Memory and the developing brain: short-term and long-term memory function and the heterogeneity of brain maturation.

Ylva Østby

Center for the Study of Human Cognition

Department of psychology

Faculty of Social Sciences

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GENERAL SUMMARY

In this thesis, the developmental brain structure and development of memory functions are investigated, both separately and conjointly. First, the different developmental trajectories of cortical and subcortical brain structures are described. Then, the neurobiological foundations of two instances of memory are investigated in the context of development. The aim of the three studies presented here is to discover relationships between brain maturation, in terms of grey and white matter volumes, cortical thickness and microstructural properties of white matter pathways, and verbal working memory and visuo-spatial long-term memory. The body of literature on brain development is currently growing fast, but unresolved issues still remain. Among these is the controversy regarding hippocampal development: does its volume increase or decrease during late childhood and adolescence? A first step towards understanding the biological foundations of memory development includes a detailed mapping of brain maturation, both in terms of cortical, sub-cortical and white matter development. While a general understanding of structural brain maturation is beginning to achieve foothold in the field of neuroscience, less is known about the relationships between brain maturational events and cognitive development. This is particularly so when it comes to memory development. Thus, although the current thesis can only handle a limited selection of remembering as performed by children and adolescents, this approach constitutes a step towards bridging the gap between biological and cognitive accounts of memory development.

In the first study, volumetric analyses showed great heterogeneity of brain maturation from 8 to 30 years, with cerebral cortex and subcortical structures differing in their declining trajectories towards adulthood. A result that stood out from the rest of the subcortical developmental paths was slight a developmental increase in volumes of medial temporal lobe structures, the amygdala and the hippocampus, of which the hippocampus is particularly important for long-term memory. On the behavioral level, in the second study, developmental differences where also found for different aspects of long-term memory, as measured by the Rey-Osterrieth Complex Figure Test. While recall performance showed a steady increase from 8-19 years, the relative retention of the material between the 30 minutes recall condition and the 1 week recall condition, remained steady at about 83 % throughout the age-span. These differences mapped onto the brain developmental differences, as recall performance was related to cortical thickness in left orbitofrontal cortex, while retention was related to

hippocampal volume. Another way that diversity in brain maturational processes proved to be important in memory development was shown in the third study, where the two processes of cortical thinning and increasing white matter pathway organization where jointly put to the test of predicting working memory performance in development. In this study, theoretically based pre-selected regions within a fronto-parietal network of the left hemisphere, and the connecting pathway of the left superior longitudinal fasciculus (SLF), were related to performance on a digit span task, showing that each of a number of regions of the parietal and lateral prefrontal cortex, as well as the SLF, were almost equally important correlates of performance of both a simple storage span task (Digit Span Forwards) and a complex span task (Digit Span Backwards). Developmentally, the contribution of each of cortical and white matter tract variables seemed to have different impact at different time periods of development, with white matter tract properties being predictive of performance in early adolescence, followed by cortical thickness being the most important correlate of working memory in late adolescence.

Taken together, the three studies underscore the importance of considering multiple facets of brain maturation in studying memory development, both for short-term and long-term memory. Not all brain developmental paths are created equal, and their relationships with various memory processes, like working memory span, long-term memory recall and – retention, are diverse and complex. Considerations of methodological constraints include, among others, the limitations inherent in a cross-sectional design, the problems with keeping the memory variables the same across age groups, and issues concerning the MRI-derived brain variables. Also, the theoretical dilemma of assigning a causal direction to the relationships between brain variables and memory performance is discussed.

LIST OF PAPERS

I. Østby, Y., Tamnes, C.K., Fjell, A.M., Westlye, L.T., Due-Tønnessen, P. &
    Walhovd, K.B. (2009). Heterogeneity in subcortical brain development: a
    structural magnetic resonance imaging study of brain maturation from 8 to 30
    years. *Journal of Neuroscience, 29,* 11772-11782.

II. Østby, Y., Tamnes, C.K., Fjell, A.M & Walhovd, K.B. (in press). Dissociating
    memory processes in the developing brain: the role of hippocampal volume and
    cortical thickness in recall after minutes versus days. *Cerebral Cortex*. doi:
    10.1093/cercor/bhr116.

III. Østby, Y., Tamnes, C.K., Fjell, A.M. & Walhovd, K.B. (in submission).
     Morphometry and connectivity of the fronto-parietal verbal working memory
     network in development.

AMENDMENTS:

Since the submission of my dissertation to the Faculty of Social Sciences on August 8th 2011,
a revised version of paper III has been accepted for publication in Neuropsychologia. It is
now in press, and awailable online (doi:10.1016/j.neuropsychologia.2011.10.001). The
revision resulted in additional analyses of cortical regions outside the predesignated regions of
interest. Apart from this, the discussion and conclusion have not changed substantially.

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INTRODUCTION

As humans, we probably spend as much of our time in the past and future as we do in the here and now. The past supplies us with knowledge of the world, a sense of who we are, and a means for planning for the future. Perhaps in no other period of our lives are we accumulating such a vast and diverse past as during childhood and adolescence. This is the time when our personalities are shaped, and knowledge is gathered in preparation for taking part in society. At school, information is presented that has to be learned, i.e. stored as well as held in mind long enough for the child to be able to follow the teacher's message. Childhood and adolescence is also a time of psychological development, and memory is no exception. Not only do children experience a lot of new information and episodes each day, they are reliant upon a memory system that is not fully developed.

How is the development of memory brought about? What is happening in the developing human being that makes memory ever more flexible, stable and resourceful? A multitude of influences shape the human mind, from small-scale social interactions, to entire cultural frameworks. At the same time as great psychological changes are taking place, the brain, where all memories are experienced, matures towards adulthood. The maturational changes that take place in the developing brain ultimately must play a role in memory development, whether these biological processes are prenatally pre-programmed or shaped by experience.

An understanding of brain maturation as multi-faceted in terms of micro-biological processes as well as observable changes in size and appearance of brain structure has yielded a surge of research efforts to entangle the contributions of each of many brain maturational processes to the understanding of cognitive development. Processes like reductions of abundant synapses and reduced cerebral grey matter, as well as increases of white matter due to myelination and changes in axon size and organization, each are assumed to have a bearing on the developmental outcome on a psychological level.

In order to understand the way brain maturation impacts psychological development, a detailed mapping of brain maturation in itself is necessary. This endeavor has been made possible after magnetic resonance imaging became available for researchers within the field of neuroscience of the normal brain. Structural magnetic resonance imaging studies of healthy children and adolescents have shown that after an initial increase in grey matter, the cerebral

cortex and other grey matter structures decrease in size from 6-10 years of age in some regions, and continue to decrease throughout adolescence (Giedd, Schmitt, & Neale, 2007; Giedd, Snell, et al., 1996; Gogtay et al., 2004; Gogtay et al., 2006; Mackie et al., 2007; Shaw et al., 2008; Sowell & Jernigan, 1998; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell et al., 2004; Sowell, Trauner, Gamst, & Jernigan, 2002). At the same time, white matter increases steadily throughout childhood and adolescence and continues to do so into adulthood (Ashtari, Cervellione, et al., 2007; Barnea-Goraly et al., 2005; Elizabeth R Sowell, 2002; Giorgio et al., 2008; Gong et al., 2008; Guo et al., 2007; Jernigan et al., 2001; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Li & Noseworthy, 2002; Liu et al., 2003; Nagy, Westerberg, & Klingberg, 2004; Paus et al., 1999; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Schmithorst, Wilke, Dardzinski, & Holland, 2005; Sowell, et al., 2002). These are general principles of brain maturation. Of even greater importance is to map out the variation in developmental patterns shown by different parts of the brain, in order to understand the interplay between cognitive and brain maturational changes during childhood and adolescence.

In this thesis, these principles of brain maturation are investigated, and the way in which they impact upon memory development is explored. The developmental period under investigation here spans late childhood from 8 years, through adolescence to young adulthood. Normal development must be studied in order for us to have a reference point with which abnormal development can be compared. This is especially important when it comes to developmental cognitive neuroscience, where complex interplays between brain functioning and cognition may take different forms in health and disease.

In this introduction, I will present some theories of memory, brain development, and how they may be related. I will then present the main objectives of the project.

Memory for short and long periods of time

Memory is not one uniform function. Since the structural memory model was proposed by Atkinson and Shiffrin in 1968 (Atkinson & Shiffrin, 1968), it has become established that memory for different time spans and for different subject matters are distinctly different, each being served by its own system. The original model divides memory into three main stores: sensory memory, short term memory and long-term memory. The present thesis will focus on

the two latter systems, short-term and long-term memory. The short-term memory system deals with limited amounts of information to be kept in mind for a few seconds, while the long-term store encompasses all memories that have made their way into more permanent storage, both personal events of our lives (episodic memory), and general facts and knowledge (semantic memory). The understanding of the short term memory system has been revised to encompass not only storage of information for short time periods, but also the ability to use that information in the here and now in complex tasks. Baddeley and Hitch (A. D. Baddeley & Hitch, 1974) adopted the name ―working memory‖ to describe this system, and their model of working memory as an interface between the information given in the outside world on the one hand, and people's long-term memories and plans and goals on the other, have been further revised (A. Baddeley, 1998) and is widely accepted. Their system of working memory is further divided into separate systems for verbal (the phonological loop) and visuo-spatial material, controlled by a central executive. As most experiences pass through the working memory system before entering more enduring storage in long-term memory, the two systems are connected. Working memory is also the place where memories are held in mind when re-activated from long-term memory (A. Baddeley, 2000).

Working memory has great impact on children's ability to learn and to solve problems (Alloway et al., 2005; St Clair-Thompson & Gathercole, 2006). For instance, when given a math problem, the numbers as well as the type of calculation must be kept in mind while the child at the same time manipulates the numbers to solve the problem. Working memory is often described in terms of capacity, which is limited, and which is known to increase during childhood and adolescence, making it possible for older adolescents to keep increasing amounts of information in mind (Gathercole, Pickering, Ambridge, & Wearing, 2004; Gathercole, Willis, Emslie, & Baddeley, 1992). Not only is the appreciation of children's relatively limited working memory capacity an important point for teachers seeking to adapt to the children's level of learning potential, it also raises the fundamental question of what developments in the brain makes it possible to increase working memory capacity from childhood to adulthood.

Much interest has been invested in understanding development of episodic long-term memory during the first years of life, but Gathercole (1998) states that after 7 years, not much is happening within memory development, except gradual increases in capacities and abilities. The striking changes that take place in the memory processes of pre-schoolers, and the great puzzle of childhood amnesia, perhaps overshadow the more subtle increases in memory

functioning in later childhood and adolescence. The Oxford Handbook of Memory (Tulving and Craik, 2000) reserves three chapters to the development of memory, of which none give any attention to memory development in late childhood and adolescence. Several lines of evidence do however point to qualitative and important changes in long-term memory functioning still taking place during adolescence. Evidence from an electrophysiological (EEG, event-related potentials (ERP)) studies demonstrate that children around mid-childhood are far behind adults in one of two dual processes of episodic recognition memory, the process of contextual recollection which the authors suggest relies more on frontal cortex for the integration of multiple information (Cycowicz, Friedman, Snodgrass, & Duff, 2001), as well as on tasks indexing controlled retrieval processes (Czernochowski, Mecklinger, & Johansson, 2009). Also, while age-norms of standardized episodic laboratory tests such as the Rey-Osterrieth Complex Figure Test (RCFT) (Meyers & Meyers, 1995) show a gradual increase in recall abilities through late childhood and adolescence, the introduction of executive functions to the enhancement of encoding and retrieval processes has been suggested to play an important role for memory improvement during this developmental period (Cycowicz, et al., 2001; Sowell, Delis, Stiles, & Jernigan, 2001). These executive-like functions could involve more or less automatic control processes that help filter retrieved items from long-term memory, or that allocate attentional resources at the time of encoding, at the most basic level (Petrides, 2007). At a more complex level, they encompass more or less voluntary aspects of goal maintenance, structuring and strategy use. The way events and stimuli in the environment are structured by the rememberer at the time of encounter, affects how well it later will be remembered. With a coherent understanding of the to-be-remembered material, fewer individual chunks of memory are needed, and the over-arching structure provides more opportunities for retrieval cues. A third line of evidence concerns a super ordinate level of autobiographical memory development, where research by Habermas et al. (Habermas & Bluck, 2000; Habermas, Ehlert-Lerche, & de Silveira, 2009) informs us about the ever more complex organization of life scripts during adolescence. Many processes in the lives of developing children and adolescents might contribute to these memory gains, such as increased experience, meta-memory skills (Gathercole, 1998), and psychological development as for instance the formation of identity in the case of autobiographical memory (Habermas & de Silveira, 2008). In the current thesis, the focus will be on how brain maturation might contribute to, or be related to, this development. But first, let us take a closer look at brain maturation, as a backdrop for the understanding of brain-memory-relationships in development.

