also age-related, and this could possibly explain the lack of associations between task performance and prefrontal cortical maturation observed in the present study. A related possibility is that between-subject variability in the exact prefrontal areas engaged in executive function tasks result in weaker relationships (Collette et al., 2005). In developmental samples, one might also expect correlations between anatomy and executive functions in different regions at different ages. Supporting this, a recent fMRI study suggests developmental changes to the functional networks underlying response inhibition and error-processing, with different areas of activation in young adolescents and adults (Braet, et al., 2009). Finally, the use of single task measures instead of aggregated measures or latent variables might result in relationships with cortical regions involved in the idiosyncratic requirements that are specific to each task instead of relationship with regions involved in the postulated executive functions.

4.4 Limitations and conclusions

There are some limitations of the present study. First, the links between cognitive development and structural brain maturation should ideally be investigated with longitudinal data including several time points, mapping individual developmental and maturational trajectories (but see Salthouse (2009) for a discussion of problems related to longitudinal designs). One possible confound in cross-sectional data include cohort effects other than age. These are probably negligible in this case since the age span was limited to 12 years. A more serious concern, however, is the possible loss of sensitivity due to large individual variation in brain anatomy and cognitive functioning. Thus, even though we did not observe a relationship between executive functions and age-related thinning of the prefrontal cortex, this should be tested with longitudinal data. Second, the present sample showed relatively high general cognitive function and may not be representative of the full range of individual differences in

development. Third, the tasks employed are considered to predominantly index the executive functions updating, inhibition and shifting. This choice is not exhaustive, as there are various other proposed executive functions that should also be investigated, such as dual tasking, fluency, planning and decision-making. There is no current consensus on how best to measure executive functions and comparison across studies is difficult due to the diversity of conceptualizations, tasks and measures employed (Welsh, 2002). Further, the question of measurement invariance, i.e. whether we are actually measuring the same construct across age, is a considerable challenge for developmental studies (Huizinga, et al., 2006). For instance, inhibition as measured in the Stroop task would likely be influenced by the degree to which reading is automated in children at various ages. Even though all children participating in the present study were capable readers, it appears safe to assume that the average level of reading skills was lower in 8 year olds than in 10 year olds. Further, the ability to sustain focused attention for longer time periods was likely better in the oldest compared to the youngest part of the sample. Thus, the degree to which other processes influence task performance may interact with age. By using ratio scores whenever possible, we hope that we have controlled for some of these confounding factors. Still, it is likely impossible to ensure that non-executive abilities do not have different influences at different ages. Finally, in the current study we investigated the relationships between single task measures and cortical thickness. Ideally, multiple measures for each postulated executive function should be subjected to latent variable analyses, due to idiosyncratic requirements that are specific to each task and the low reliability of many executive function tasks (Miyake, et al., 2000). This was however not pursued in the current study, as no clear organization of the measures was evident from the correlation analyses. Further, we wanted to use established tests to ease comparisons with previous research, and possibly increase the clinical utility of the results.

In summary, the results in the current study showed concurrent age-related performance improvements on the Keep track, Letter memory and Antisaccade tasks, respectively, and age-related cortical thinning. Negative age-independent associations between a measure of working memory updating (Keep track) and a measure assumed related to inhibition (Antisaccade), and cortical thickness, were found in parietal and frontal and occipital and parietal regions, respectively. Further, individual differences in task performance presumed to index inhibition (Antisaccade and Stoop) were related to differences in cortical maturation in posterior brain regions. No evidence was found in the current cross-sectional study supporting the hypothesis that individual differences in maturation of the prefrontal cortex is related to individual differences in levels of executive functioning. This should however be tested with longitudinal data, mapping individual maturational trajectories.

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Note: Supplementary figures are available online.