Brain maturation

The development of the brain starts before we are born, with the shaping of the embryonic tract and migration of neurons (Sidman & Rakic, 1973; Stiles & Jernigan, 2010). While we are born with almost a complete number of neurons, our brains are still not completely developed until late adolescence or early adulthood (Stiles & Jernigan, 2010). In the early post-natal years, grey matter, where cell bodies and synapses are situated, continues to grow, driven by the increase in size of cell bodies and a flourishing number of dendrites and synapses (Huttenlocher, 1990; Stiles & Jernigan, 2010). This is thought to lead to an abundance of synapses, which later are reduced in numbers (Huttenlocher, 1979, 1984). The development of most grey matter regions of the brain, including cortical and subcortical regions, is thus characterized by an inverted U-shaped curve: an increase in size in early years, followed by a decrease throughout late childhood and adolescence. The long-distance connections between neurons also undergo development. The process of myelination starts prenatally, and continues throughout development, possibly into early adulthood (Benes, Turtle, Khan, & Farol, 1994; Yakovlev & Lecours, 1967). This is believed to cause white matter volume increase, which is observed to follow a steady, developmental path throughout adolescence (Giedd et al., 1999; Rhoshel K. Lenroot et al., 2007; Reiss, et al., 1996; Sowell, et al., 2002). Two opposing developmental processes, increase of white matter and decrease of grey matter, together characterize brain maturation throughout late childhood and adolescence.

Since the 1990'ies, structural magnetic resonance imaging (MRI) with various analysis techniques have been used to demonstrate these developmental changes in grey and white matter size (Ashtari, Cervellione, et al., 2007; Giedd, et al., 2007; Giedd, Snell, et al., 1996; Gogtay, et al., 2004; Gogtay, et al., 2006; Guo, et al., 2007; Jernigan, et al., 2001; Jernigan, Trauner, Hesselink, & Tallal, 1991; Liu, et al., 2003; Mackie, et al., 2007; Paus, et al., 1999; Reiss, et al., 1996; Shaw, et al., 2008; Sowell & Jernigan, 1998; Sowell, et al., 1999; Sowell, et al., 2004; Sowell, et al., 2002). Of great interest was the finding that different parts of the brain do not mature at the same rate and magnitude. Studies using cross-sectional and longitudinal analysis methods found evidence of protracted developmental trajectories of frontal and temporal cortex (Shaw, et al., 2008). This delay was found both for the top of the curve, the turning point in cortical grey matter development as well as the rate of decline towards adulthood (Giedd, et al., 1999; Shaw, et al., 2008). Subcortical structures have received less research interest, and the developmental trajectories of basal ganglia,

hippocampus, amygdala, thalamus and cerebellum have not been mapped to the same extent as cortical regions. The caudate and the lenticular nuclei (putamen and pallidum) have shown volume decreases, but to varying extent (Jernigan, et al., 1991; Sowell, et al., 1999; Sowell, et al., 2002; Wilke, Krageloh-Mann, & Holland, 2007). Investigations of the hippocampus have yielded conflicting results, with some studies showing a decline like the rest of grey matter structures (Sowell, et al., 2002), while other have shown an increase (Giedd, Vaituzis, et al., 1996; Guo, et al., 2007), yet others have shown different developmental trajectories of frontal and posterior parts of the hippocampus (Gogtay, et al., 2006). This has raised the question of which neurobiological processes might be behind a possible volume increase. The hipocampus is characterized by a plasticity of connections throughout life, which is what may make its contribution to memory consolidation possible (Leuner and Gould 2010). A volume increase could also be explained by processes such as myelination (Benes et al. 1994) and neurogenesis (Leuner and Gould 2010), the making of new neurons from stemcells, found only in a few regions, including hippocampal tissue in humans. Furthermore, the debate also concerns the timing of the developmental trajectory of the hippocampus, with some arguing that, at least functionally, it develops early (Menon, Boyett-Anderson, & Reiss, 2005; Ofen et al., 2007), while others point to its life-long potential for plasticity as proof of its late maturation (Leuner & Gould, 2010). These differences point to the importance of continued research in this field. A clarification of the developmental patterns within the brain may have profound impact upon the understanding of how memory development is related to brain maturation.

While measuring the size of white matter of the brain gives us important information about development, there are other ways of studying white matter maturation in more detail. Diffusion tensor imaging (DTI) is an MRI technique where the diffusion of water molecules in brain tissue lends itself to quantification. Where no obstacles are present, water molecules diffuse in any direction, with their typical diffusion pattern forming a sphere. When obstacles are present on either side of the water molecules, as will typically be the case in a bundle of axons, diffusion is hindered by the membranes, and water molecules travel along the length of the axons, forming an ellipsoid shape. These patterns are picked up on the diffusion-weighted image, where measures of diffusivity are calculated. The mean diffusivity (MD) indicates the degree to which diffusion is free or restricted, and this measure is typically shown to decrease as density of white matter increases (Tamnes, Ostby, Fjell, et al., 2010). The directionality of water diffusion is considered a promising tool for indirectly measuring organization of fiber

pathways. The measure used is called fractional anisotropy, and is a number between 0 and 1, where numbers approaching 1 denote higher degree of directionality of water diffusion. The more uniform the organization of axons, combined with little diffusion across cell membranes, the higher directionality of diffusion. This measure has been shown to increase during childhood and adolescence (Ashtari, Cervellione, et al., 2007; Giorgio, et al., 2008; Lebel, et al., 2008; Tamnes, Ostby, Fjell, et al., 2010). For further specificity, measures of diffusivity along axons and diffusivity across or perpendicular to axons, are also given in these analyses, called axial diffusivity and radial diffusivity, respectively. This is a way of inspecting the separate contributions to FA. Radial diffusivity goes down during development, in pace with the increase of FA (Tamnes, Ostby, Fjell, et al., 2010). DTI has been hypothesized to yield measures of myelination of axons. In support of this, it has been shown in post mortem studies that myelin increases during childhood and adolescence (Yakovlev & Lecours, 1967), at the same time as FA has been shown to increase in the in vivo DTI studies. Also, combined histological and post mortem studies of both humans and animals have shown a relationship between myelin structure and DTI measures, notably RD (Klawiter et al., 2011; Song et al., 2003; Song et al., 2005). Other processes can also be hypothesized to contribute to increased FA and decreased RD, such as axon diameter and density of axons as they may get packed tighter together(Concha, Livy, Beaulieu, Wheatley, & Gross, 2010). DTI has been proven a valuable tool for assessing white matter properties, especially in development and disease.

Theoretical accounts of relationships between brain maturation and cognition

The reduction of grey matter during development is likely to be related to cognitive development. A widespread assumption of the significance of grey matter reduction observed on structural MR images, is that this is reflective of synaptic pruning (Giedd, 2004). The reduction of abundant synapses has been hypothesized to be based on the usage and relevance of these synapses, so that synapses that are not in regular use, whither away and are lost (Huttenlocher, 1984). The result of loosing abundant connections could be a more fine-tuned nervous system where signals are transmitted through the networks that are relevant and not sent astray through additional routes. This likely also gives less noise, and thus a clearer signal transmission. The hypothesis of usage-dependent pruning of synapses could mean that environmental influences are partly responsible for children's brain development. The

reduction of cortical thickness signifies maturational processes that are likely to go alongside developmental increases in cognitive functioning. The finding that different regions of the brain mature at different rates also has consequences for cognitive development. While children can rely on mature functioning of some brain regions, other regions are yet to be fully developed and put constraints on children's usage of the biological basis of cognition. The frontal lobes are traditionally considered the seat of control processes that guide the resources and functioning of other domains of the brain (Lezak, 1995; Miyake et al., 2000). Many functions are thought to be reliant on networks within the brain, consisting of both frontal involvement and more posterior regions. Therefore, the late maturation of frontal cortex likely impacts many cognitive domains during development.

The relevance of studying diffusion parameters in relationship with cognitive development is rooted in the assumption that cognition is a joint endeavor of many brain regions working together. These regions must be able to communicate in order to cooperate smoothly. By holding the potential of indirectly measuring development of myelination, DTI is thought to contribute to the understanding of how increases in inter-region communication contribute to increased levels of functioning. One way in which structural connectivity is related to function is by increasing the speed of signal conduction through the axons. The better the myelination of axons, the faster and more reliable is the action potential likely to travel. This could have major impact on the working together of different brain regions.

Memory in the brain

In the adult brain, memory is not placed in a single spot, but rather is dependent on multiple regions throughout the brain. In the case of working memory, a core network consisting of fronto-parietal regions has been established through functional magnetic resonance imaging and lesion studies (D'Esposito et al., 1998). This network consists of dorso- and ventrolateral prefrontal cortex and posterior parietal cortex on the lateral surface. Different neural support of the phonological loop and the visuo-spatial sketchpad (two of the originally proposed ‒slave-systems" of working memory) have been reported, although the exact nature of hemispheric lateralization or involvement of subregions is not altogether clear (D'Esposito, et al., 1998). The development of working memory has been investigated using functional MRI studies, where increased blood flow indicative of activation in fronto-parietal regions during working memory tasks have been found with increasing age. These changes in cortical

metabolism must be understood in relation to the structural development of these regions through adolescence. Put in another way: we know that working memory develops; we know that brain activation during working memory develops, and we know that cortical thickness develops. But to what extent is structural cortical development a measurable prerequisite for working memory development? So far, it has only been assumed that the structural development is indicative of the functional development, both on the physiological level and the behavioral level, but few efforts have been made to see if it actually is so, and no studies have done this in relation to cortical thickness and working memory. Another line of brain maturational evidence is of great interest in understanding working memory development. The maturation of axonal pathways between the frontal and parietal nodes of the network is likely to play a role in the increased cooperation and speed of processing in the fronto-parietal network. Indeed, a few studies so far have found evidence for the importance of diffusion characteristics of the Superior Longitudinal Fasciculus (SLF), one of the major pathways connecting lateral prefrontal and posterior parietal regions (Petrides & Pandya, 2006), for working memory performance in both adults (Burzynska et al., 2011) and children (Vestergaard et al., 2011), although one study failed to find such a relationship in a sample of children under the age of 10 (Niogi & McCandliss, 2006). Thus, there is evidence for, or hypothesized grounds for, two brain maturational processes being important for working memory development – cortical and white matter maturation. The next question that then arises is how these processes contribute relative to each other in development of working memory. This has been investigated by relating functional brain activation to microstructural properties of white matter (Olesen, Nagy, Westerberg, & Klingberg, 2003), but the processes of cortical thinning in itself and increased white matter organization and maturation as simultaneous prerequisites for working memory development has so far not been investigated directly.

The neurobiological foundations of long-term memory has been investigated with increasing interest since the studies of the amnesic patient H.M in the 1950'ies and onwards (Scoville & Milner, 1957). The misfortune of the epileptic who was partly relieved of his devastating seizures by having the medial part of both of his temporal lobes removed, helped establish the notion of a dissociation between hippocampus and cerebral cortex in forming and maintaining long-term episodic and semantic memories. The hippocampus is seen as the main route through which memories must take in order to be firmly established in long-term memory, perhaps through its contribution of binding together neural activation patterns on the cortical

level until the cortical traces are linked strongly enough to work on their own (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Shimamura, 2002; Squire & Alvarez, 1995; Squire & Bayley, 2007). This process is called memory consolidation, and is a process that can be inferred when comparing what we have experienced (and thus ideally ought to have remembered) with what we can remember of it days and then weeks later. The process of consolidation is obviously of great importance to developing minds, given the enormous amount of information that is new to us in the first two decades of life. Yet, little is known about the development of this process, and how it relates to hippocampal development. If the hippocampus develops relatively early, it might be expected that consolidation, and thus keeping of memories over longer time delays, also develops relatively early. Alternatively, if the hippocampus follows a protracted developmental trajectory, it could help explain why children are still developing their memory skills during late childhood and adolescence. As was noted above, the development of the hippocampi is still under debate, concerning its increase, decrease, or even a more complex trajectory, and whether its development is early or prolonged. Consolidation may also be dependent upon cortical development, as the consolidation process could be seen as a mutual effort of hippocampal binding and cortical representation (Shimamura, 2002), and hence, the prolonged maturation of the cerebral cortex must be seen in relationship with long-term retention as well.

Another way in which brain maturation might be related to memory development is through the processes of attentional control or strategies during encoding, and strategies, and search/matching processes during retrieval. Some of these processes have been linked to the frontal lobes (Dobbins, Foley, Schacter, & Wagner, 2002; Incisa della Rocchetta & Milner, 1993; Petrides, 2007; Simons & Spiers, 2003; Spaniol et al., 2009), which have been shown to develop more slowly than posterior regions, as noted earlier. A few studies have linked structural brain maturation with declarative memory, finding relationships between frontal cortical measures and recall performance (Antshel et al., 2008; Sowell, et al., 2001), but the temporal lobes where not found to be related to any of the recall scores, or only at trend-leve significance, thus still leaving it to further research efforts to find links between hippocampal structure in development and its bearing on memory development. Functional MRI studies of long-term memory encoding have found evidence for a developmental increase of frontal involvement, or connectivity between medial temporal lobe and frontal regions, during memory encoding (Menon, et al., 2005; Ofen, et al., 2007) and a decrease in medial temporal lobe involvement (Maril et al., 2010; Menon, et al., 2005), suggesting that as prefrontal

regions mature, they enable the help from frontal systems of strategy employment or executive control during encoding. These studies focus on the activity of the brain at the time of encoding, and relate this to success of retrieval outside the scanner. Retrieval processes per se have received less attention in the developmental fMRI literature. In the present thesis, the role of different brain regions in different aspects of declarative long-term memory functioning will be explored and discussed.

The diversity of brain maturation, and its role in explaining working memory development as well as long-term memory retention and recall, constitutes the focus of the objectives of the present thesis. This is elaborated in further detail in the following.

MAIN RESEARCH OBJECTIVES

The main purpose of the thesis is to contribute to an increased understanding of the neurodevelopmental foundations of memory functioning. The field of memory and the field of brain development are both too vast to be captured in three focused research articles. Therefore, the main objective is limited to two aspects of memory functioning, chosen as examples of brain-behavior relationships within memory development. These two are quite basic aspects of working memory on the one hand, and long-term memory on the other. By including examples of functions from these different realms of memory, the opportunity to differentiate memory development in the brain is increased. While the aim of the thesis is not to discern the different neural underpinnings of short-term and long-term memory - that has long been established – the different impact of brain maturation on different parts of our memory may give us valuable insight into the developmental processes within brain systems. This over-arching research question will be answered through three more specific research objectives, each covered in its own delineated study. These three objectives are as follows:

1. Brain maturation – what changes in the brain, and how does development unfold across various parts of the brain?

In order to understand the neurobiological foundation of memory development, an account of brain maturation must be present. In the first research paper, the heterogeneity, or diversity of brain maturational trajectories among structures, with an emphasis on subcortical structures, is described in detail. The questions that are sought answered are: what are the effects of age on different brain structures? Do different parts of the brain follow different developmental trajectories? Are subcortical structures different from the cerebral cortex in terms of development? Subcortical structures have received less attention in developmental studies, and understanding brain development needs a full account of patterns of development both within cerebral cortex, white matter and subcortical structures. Of special interest in the area of memory is the development of the hippocampus, where there is still a controversy regarding its developmental course. Therefore, the development of the hippocampus will be discussed later in the thesis with special emphasis on its importance for memory processes. In the first article, gross measures of cortical thickness and white matter volume are presented.

However, the research objective as stated in this paragraph also concerns a more fine-grained understanding of cortical and white matter development, in terms of cortical thickness across the cortical mantle, and white matter microstructure in terms of DTI properties of connections between brain regions. These topics will be dealt with in the second and the third articles, alongside the topics of working memory and long-term episodic memory functions.

Hypotheses: Cortical grey matter is hypothesized to decrease, and this reduction is expected to follow somewhat different rates of decline in different lobes of the brain, with frontal and temporal lobe cortical grey matter volume showing the latest development. Subcortical structures are expected to follow mainly the same pattern of grey matter reduction, with the exception of the amygdala and hippocampus, where grey matter volume increase may be found. Cerebellar grey and white matter development has not been characterized in development prior to the study of Paper I, but it is here expected that cerebellar grey matter volume will decrease in line with most cortical and subcortical grey matter. White matter is hypothesized to increase, perhaps at a steeper rate during childhood and adolescence than adulthood. Diffusion properties of white matter (as described briefly in Paper III) are hypothesized to develop, with increased fractional anisotropy and decreasedradial diffusivity.

2. Long-term memory – how are different aspects of a long-term memory task related to cortical and subcortical grey matter maturation?

Testing long-term memory for a visuo-spatial material, the questions that are asked within the second objective are: How do recall, organizational abilities and retention develop between 8 and 19 years? How are recall abilities (after 30 minutes and 1 week) related to cortical (possibly frontal) and hippocampal development? And how does organizational ability influence such relationships? It is hypothesized that the employment of organizational strategies during encoding relies on prefrontal cortical regions, and that organizational strategy influences how well the material is recalled, thus causing a relationship between prefrontal cortical thickness and recall. Further, it is asked how retention over an extended time period (1 week) is related to cortical thickness and hippocampal volume. Is the relationship between hippocampal volume and memory performance dependent upon the duration of the delay? The kind of long-term memory will be mainly episodic since the instance in which the material is learned is of importance for retrieval of the material. The key processes that are investigated may be generalized across different classes of explicit long-

term memory, though. A fourth question is then asked: is level of memory performance associated with different developmental trajectories in any of these brain variables? If so, this may mean that rate and pattern of brain maturation may be related to memory performance.

In answering these questions, the Rey-Osterrieth Complex Figure Test (Meyers & Meyers, 1995; Osterrieth, 1944) was chosen as the measure of long-term visuo-spatial memory. This is a laboratory-based memory test with standardized scoring criteria, which has been widely accepted in neuropsychological practice (Lezak, 1995). Most importantly, it holds the opportunity to measure recall after various time delays, as well as measures of organizational strategy (Deckersbach et al., 2000). Because retention across longer time delays is an important facet of memory that has not been fully investigated in development using standardized tests before, the standard procedure of the RCFT was supplemented by adding a 1 week recall condition.

Hypotheses: it is hypothesized that recall performance will increase with increasing age, as will organizational strategy employment. The development of retention of the material over a week's delay is difficult to predict, as there are no studies available on this. Relating these memory measures to brain structure, it is hypothesized that recall performance will be related to cortical thickness in prefrontal areas, and that this relationship may be mediated by the ability to apply structure to the figure, thought of as organizational strategy employment. Based on a study using a list-learning memory task and extended delays (weeks) in adults (Walhovd et al., 2004), hippocampal volume may show involvement at longer time delays.

3. Working memory development – how is it related to different aspects of brain maturation during late childhood and adolescence?

A fronto-parietal network has been established as important for working memory, and the objective of the third study was to investigate the importance of cortical thickness and structural connectivity within this network for working memory performance in development. The question of which of the maturational processes –cortical thinning or white matter development- is responsible for the increase in simple and complex working memory span is approached by delineating the core regions of the network and its main route of communication, and testing the contributions of each to working memory performance individually and together. A related question is whether these two maturational processes play

different roles during development: are they equally important for working memory performance across development, or is one more important than the other at one period of time and vice versa? Answering this question not only gives us information about the development of the working memory network, but also a general understanding of the working together of different brain maturational events.

The working memory measure used in this thesis to answer these questions, is the Digit Span subtest of the Wechsler Intelligence Scale for Children, 3rd edition (WISC III (Wechsler, 1992)), with its two sub-tests of Digit Span Forwards and Digit Span Backwards. This test was chosen because it is a well-known measure, yielding scores that tap either simple short-term storage capacity, or complex manipulation within working memory. The task is easy to administer and takes minimal time, an attribute that is of importance within the context of measuring multiple cognitive functions during limited time in the laboratory.

Hypotheses: It is hypothesized that cortical thickness in regions within the left fronto-parietal network (superior parietal, inferior parietal, supramarginal, caudal middle frontal, rostral middle frontal, pars opercularis and pars triangularis) will correlate with working memory performance independently of age, as will microstructural properties (FA and RD) of the SLF. Further, it is hypothesized that cortical maturation and fiber tract development will contribute uniquely to working memory performance. No exact hypotheses are set forth in relation to the division of the sample into age groups, as no such studies have previously been undertaken. Grey and white matter development may have different impact on working memory performance across development, if they are independent contributors to working memory performance. On the one hand, white matter development is a continuing process throughout late adolescence and early adulthood, and could play a greater part in the oldest adolescents by refining the network. On the other hand, connecting the regions within the fronto-parietal network could be more important earlier in development, in order for the cortical regions to come into play in predicting individual differences in working memory performance.

Summary of main hypotheses

It is hypothesized that brain maturation is characterized by great diversity between structures in their developmental trajectories, and that this diversity or heterogeneity in brain maturation may relate to different aspect of short- and long-term memory processes.

METHODS

Design

1. Cross sectional description of brain development

In the current study, a cross-sectional design was employed to describe brain maturation. Children, adolescents and young adults were compared at one time-point, at different ages. We strived towards including an equal number of participants in each age cohort, with an equal number of males and females. The cross sectional approach is valuable in that it gives us a ―snapshot" of development within an obtainable time frame. The design has its limitations, though. One of them is the possibility of cohort effects. This could cause a false developmental effect when characteristics typical of one cohort or time period also cause changes in brain or cognition. Factors include nutritional differences in both childhood and in utero, differences in educational practices and intellectual stimulation, and other health-related differences. When these factors are different in different age cohorts, they may give a false impression of developmental effects. On the other hand, developmental effects may be harder to detect in a cross-sectional design, due to the great variability in brain size and brain function between individuals. Also, individual differences in maturational trajectories could cause a lack of observed developmental effects. For instance, in a period when grey matter changes its course from an increasing to a decreasing trajectory, some participants may be on their way ―up", while others may be on their way ―down", i.e. at different points in their maturational curves. When only one time point is available, this information is lost.

2. Relationships between brain maturation and memory, and inferring causality

The current study uses correlations and regression analyses to describe the relationships between brain variables and memory function in development. This design is based on the assumption that there are individual differences in brain structure and in memory scores, and that these individual differences are coherent with each other. An implicit assumption is that brain structure causes people to perform psychologically. However, causality is not possible to ascertain in the present design, and could potentially also go in the opposite direction. Further discussion of this topic is given in the Discussion part of the thesis.