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Tables

Table 1

Sample characteristics

Age group (years)	Total n	Females n (%)	IQ mean	IQ SD (range)
08 – 10	20	7 (35.0)	108.2	10.8 (87-127)
11 – 13	24	13 (54.2)	106.9	10.9 (92-141)
14 – 16	26	13 (50.0)	109.6	9.5 (91-124)
17 – 19	28	15 (53.6)	113.7	10.6 (91-132)
Total	98	48 (49.0)	109.8	10.6 (87-141)

Table 2

Descriptive statistics for separate conditions in the completion time tasks

	Completion time (seconds)				Errors (number)			
Task: Condition	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.
Stroop: Color naming	33.08	8.48	20.8	63.0	0.52	0.86	0	5
Stroop: Inhibition	60.26	22.25	32.1	135.0	2.55	2.52	0	11
Plus minus: Plus	58.45	30.94	18.0	164.1	0.35	0.66	0	3
Plus minus: Minus	72.86	44.07	22.0	240.0	0.40	0.77	0	4
Plus minus: Shifting	89.51	52.14	25.0	252.9	0.46	0.84	0	4
Trail making: Numbers	29.54	9.78	11.0	64.7	-	-	-	-
Trail making: Letters	31.27	14.61	11.1	101.6	-	-	-	-
Trail making: Shifting	71.35	27.60	28.6	185.8	-	-	-	-

Notes: Number of errors was not recorded for Trail making. N = 98.

Table 3

Descriptive statistics for raw executive function measures

Measure	Mean	SD	Min.	Max.
Keep track	69.29	12.31	30.30	93.94
Letter memory	80.93	10.68	36.36	97.73
Antisaccade	76.46	15.24	30.83	98.33
Stroop	1.80	0.31	1.32	2.66
Plus minus	1.36	0.23	1.02	2.05
Trail making	2.43	0.71	1.08	4.89

Notes: Raw executive function measures are shown. For Keep track, Letter memory and Antisaccade, percentage correct are shown. For Stroop, Plus minus and Trail making, ratio scores based on completion times in separate conditions are shown. N = 98.

Table 4

Correlations among executive function measures, sex and age

Measure	1.	2.	3.	4.	5.	6.
1. Keep track	-					
2. Letter memory	**.58**	-				
3. Antisaccade	**.51**	**.56**	-			
4. Stroop	**.45**	**.37**	**.32**	-		
5. Plus minus	.16	.07	.01	.13	-	
6. Trail making	.07	.14	.04	.00	.08	-
Sex	.00	.10	.01	**.22**	.18	.03
Age	**.63**	**.63**	**.66**	**.38**	.04	.07

Notes: Z-transformed executive function measures were used. For Keep track, Letter memory and Antisaccade, percentage correct were used. For Stroop, Plus minus and Trail making, inverted ratio scores based on completion times in separate conditions were used. Higher scores on all measures reflected better performance. Males are coded as 0 and females as 1. Bold characters indicate $p < .05$ and underlined characters indicate $p < .01$. $N = 98$.

Table 5

Partial correlations among executive function measures controlling for age and sex

Measure	1.	2.	3.	4.	5.
1. Keep track	-				
2. Letter memory	**.31**	-			
3. Antisaccade	.17	**.24**	-		
4. Stroop	**.32**	.18	.12	-	
5. Plus minus	.19	.05	-.01	.10	-
6. Trail making	.04	.13	-.01	-.03	.07

Notes: Z-transformed executive function measures were used. Higher scores on all measures reflected better performance. Bold characters indicate $p < .05$ and underlined characters indicate $p < .01$. $N = 98$.

Table 6

Details on clusters showing significant associations with cortical thickness

Analysis	Hemi-sphere	Cluster size (mm^2)	Talairach max vertex (X, Y, Z)	Cluster-wise p	Confidence limits for cluster-wise p	Annotation
Keep track	Left	8379.6	-39.6, -22.9, 59.1	0.0002	0.0000, 0.0004	Postcentral
Keep track	Right	4574.9	12.2, -35.2, 52.6	0.0144	0.0122, 0.0166	Paracentral
Antisaccade	Left	10258.6	-6.6, -87.1, 6.4	0.0002	0.0000, 0.0004	Peri-calcarine
Antisaccade	Right	4974.7	5.8, -75.3, 17.7	0.0074	0.0058, 0.0090	Cuneus
Antisaccade x age	Left	7136.4	-37.5, -79.4, 26.3	0.0002	0.0000, 0.0004	Inferior-parietal
Antisaccade x age	Right	5827.2	23.7, -77.0, 30.3	0.0020	0.0012, 0.0028	Superior-parietal
Stroop x age	Right	5147.4	42.9, -54.1, 9.5	0.0054	0.0040, 0.0068	Inferior-parietal

Notes: Summary of results from GLMs testing the effects of executive function measures and executive function measures × age, respectively, on cortical thickness. The effects of age and sex were controlled in all analyses and the effects of the respective executive function measures were additionally controlled in the analyses involving interaction terms. Further, permutation based cluster-wise correction for multiple comparisons with a cluster-wise p <

.05 was employed. Only significant clusters are shown. All clusters, except the Stroop x age cluster, showed negative associations with cortical thickness. N = 98.

Figure legends

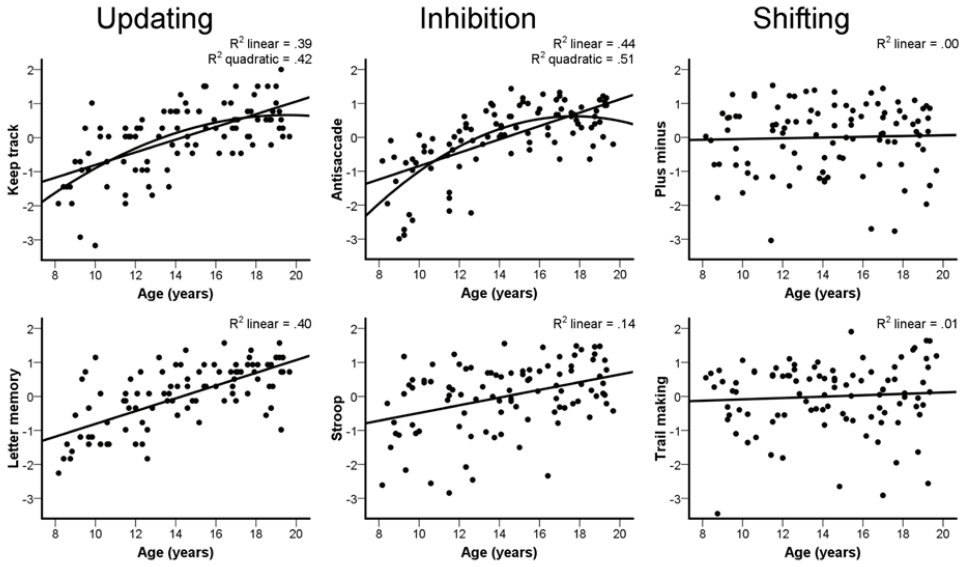

Figure 1. Relationships between executive functions and age. Scatter plots for, column wise from left to right: the two updating measures (Keep track, Letter memory), the two inhibition measures (Antisaccade, Stroop) and the two shifting measures (Plus minus, Trail making), by age. For Keep track, Letter memory and Antisaccade, z-transformed percentage correct are shown. For Stroop, Plus minus and Trail making, inverted z-transformed ratio scores based on completion times in separate conditions are shown. Higher scores on all measures reflect better performance. Linear and significant quadratic models are fitted and explained variance is reported. The quadratic age term added significantly to the amount of explained variance for Keep track and Antisaccade.