3. The third variable

In order to find out whether individual differences in brain structure are correlated with, or predictive of individual differences in memory function, other factors that might induce a correlation, i.e. a possible third variable, must be accounted for. Even though there may be numerous extraneous variables present in the study, which we hope to indirectly control by making sure that the age cohorts are as similar as possible, there is one factor that has substantial impact on both main variables under study. This is of course the participants' age. When both brain structure and memory functioning changes as children grow older, the finding that, for instance, higher memory functioning comes with thinner cortex might just be caused by the fact that those with higher memory scores happen to be the oldest adolescents, who have the thinnest cortices. Therefore, the problem of age effects must be overcome. This has been done in three ways in the study. The perhaps simplest way is to control for the effect of age in all analyses. This is a conservative approach, which will only make us certain that when an effect withstands this correction, it is most likely a genuine effect. It will however not guarantee that the effects that remain are the only true relationships. More subtle relationships may be lost. Also, by controlling for age, the main reason for studying development in both brain structure and memory function is in some ways lost. After all, it is development that is of importance. By controlling for age, the results describe relationships between brain variables and memory function, as they appear *in a sample of developing people.* The second method to deal with the age effect, is to separate the sample into age groups. The age effect will be smaller within each age span, and if the age groups are narrow enough, it may not be necessary to control for age at all. Using an age group approach also enables us to investigate developmental changes in the patterns of brain-behavior relationships. The third method is to include an age interaction term in regression analyses. This interaction term can be an age x performance variable, or an age x brain structure variable. This analysis will yield insight into the developmental trajectories of different performance levels, in other words, answer the question: are age effects on brain structure dependent upon individual differences in cognitive performance? This analysis has great potential to reveal interesting patterns of development, where advantageous brain structural trajectories can be isolated. The downside of it is the high level of statistical control, which makes it a conservative analysis. By introducing all three of these approaches in the study, the hope is that brain-behavior relationships will be covered in relationship with age in an extensive manner. However, it must be noted that the choice of each of these analyses were

made on different grounds in the three papers, depending on the specific objectives of the studies.

Participants

A total of 171 children, adolescents and young adults participated in the study. Of these, 171 participated in the study of paper I, 107 participated in the study of paper II and 108 participated in the study of paper III. Of the 171, 60 were adults between 20 and 30 years old, who participated in a parallel project on plasticity through the life span. The reason for the varying number of participants in the three studies is that not all participants completed all examinations, and because the young adults originally took part in a partly different study where behavioral measures were not directly comparable to the child equivalents used in the developmental study. The three sets of participants will be described in detail below, after a general description of recruitment and inclusion criteria.

Recruitment

Participants were recruited through newspaper advertisements, through mass e-mails to University of Oslo staff at various departments, students, through contact with schools within Oslo, and through ―snowball sampling", i.e. recommendations from other participants. This kind of convenience sampling increases the risk of a sample that is not representative of the general population. This is important to bear in mind, as developmental trajectories could be different at different levels of functioning. Shaw et al (Shaw et al., 2006) found evidence for this in a longitudinal study. Thus, by including too many children with abilities above the average (given that their parents are highly educated which in turn may reflect on genetic material as well as stimulating upbringing), only a part of the picture of brain maturation might be captured. Nevertheless, we deemed this to be an acceptable approach for three reasons: 1. the recruitment through newspaper advertisements, while directed at the general public, might also lead to a biased sampling of children and parents with a special interest in science. 2. As long as IQ and demographic variables are evenly distributed across the age span, it should not be the source of false developmental effects, and 3. Some general principles of development will be revealed if 2. is fulfilled, even though the description of brain volumes and test scores are not generalizable to the population as a whole. In Table 1,

the mean full scale IQ, as measured by the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler, 1999), is shown for the whole sample, divided into 4 age groups.

Inclusion

All participants were screened before entry into the sample, using a short structured interview, performed with participants 12 years and older, and with parents of participants aged 8-19. Potential participants were asked about sight and hearing, handedness, Norwegian language skills, history of psychiatric and neurologic disorders, head trauma, medication, history of special education, birth circumstances, and, for the purpose of the MRI scanning, whether they had a history of claustrophobia and whether they used metallic dental braces. Exclusion was based on the presence or history of psychiatric disorders of some severity (grief and reactions to divorce were not reasons for exclusion), neurological conditions such as epilepsy, and head trauma with loss of consciousness or post-traumatic amnesia. Premature birth or traumatic birth with asphyxia were also reasons for exclusion, as were a history of receiving special education due to learning disabilities or developmental delays. Only right handed participants who spoke Norwegian fluently were entered into the study. Further exclusion was based on missing data from one or more investigations (MRI or cognitive testing). An overview of the inclusion of participants in the three studies is given in Figure 1.

Characteristics of samples

Paper I participants: 171 children and young adults (84 males) were included. Pearson's Chi square test revealed no differences in gender distribution for the age groups shown in table 1 (Pearson's Chi square = .870, p = .93). Participants were tested using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), and all participants scored above 80 on full scale IQ (M = 110.27, SD = 9.96). There was no difference in IQ between males (M = 111.8, SD = 10.5) and females (M = 109.2, SD = 9.2; t [168] = -1.697, p = .10). Among the 176 participants who met inclusion criteria, 4 had no useable MRI scans due to movement artefacts. All participants' scans were examined by a neuroradiologist, which led to the exclusion of one additional participant, reducing the total number of participants to 171.

Paper II participants: 107 children and adolescents (55 males) aged 8 to 19 years participated in the study (M = 13.90, SD = 3.42). The distribution of sex and age in three age groups is shown in Table 1. Among the initially 116 children and adolescents who met the inclusion
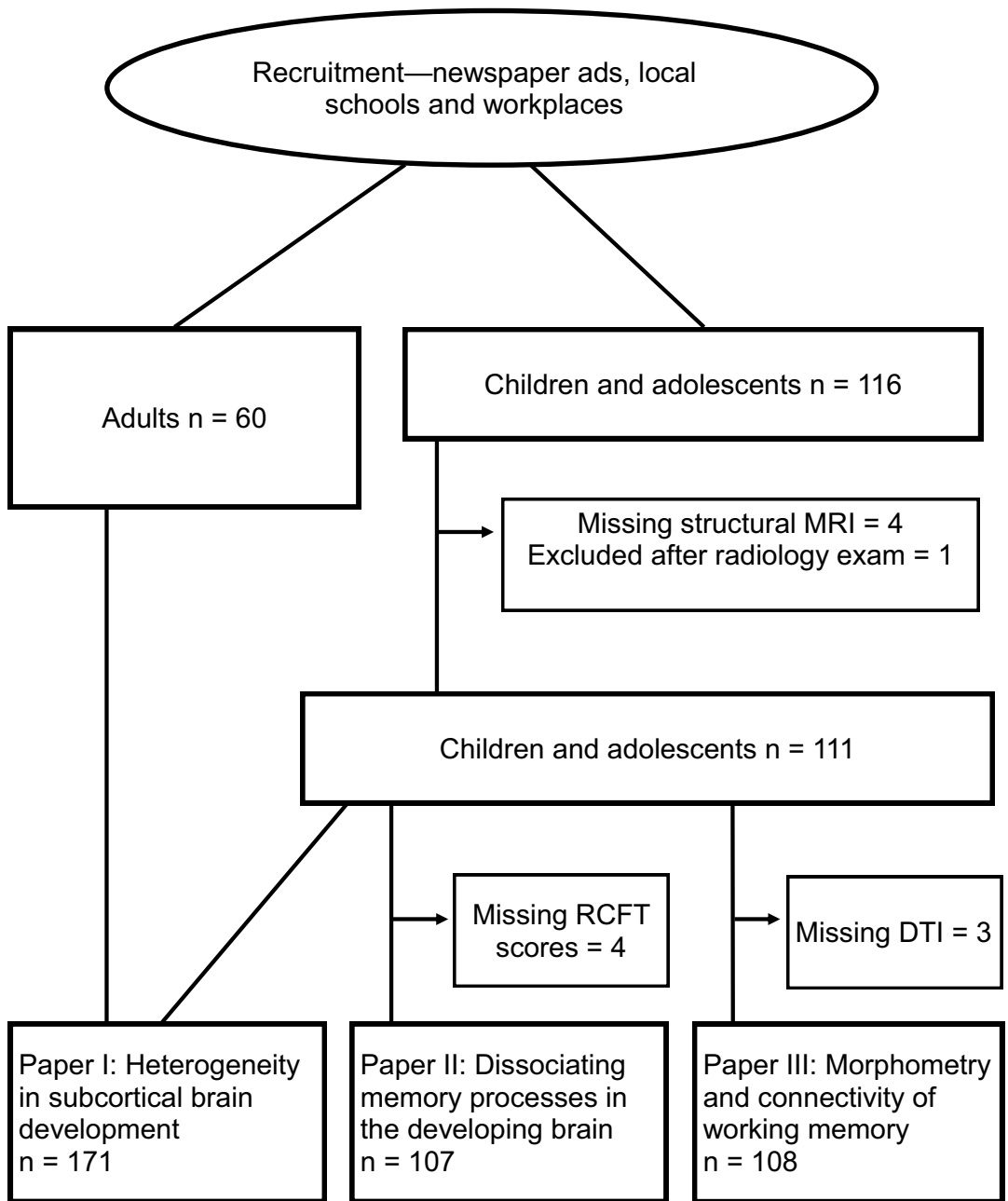
Figure 1. Participant recruitment and inclusion in the three studies. Paper 1 includes all children/ adolescents with usable scans + all adults aged 20-30 years. Papers II-III include only children and adolescents, with varying amount of excluded participants due to missing memory scores or DTI scans.

Table 1

Characteristics of the three samples, divided into age groups.

Age groups

	8-11		12-15		16-19		20-30	
Paper I participants								
N	38		37		36		60	
Males/Females	21/17		18/19		17/19		28/32	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Full scale IQ	107 (11.1)	82-127	108 (10.7)	91-141	112 (10.5)	91-132	113 (7.1)	100-126
Paper II participants								
N	36		36		35			
Males/Females	21/15		17/19		17/18			
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range		
Full scale IQ	108 (11.0)	82-127	108 (10.7)	91-141	113 (10.4)	91-132		
Paper III participants								
N	36		37		35			
Males/Females	19/17		18/19		16/19			
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range		
Full scale IQ	107 (11.0)	82-127	108 (10.7)	91-141	112 (10.5)	91-132		

criteria, 4 had no useable MRI scans. All participants' scans were examined by a neuroradiologist, which led to the exclusion of one additional participant. Of the 111 remaining participants, 4 participants did not complete all memory tests at all trials, leaving the sample with 107 children and adolescents. There was no correlation between sex and age in the current sample ($r = -.08$, $p = .405$, females coded as 1, males as 2). Participants were tested using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999), and all participants scored above 80 on full scale IQ ($M = 109.11$, $SD = 10.92$, range: 82-141). The

distribution of WASI full-scale IQ in three age groups is shown in Table 1. There was no difference in IQ between males (M = 110.34, SD = 11.88) and females (M = 107.85, SD = 9.787; t [109] = -1.201, p = .232).

Paper III participants: 108 children and adolescents (53 males) aged 8 to 19 years participated in the study (M = 13.89, SD = 3.46). The distribution of sex and age in three age groups is shown in Table 1. Among the initially 116 children and adolescents who met the inclusion criteria, 4 had no useable MRI scans due to movement artifacts. All participants' scans were examined by a neuroradiologist, which led to the exclusion of one additional participant. Of the 111 remaining participants, 3 participants did not complete DTI sequences, which resulted in a final sample of 108. There was no correlation between sex and age in the current sample (r = -.07, p = .453, females coded as 1, males as 2). Participants were tested using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), and all participants scored above 80 on full scale IQ (M = 108.91, SD = 10.90, range: 82-141). The distribution of WASI full-scale IQ in three age groups is shown in Table X. There was no difference in IQ between males (M = 110.00, SD = 11.94) and females (M = 107.85, SD = 9.79; t [106] = -1.023, p = .309).