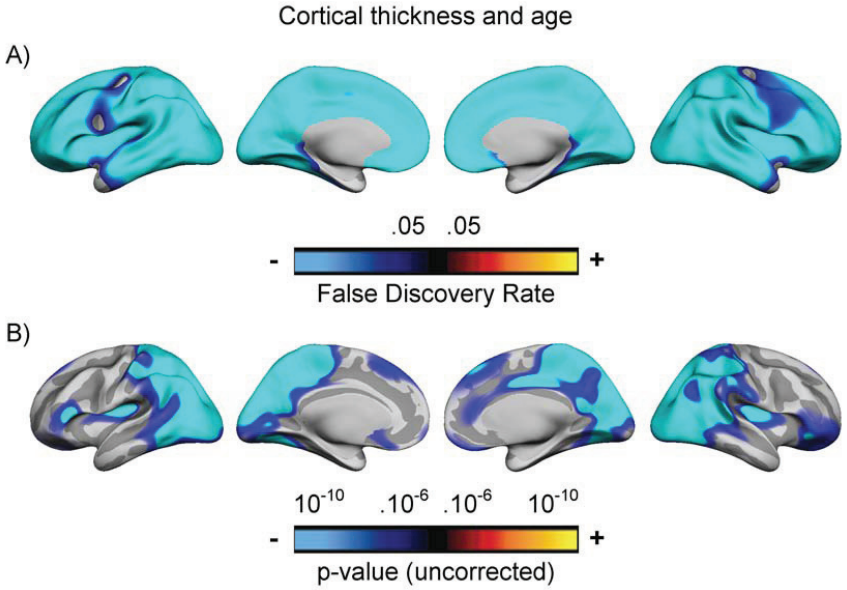

Figure 2. Relationships between cortical thickness and age. The significance (p-values) of the effect of age on cortical thickness when controlling for effect of sex is color coded and projected onto a semi-inflated average template brain. The medial wall and corpus callosum are masked. N = 98. Panel A shows linear relationships corrected for multiple comparisons by using a p-value threshold corresponding to a commonly used criterion (FDR 5 %, upper threshold $p = 10^{-5}$). Panel B shows linear relationships with a more conservative significance level ($p < 10^{-6}$).

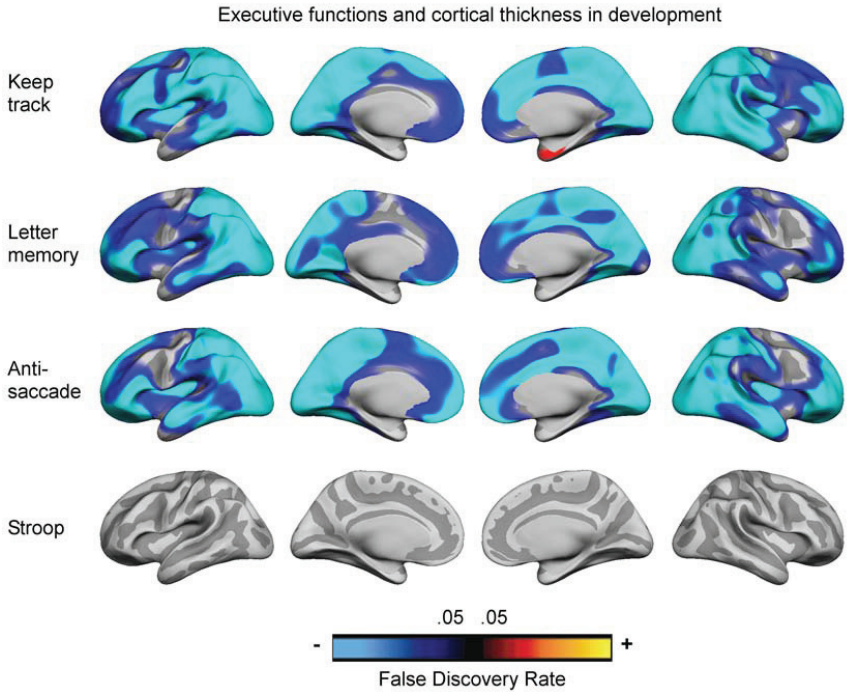

Figure 3. Relationships between executive functions and cortical thickness. The significance (p-values) of the effects of task performance on cortical thickness is color coded and projected onto a semi-inflated average template brain. The effects of sex were regressed out, but note that the effects of age were not controlled for. The medial wall and corpus callosum are masked. A commonly used statistical threshold taking multiple comparisons into account was used (FDR 5 %, upper threshold $p = 10^{-5}$). N = 98.

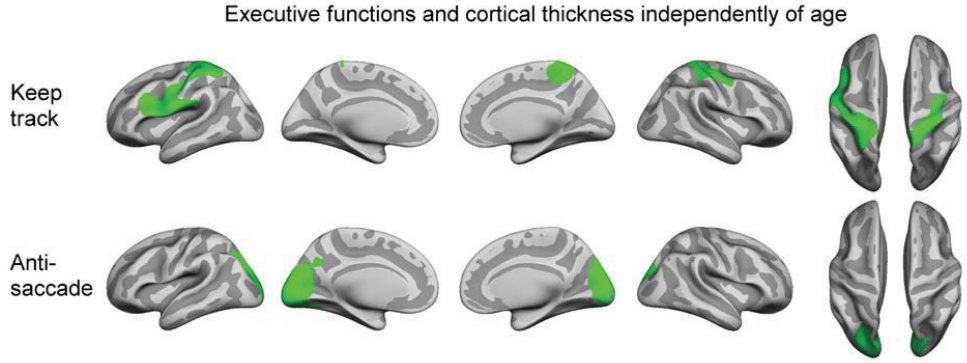

Figure 4. Age-independent relationships between executive functions and cortical thickness. Clusters of vertices with significant associations between task performance and cortical thickness when controlling for the effects of age and sex are projected onto a semi-inflated average template brain. All clusters had negative associations between task performance and cortical thickness. The medial wall and corpus callosum are masked. Cluster-wise $p < .05$ (corrected for multiple comparisons across the surface) was employed. No clusters with significant associations between cortical thickness and Letter memory or Stroop, respectively, were found. N = 98.

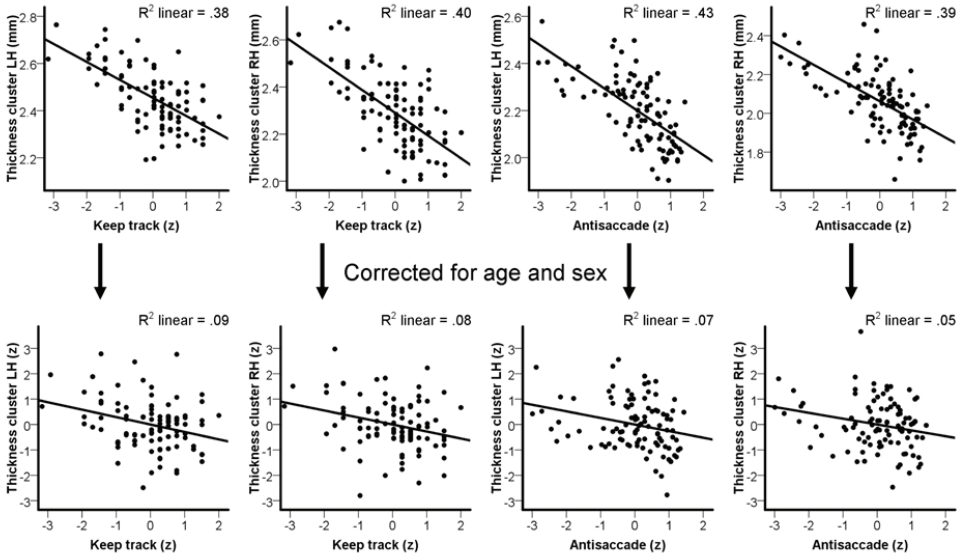

Figure 5. Plots of the relationships between executive functions and cortical thickness. Average cortical thickness in clusters with significant associations (see Figure 4) plotted against task performance. For Keep track, the clusters encompassed parietal and frontal areas around the central sulcus, and also the left inferior frontal gyrus and paracentral areas in the right hemisphere. For Antisaccade, the clusters encompassed occipital and parietal areas, including parieto-occipital cortices, cuneus, pericalcarine and the lingual cortices. The top panel shows raw cortical thickness in mm by executive function measures. The lower panel shows cortical thickness corrected for the effects of age and sex in z-scores. For the task performance measures, z-transformed percentage correct is shown. N = 98. LH: left hemisphere, RH: right hemisphere.