Magnetic resonance imaging

MRI acquisition

Participants underwent magnetic resonance imaging (MRI) in a 1.5-Tesla Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany), using a 12-channel head-coil. The main sequences were two structural scans and a diffusion weighted scan. Two structural MRI sequences, each consisting of a 3-D T1-weighted image magnetization prepared rapid gradient echo (MP-RAGE) were run for each participant, with the following parameters: time repetition/time echo/time to inversion/Flip Angle= 2400 ms/3.61 ms/1000 ms/8°, matrix 192 × 192, field of view = 192. Each scan took 7min, 42 s. Each volume consisted of 160 sagittal slices with voxel sizes 1.25 × 1.25 × 1.20 mm. Each MP-RAGE was visually inspected and only scans deemed to have no or minimal movement artefacts were included in analyses. The two MP-RAGEs were averaged to increase the signal-to-noise-ratio. Where there were problems achieving two high quality scans due to motion artefacts etc, only one scan was used in the analysis. This was the case for 15.2% of the participants in the sample of Paper I,

of whom most (73%) were in the 8-11-year cohort. The percentage of participants of Paper II with only one scan was 22.4 (with 75 % within the 8-11 group); while 23.1 % of the participants of Paper III had only one scan (72% were in the 8-11 group). Diffusion-weighted images were acquired using a single-shot twice refocused spin echo planar imaging pulse sequence with 30 diffusion sensitized gradient directions and the following parameters: time repetition/time echo = 8200 ms/82 ms, b value = 700 s/mm2, and voxel size = 2.0 3 2.0 3 2.0 mm, with a total scanning time of 11 min, 21 s. This sequence is optimized to minimize eddy current- induced image distortions (Reese, Heid, Weisskoff, & Wedeen, 2003). The sequence was repeated in 2 successive runs with 10 non-diffusion-weighted images (b = 0) in addition to 30 diffusion-weighted images collected per acquisition. The 2 acquisitions were averaged during postprocessing to increase signal-to-noise ratio. Each volume consisted of 64 axial slices. Further, in order to aid the neuroradiological examination of subjects, a T2-weighted fluid-attenuated inversion recovery sequence was run.

Morphometric analyses

The structural MRI scans (MP-RAGEs) were used to obtain measures of cortical thickness, cortical volume, cortical surface area, white matter volumes and volumes of subcortical structures, cerebellum and brainstem.

Cortical surface-based analyses

Regional cortical thickness was estimated using FreeSurfer 4.0.5 (http://surfer.nmr.mgh.harvard.edu/fswiki) by means of an automated surface reconstruction procedure (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Segonne et al., 2004). The main principle behind the surface-based analysis is that two surfaces are generated from the MR images: a white matter surface and a pial surface (the surface of the cortex), based on intensity and continuity information from the MR image, i.e. the border between white matter and the cortex, and between cortex and cerebrospinal fluid. The two borders are shown in a MR image from one participant in Figure 2. Then, a mesh of vertices are overlaid the surface, each vertex being a point of measure of cortical thickness, which is the distance between the two surfaces as shown in Figure 2. The mesh of vertices is shown in one participant's
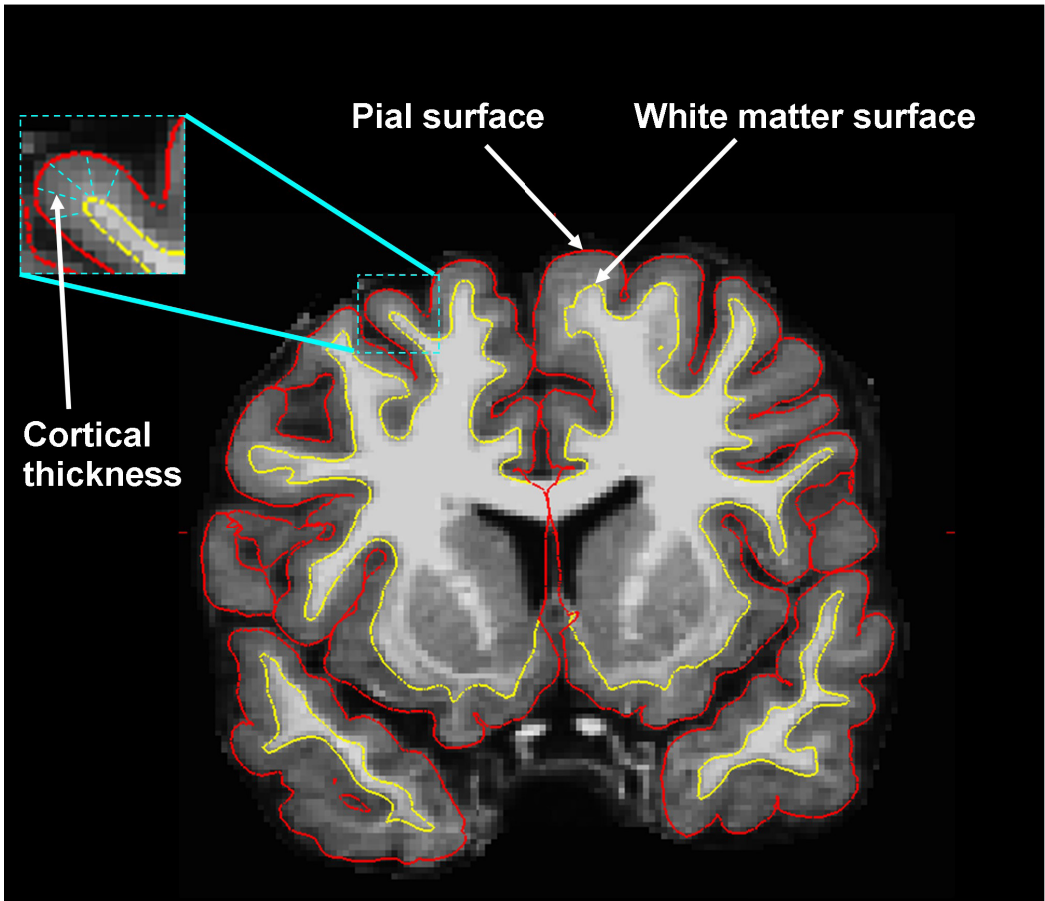
Figure 2. The two surfaces and the thickness measure between them. The red outline is the border between grey matter and cerebrospinal fluid/non-brain tissue (pial surface), while the yellow outline is the border between white matter and grey matter (white matter surface). An illustration of how the distance between the surfaces might be measured is shown in the enlargement in top left.
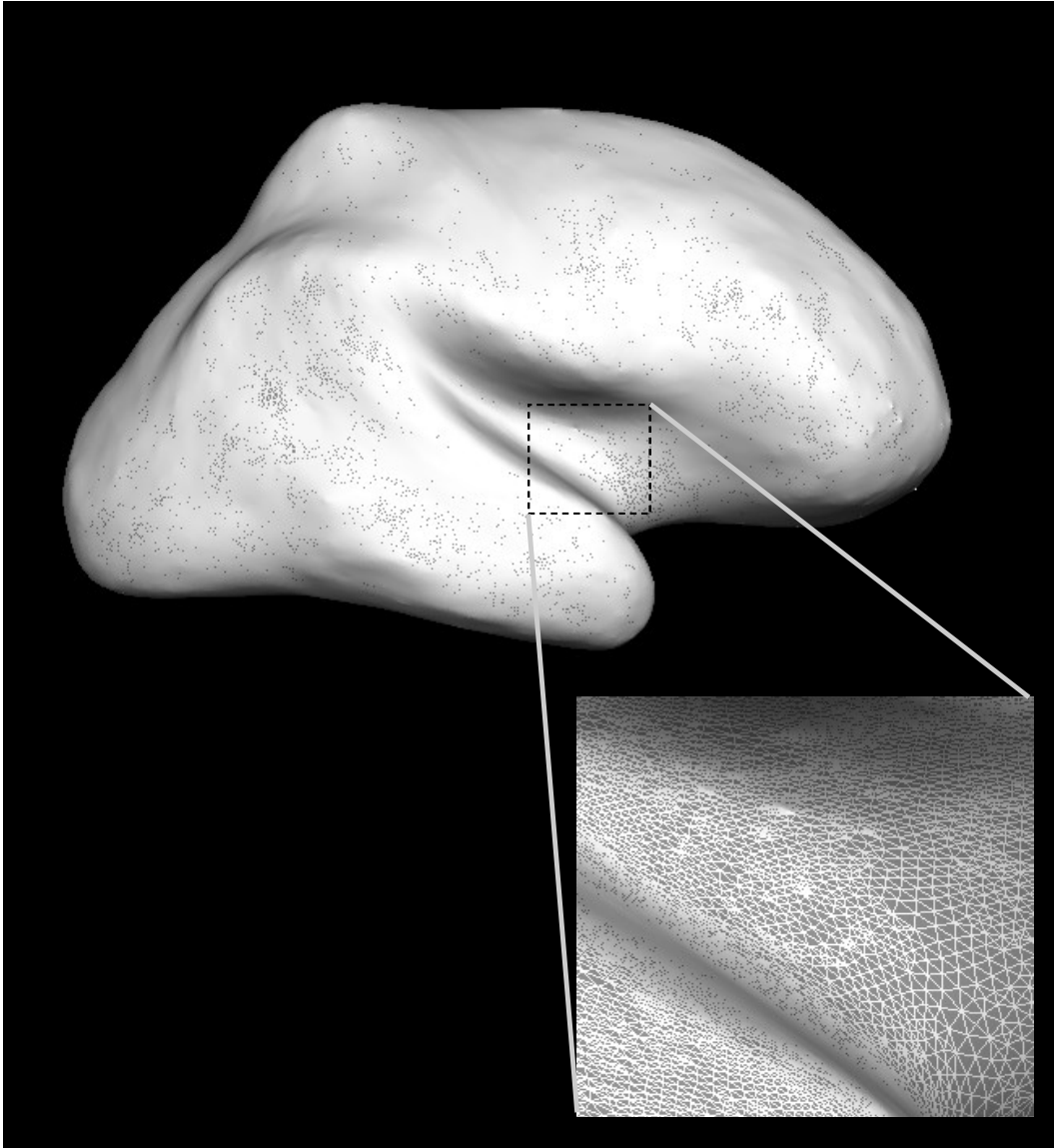
Figure 3. Example of vertices on a semi-inflated right hemisphere, taken from a 3D re-construction of the MR-images of one participant. The mesh of vertices can be seen in the enlargement.

reconstructed and semi-inflated right hemisphere in figure 3. Likewise, a measure of cortical surface area is calculated at the 2D surface level. Cortical volume can then be calculated as thickness x surface area. Minor manual editing of vessels and dura was routinely performed, according to Freesurfer guidelines (See http://surfer.nmr.mgh.harvard.edu/fswiki). The main ―problem areas" included insufficient removal of non-brain tissue, especially blood vessels, among other places in the vicinity of the orbitofrontal cortex. The surface reconstruction procedure makes it possible to compare participants on similar surface locations independently of each person's unique morphological signature, by aligning them according to major landmarks on the surface. Additionally, the surface reconstruction is not restricted to the original voxel size of the MR images, thus making it possible to calculate thickness and area at a sub millimeter level. The measures of thickness, surface area and volume can be obtained for the whole hemisphere, or they can be divided into 33 cortical parcellations, based on the main gyri. In this case, mean cortical thickness within a parcellation is given. The 33 parcellations are shown in Figure 4. Alternatively, cortical thickness at each vertex can be entered into general linear models for whole-brain surface analyses.