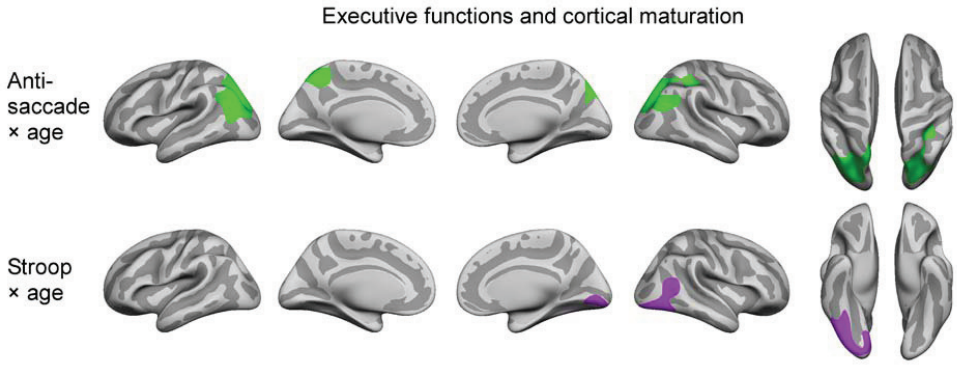

Figure 6. Relationships between executive functions and cortical maturation. Clusters of vertices with significant associations between the interaction terms task performance × age and cortical thickness, while controlling for the effects of age, sex and the respective behavioral measure are projected onto a semi-inflated average template brain. Antisaccade × age showed negative associations with cortical thickness, while Stroop × age showed a positive association. The medial wall and corpus callosum are masked. Cluster-wise $p < .05$ (corrected for multiple comparisons across the surface) was employed. No clusters were found with significant associations between cortical thickness and either Keep track × age or Letter memory × age, respectively. N = 98.

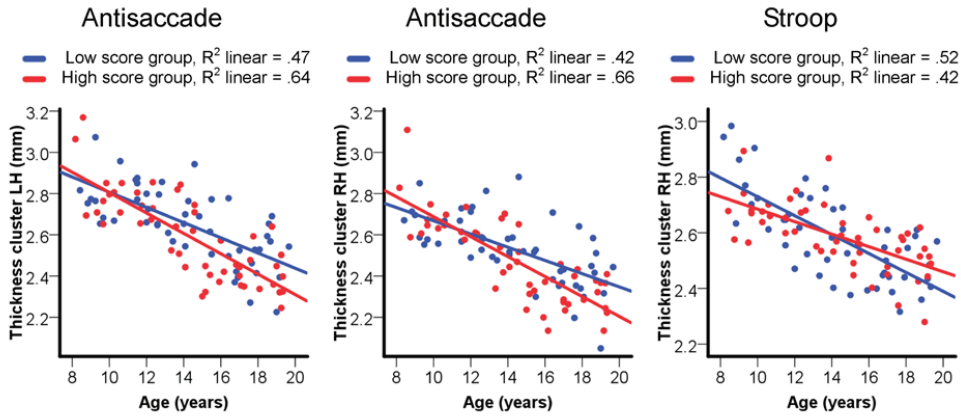

Figure 7. Plots of the relationships between executive functions and cortical maturation. Average cortical thickness in clusters with significant associations (see Figure 6) plotted against age separately for two groups with lower and higher levels of performance, respectively. For Antisaccade, the clusters encompassed mainly the parieto-occipital cortices, with effect extending into the parietal cortices. For Stroop, the cluster was located around the right posterior lingual and fusiform cortices, but also extended into the inferior parietal cortex. Details on group assignment are given in the Methods section. The group labels refer to over and below median performance for that age in the current sample. LH: left hemisphere, RH: right hemisphere. Linear models were fitted for each group and explained variance in both groups is shown. N = 98.

Supplementary Material:

Neuroanatomical correlates of executive functions in children and adolescents: A magnetic resonance imaging (MRI) study of cortical thickness

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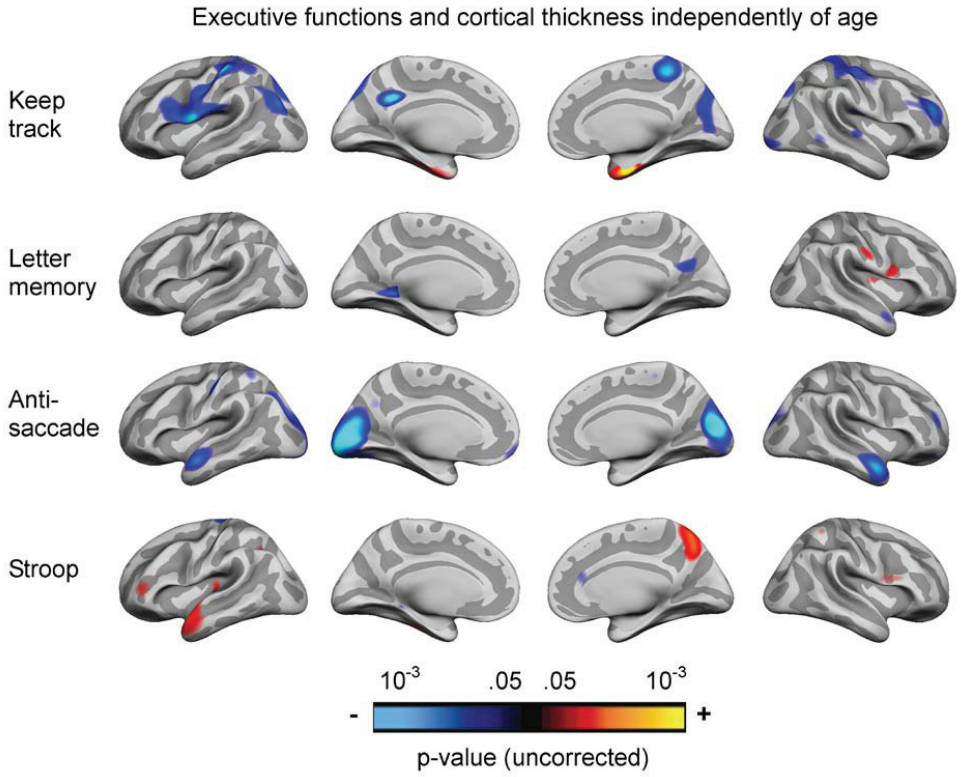
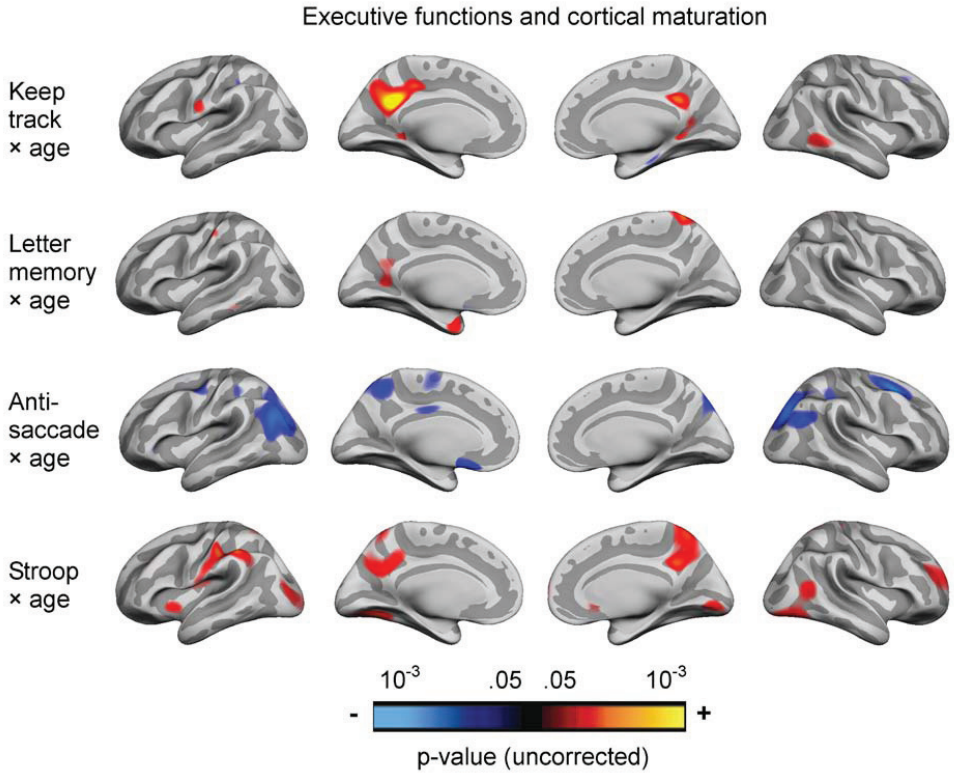


Supplementary Figure 1. Uncorrected age-independent relationships between executive functions and cortical thickness. The significance (p-values) of the associations between executive function measures and cortical thickness, while controlling for the effects of age and sex, are color coded and projected onto a semi-inflated average template brain. The medial wall and corpus callosum are masked. N = 98.



Supplementary Figure 2. Uncorrected relationships between executive functions and cortical maturation. The significance (p-values) of the associations between the interaction terms executive function measures × age and cortical thickness, while controlling for the effects of age, sex and the respective executive function measure, are color coded and projected onto a semi-inflated average template brain. The medial wall and corpus callosum are masked. N = 98.