Volumetric analyses

The size of brain structures was obtained by segmenting the MR images into grey and white matter based on intensity and continuity information, using Freesurfer 4.0.5. A probabilistic atlas approach was used, which takes into account the positioning of each structure relative to each other when assigning labels to the resulting brain regions. The procedure is automatic, and is described in detail by Fischl et al. (2002). The segmentation yields volumes of the caudate, putamen, pallidum, accumbens, thalamus, hippocampus, amygdala, cerebellum cortex, cerebellum WM, lateral ventricles, inferior lateral ventricles, 3rd and 4th ventricles, and total cerebral WM. Examples of the segmentation is shown in Figure 5. The automated segmentations have been found to be statistically indistinguishable from manual labelling (Fischl, et al., 2002), and correlations between Freesurfer segmentation and manual labelling of hippocampal volume reached .85 in a study by Tae et al (2008). The segmentations were visually inspected for accuracy, but no editing was performed. The ventricles are only partly segmented, particularly the 3rd ventricle and the inferior lateral ventricle. This should be kept in mind when considering the results. The brainstem is not segmented further into separate WM and GM volumes. All volumes were used as variables of interest in Paper I, while only
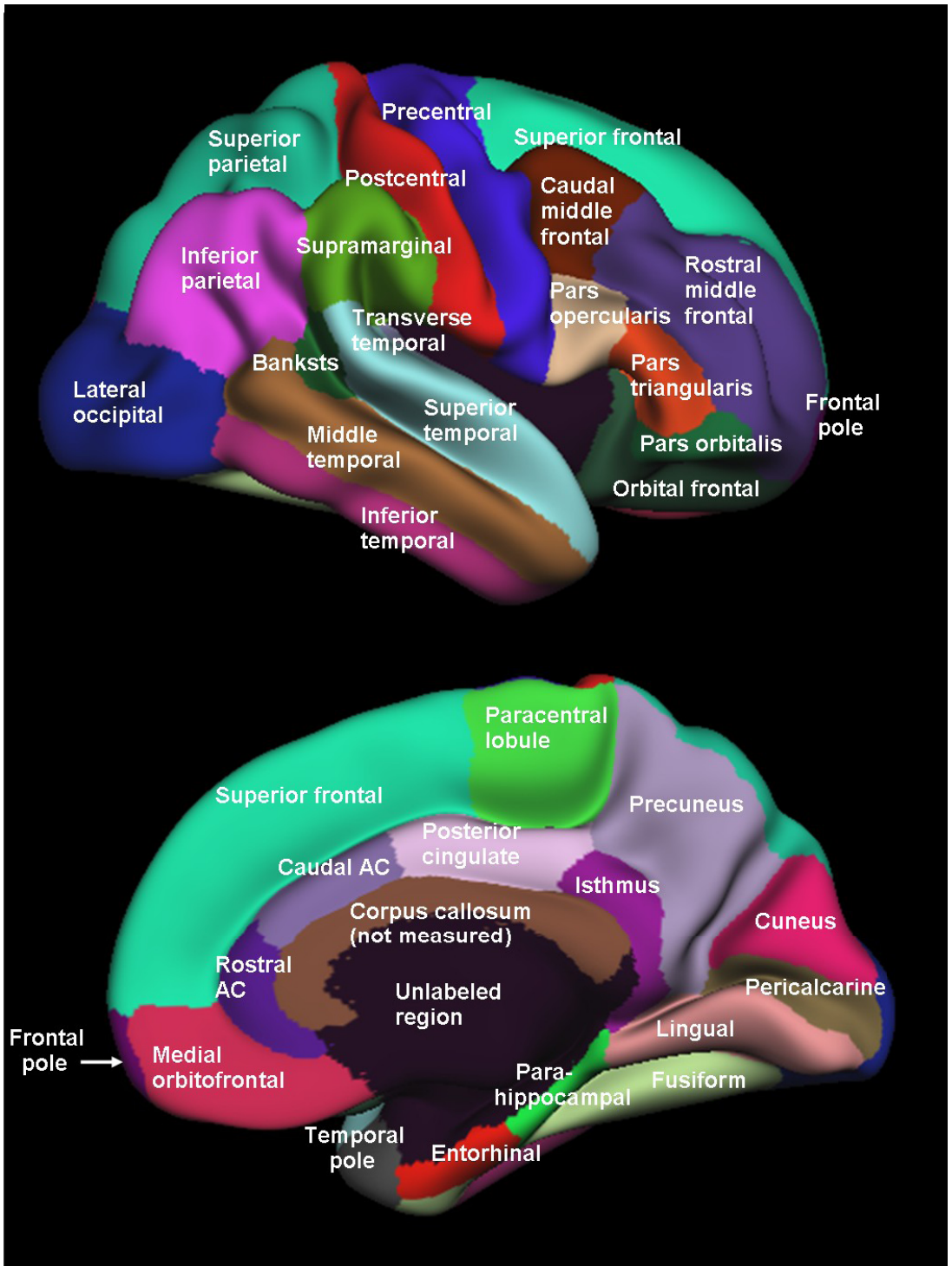
Figure 4. Cortical parcellations. Tops panel shows the parcellations on the lateral surface, while bottom panel shows parcellations on medial surface of an average semi-inflated right hemisphere.
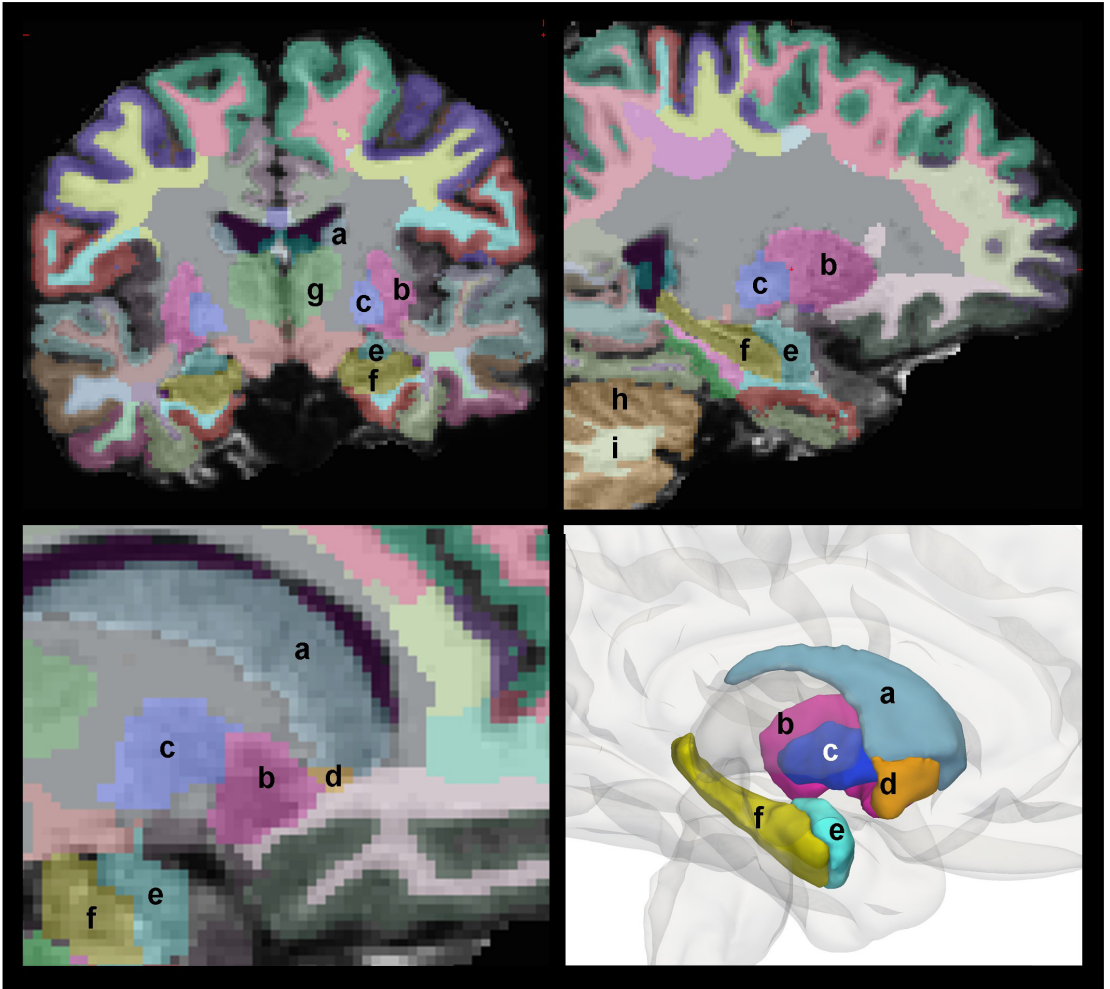
Figure 5. Segmentation. The first three panels show the segmentation as a coloured overlay on the MR images of one participant, in (from top left) coronal view, sagittal view and close-up of another sagittal view. In addition to the subcortical structures, white matter and cortical parcellations are also given different colours in these images, but the reader may only concider the subcortical structures which here are given letters. a = caudate, b = putamen, c = pallidum, d = accumbens area, e = amygdala, f = hippocampus, g = thalamus, h = cerebellum cortex, i = cerebellum white matter. The bottom right panel shows a 3D rendering of some of these subcortical structures, based on an average of participants, using Slicer software.

the hippocampus was included in the study of Paper II (although all brain matter volumes were used as a combined total brain volume (TBV) variable in order to control for individual differences in brain size).

Diffusion tensor imaging analyses

DTI analyses were performed using Tract Based Spatial Statistics (TBSS) in FSL (http://www.fmrib.ox.ac.uk/fsl/index.html) (S. M. Smith et al., 2004; Woolrich et al., 2009). Here, a common white matter ―skeleton" is derived, which maps only the white matter bundles, based on high Fractional Anisotropy (FA), that is common to all participants. 168 participants with full sets of diffusion weighted images (aged 8-30, although statistical analyses were done with participants aged 8-19) were used to derive the common FA skeleton. Each participant is then aligned with the common skeleton, and FA values are sampled from within a limited distance from the core of the skeleton. This is done to ensure that only axon pathways are being used to generate the diffusion variables, not white matter or even grey matter where axons go in multiple directions. The same steps of analyses were performed, this time using RD (radial diffusivity) instead of FA values. Examples of the FA skeleton are shown in Figure 6. In order to obtain DTI measures from predefined white matter tracts, binary masks based on a probabilistic tractography atlas (the Johns Hopkins University (JHU) white-matter tractography atlas) (Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005), as provided in FSL, were created. Voxels intersecting both the skeleton and the white matter tract were used in subsequent regional analyses, and mean FA and RD within the tract were calculated. The superior longitudinal fasciculus (SLF) was the main tract of interest in paper III, and a 3D reconstruction of this pathway is shown in Figure 7 along with the cortical ROIs that were used in paper III.

Memory assessment

In order to approach the development of memory functioning from two different angles, a working memory test and a long-term memory test were chosen for analyses. The two tests were part of a larger battery of neuropsychological and experimental tests, some of which have been reported on earlier (Tamnes, Ostby, et al., 2010a, 2010b). Both tests were included in the study based on widespread recognition of their psychometric properties. Also, it was
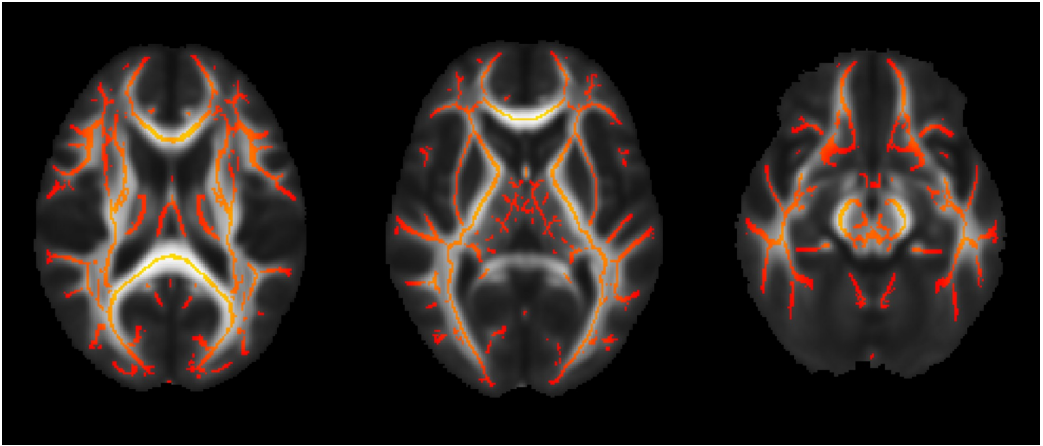
Figure 6. White matter "skeleton". Red/orange voxels indicate the "core" of white matter pathways common to all participants, overlaid a fractional anisotropy (DTI) image based on average of participants. The sceleton shown here is based on FA values.
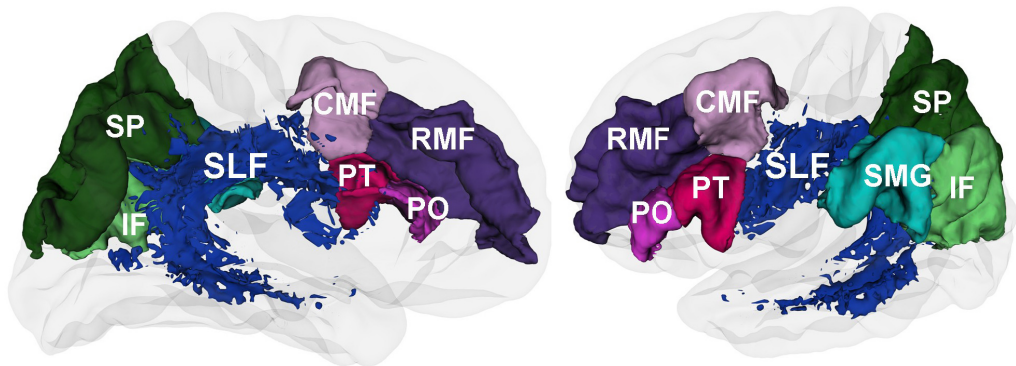
Figure 7. Regions of interest used in Paper III. 3D rendering of cortical parcellations based on Freesurfer, and white matter tract (superior longitudinal fasciculus) based on TBSS. Image made using Slicer software (www.slicer.org). SP = Superior Parietal, IF = Inferior Parietal, SMG = Supramarginal Gyrus, SLF = Superior Longitudinal Fasciculus, CMF = Caudal Middle Frontal, RMF = Rostral Middle Frontal, PT = Pars Triangularis, PO = Pars Opercularis.

considered advantageous that test results could be compared with other studies using the same material.

Long-term memory task

The Rey-Osterrieth Complex Figure Test (RCFT)(Meyers & Meyers, 1995; Osterrieth, 1944) was used to assess various qualities of long-term memory processes. The task consists of a geometrical figure which can be divided into different elements. The main element is a rectangle, which is crossed by vertical, horizontal and diagonal lines. Smaller elements within the rectangle as well as outside the rectangle include smaller lines, smaller rectangles, triangles, crosses and a circle. Examples of drawings of the figure by some of the participants are shown in Figures 8 and 9. In the first part of the test, participants are presented with the figure and asked to copy it as accurately as possible without the aid of a ruler. They are given five minutes to complete their drawing, and they are not told in advance that they will be asked to draw it from memory. This constitutes the copy trial. While the participant is drawing the figure, the test administrator watches the way in which each of 6 crucial parts of the figure are drawn, and writes down each element that is drawn in a unified manner, signifying the participant's understanding of the general organization of the figure. This yields an organizational strategy score. After approximately 30 minutes, in which time other cognitive tasks with mainly verbal material were administered, the participant is asked to draw the figure from memory. This is the 30 minutes recall condition. After approximately one week (ranging from 6 to 9), most participants returned to the laboratory for further testing, and were met with yet another surprise memory test of the RCFT. This is the 1 week recall condition. In the case of the second laboratory appointment not being one week after the first session for various reasons, the participants were given this task over the telephone. This was the case for 19 participants (evenly distributed among age groups). Scoring was done according to the scoring criteria given by Meyers and Meyers (1995), in which 18 units of the figure can be identified. In each of the drawing conditions, points are given to units, based on whether they are correctly drawn and correctly placed (2 points), correctly drawn but incorrectly placed (1 point), incorrectly drawn but correctly placed (1 point), or both incorrectly drawn and placed, but recognizable (1/2 point), or unrecognizable (0 points). The organizational strategy score was derived by awarding two points for drawing the main rectangle as a whole, and one point for each of the elements: horizontal line through rectangle,
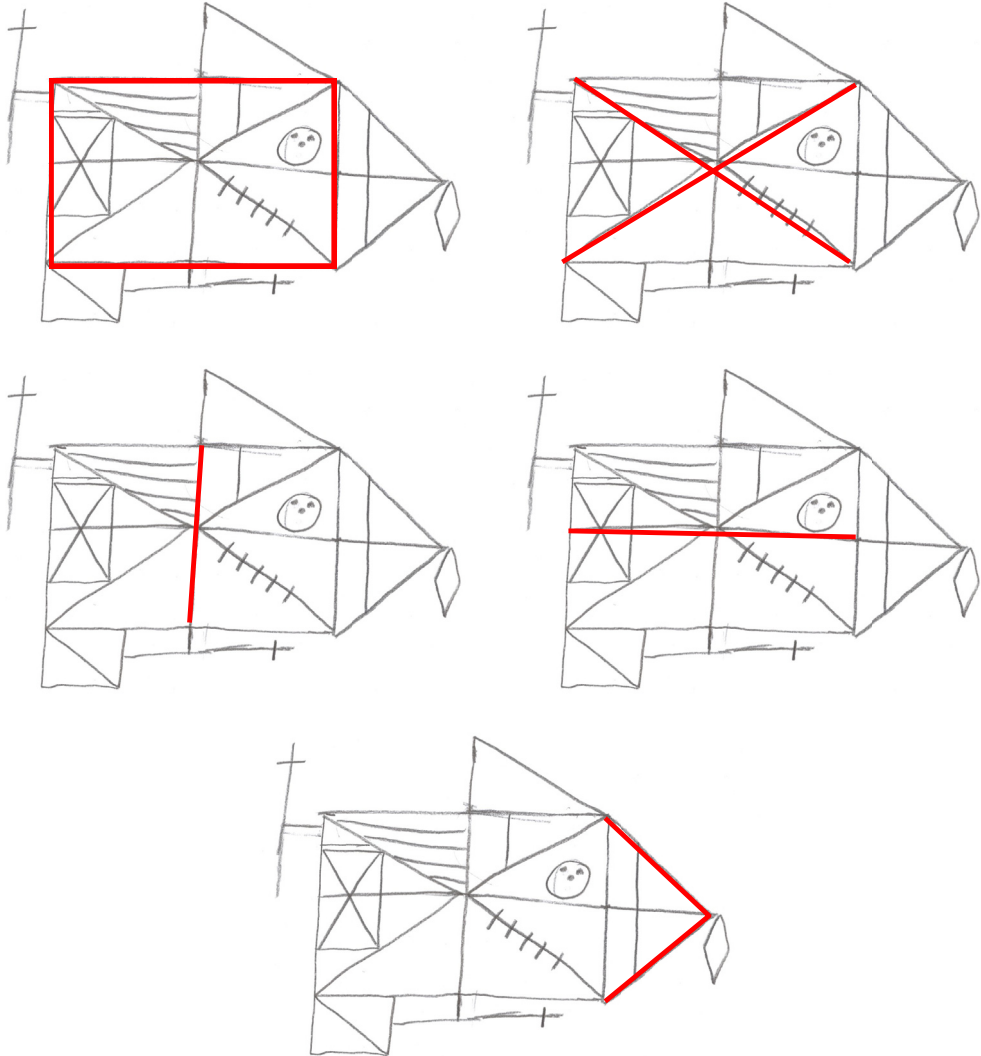
Figure 8. Scoring of organizational strategy. Each element shown in red is awarded a point if it is completed before proceeding to other elements of the figure. The large rectangle is awarded 2 points, while the other elements are awarded 1 point each. The elements are here superimposed on a copy drawing made by one of the participants.

vertical line, diagonal lines forming and X, and triangle attached to the rectangle on the right, yielding a total score of 6 points. The elements of this scoring procedure are illustrated in Figure 8. This scoring system was developed by Deckersbach and colleagues (Deckersbach, et al., 2000; S. R. Smith et al., 2007). In order to measure long-term memory retention, i.e. the keeping of the material independently of encoding or retrieval skills, the proportion of what was recalled after a week relative to what was recalled after 30 minutes, was calculated (1 week recall/30 minutes recall). Thus, 5 memory scores were derived: Copy, Organization, 30 minutes recall, 1 week recall and 1 week retention. An illustration of the three drawing trials and the retention measure is given in Figure 9.

Working memory task

The Digit Span test from the Wechsler Intelligence Scale for Children, 3rd edition (WISC III (Wechsler, 1992)) consists of two sub-tests: Digit Span Forwards and Digit Span Backwards. In the Digit Span Forwards condition, participants are presented with strings of digits read out aloud to them by the test administrator. Their task is then to repeat the digits in the same order as they were presented. The task starts with three consecutive digits and progresses with one additional digit for every two strings of digits. The task is completed when the participant has failed two strings at the same level of difficulty. In the Digit Span Backwards task, the digit strings are to be repeated in the reversed order, and the task starts with only two digits. Otherwise the task is executed similarly as the Digit Span Forwards task. In both tasks, one point is given for each correctly repeated or reversed string of digits, and points in each condition were added together. The two scores were not added together in a total score, which is normally done in accordance with scoring criteria in the WISC III. The reason for this is that two separate scores might capture different aspects of short-term memory span and working memory manipulation, the latter being more reflective of involvement of the central executive (A. D. Baddeley & Hitch, 1974; Bayliss, Jarrold, Gunn, & Baddeley, 2003; Gathercole, et al., 2004).

General considerations of memory tasks

These tasks were used to get an example of memory development within working memory and long-term memory. They are by no means exhaustive measures of memory function. The
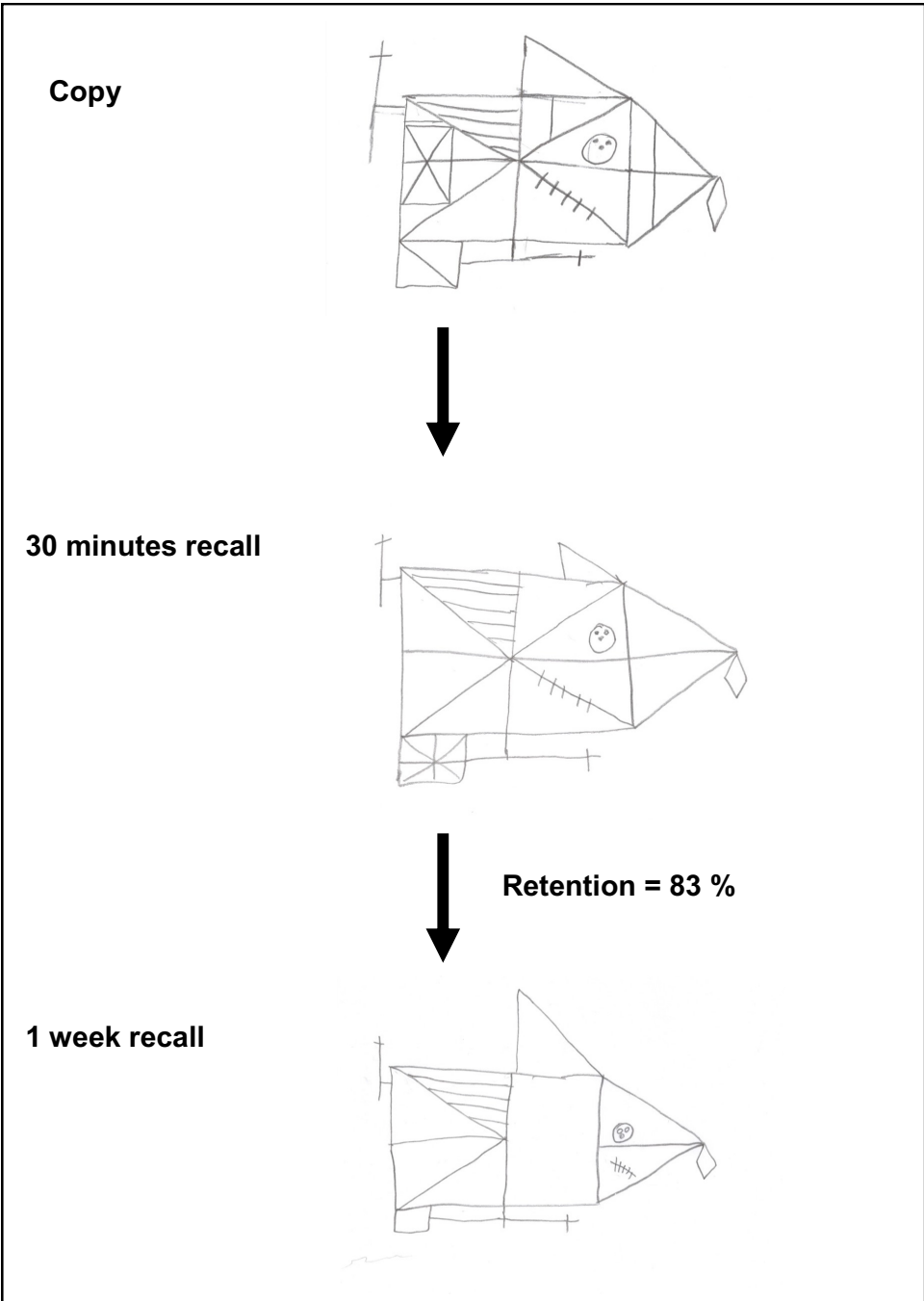
Figure 9. Rey-Osterrieth Complex Figure Test (RCFT) conditions and scores. Copy, 30 minutes recall and 1 week recall performance of one participant is shown. The retention score is the proportion of remembered material after a week relative to the 30 minutes recall condition, and the mean percentage of retention across all ages is 83 %.

fact that the tests were administered in the laboratory means that real-life memory function with all its complexities is not measured directly. However, testing in the laboratory gives an opportunity to measure functions as ―purely" as possible, without too many extraneous factors. Nevertheless, complete control over the underlying processes that influence task performance is not possible to achieve in any of these tests. For instance, in the RCFT recall conditions, it is not possible to extract the relative contribution of encoding and retrieval, and the influence on attention and deliberate strategy use on digit span performance are likely factors that are not measurable in this test format.

Statistical analyses

The statistical analyses used in the three papers are regression analyses, correlational analyses and general linear modeling. The specific statistical analyses used in each paper are given separately below.

Paper I

In order to investigate the development of brain structures, the effect of age on brain volumes, cortical thickness and surface area was assessed using regression analyses with age as predictor variable and brain volumes/thickness/area as dependent variables. This yielded effect size estimates that show how much of the variance in brain measures that is accounted for by the age of the individuals. Furthermore, we were interested in how the developmental trajectories could be characterized. This was done in two ways. Firstly, by doing regression analyses with both age and age2 as predictor variables, so that the question of whether development was faster or slower during one part of the age span, i.e. whether there are significant breaking points in the curve, could be answered. Secondly, for volumes where age^2 gave a significant contribution, exponential curves were calculated. The data points were fitted iteratively to exponential functions of the form $f(x) = b_1 + b_2 \times e^{(-age/t)}$ where b_1 is the estimated value at the asymptote, b_2 is the difference between b_1 and the estimated value of x at age zero and t is a time constant reflecting rate of development. A larger t indicates a slower progression towards adult maturity, while a smaller t reflects that the brain variable reaches a plateau earlier. For both the exponential and linear fits, absolute and relative change in volume from 8 to 30 years was calculated. The relative change of nonlinearly developing

volumes was calculated from the exponential function. A hypothesis that was tested statistically was whether age effects were different in different brain structures. This was done by comparing correlation coefficients using the t-test of Fisher's z-transformed correlations.

Paper II

Age effects on brain measures (cortical thickness and hippocampal volume) were assessed using regression analyses/general linear modelling with age as predictor variable and brain measure as dependent variable. This was done purely as a descriptive step. Age effects on memory measures were tested using regression analyses with age and sex as predictor variables, and memory scores as dependent variables. To test the relationship between brain structure and memory functioning, two sets of analyses were performed. Relationships between cortical thickness across the whole surface and memory scores were tested using general linear modelling in Freesurfer. Memory scores were modelled to predict cortical thickness at each vertex of each hemisphere, while controlling for sex. The analyses were also done with age as an additional predictor, to control for the common effect of age. The huge number of statistical tests increases the risk of rejecting the null hypothesis when there actually is no relationship, because relationships might occur by chance. Therefore, steps were taken to control for multiple comparisons. In the case of testing relationships between brain structure and memory without taking out the effect of age, a false discovery rate of .05 was applied. In the case of the age-corrected results, a cluster-based approach was deemed more appropriate, because it allows for smaller effects to survive statistical testing as long as the effect is clustered in a sufficiently large area. This testing was done using a monte-carlo simulation, using FreeSurfer (Hayasaka and Nichols 2003; Hagler et al. 2006). This analysis is done by performing simulations with 5000 iterations per analysis, to get a measure of the distribution of the maximum cluster size under the null hypothesis and then determine the probability of a certain cluster size under the empirical null. The interaction between level of memory performance and age was also tested, by using age, memory score and age x memory score as predictor variables. In the second set of analyses, hippocampal volume was used as a predictor variable, with memory scores as dependent variables, while including sex as additional predictor variable, and then with age also as an additional predictor variable. Further steps were also taken to control for effects of extraneous variables. The effect of general intellectual level (IQ) was tested by including WASI IQ among the predictors. The

relationships between recall conditions and brain variables were submitted to analyses where copy score and organizational score were controlled for.

Paper III

In this paper, relationships between pre-selected regions of interest (ROI) in the fronto-parietal network of the left hemisphere and working memory scores were tested. Preliminary analyses included regression analyses of the effects of age on the working memory scores, cortical thickness ROI, tract FA and tract RD (diffusion measures) variables. In the main analyses, relationships between working memory scores and brain variables were investigated using regression analyses with Digit Span scores as dependent variables, and age and brain variables as predictor variables. Regressions were then performed with working memory scores as dependent variables, and a combination of cortical thickness and diffusion measures from among the variables that were significant predictors in the first set of analyses. Furthermore, the developmental patterns of these relationships were investigated by calculating correlation coefficients between brain variables and working memory scores in three age groups. Specificity of the results was tested by controlling for IQ. The multiple comparison problem was dealt with by applying Bonferroni correction of the results, but in a liberal manner: the a level was divided by the number of variables within a set of related variables, such asset of cortical ROIs, set of DTI variables, and set of working memory tasks. This was deemed appropriate because the selection of variables was based on theory.

Ethical considerations

The project was approved by the Regional Ethical Committee of South Norway. Written informed consent was obtained from all participants from 12 years of age, and from parent/guardian for participants under 18 years. Oral informed consent was given by participants under 12 years of age. The study has important benefits at a societal level, including the basal understanding of brain development and brain functioning that constitutes the ground on which clinical research builds. Educational interests might also be informed by the study. For the individual participant, benefits of participating in the study included the gift certificates and money they received for spending time and effort in the study, as well as some insight into brain research. The risks included discomfort experienced during lengthy test

sessions and having to lie still in the scanner for almost an hour (scan time included additional sequences not described here). They also ran the risk of becoming claustrophobic. At the time of the study, there are no known long-term side effects of MRI. The cognitive assessment could be experienced as challenging, but most participants seemed to find it engaging. The major ethical concern of the study is the inclusion of children. While children should have the same opportunity to take part in the development of science as adults, they may not fully comprehend the extent of the participation. Furthermore, they may feel pressured to consent. All participants, adults as well as children, were explicitly told that they could withdraw their consent at any time. Children might nevertheless feel a responsibility towards authorities, i.e. the parents and the researchers, that might hinder them from saying no. Care was therefore taken to make sure that tests and MRI scanning was stopped if the child exhibited discomfort.

SUMMARY OF PAPERS

PAPER I

Objectives: To contribute to a fuller picture of the dynamics of brain development, by characterizing and comparing developmental parameters of multiple brain structures, utilizing a whole-brain segmentation approach. It is hypothesized that developmental trajectories of cortical and subcortical grey matter volume may differ in both the impact of age, and the rate of development, and that white matter volume increases, while grey matter decreases, with the possible exception of the amygdala and hippocampus.

Methods: The size of 16 neuroanatomical volumes was estimated for 171 children, adolescents and young adults aged 8 -30 years. The cerebral cortex, cerebral white matter (WM), caudate, putamen, pallidum, accumbens area, hippocampus, amygdala, thalamus, the brainstem, cerebellar grey matter (GM), cerebellar WM, the lateral ventricles, inferior lateral ventricles, 3rd ventricle, and 4th ventricle were studied. The cerebral cortex was further analyzed in terms of lobar thickness and surface area.

Results: Substantial heterogeneity among brain structures in developmental trajectories was observed. GM decreased nonlinearly in the cerebral cortex, and linearly in the caudate, putamen, pallidum, accumbens and cerebellar GM, whereas the amygdala and hippocampus showed slight, nonlinear increases in GM volume. WM increased nonlinearly in both the cerebrum and cerebellum, with an earlier maturation in cerebellar WM. In addition to similarities in developmental trajectories within subcortical regions, our results also point to differences between structures within the same regions: among the basal ganglia, the caudate showed a weaker relationship with age than the putamen and pallidum, and in the cerebellum, differences were found between GM and WM development.

Conclusion: These results emphasize the importance of studying a wide range of structural variables in the same sample, for a broader understanding of brain developmental principles.

PAPER II

Objectives: To explore the neural correlates of memory performance after a short delay of 30 minutes and a long delay of one week, as there is not enough knowledge about how structural maturation of the brain contributes to the differential development of these functions. It is hypothesized that recall is related to cortical thickness in prefrontal areas, and that organizational strategy may mediate such a relationship. The hippocampus is hypothesized to be predictive of memory performance after a long time delay of 1 week.

Methods: 107 children and adolescents aged 8-19 years underwent structural MRI and memory testing using the Rey Complex Figure Test copy, organizational strategy, 30 minute and one week recall.

Results: While the amount of details copied and later recalled after both 30 minutes and one week increased with age, the relative saving over one week (1 week/30 minutes ratio score) did not increase with age. 30 minutes recall performance was related to thinner left orbitofrontal cortex independently of age and organizational strategy measured during copy, possibly reflecting executive components of retrieval or encoding processes. In contrast, the 1 week/30 minutes ratio, likely reflecting consolidation of memory traces, was related to larger bilateral hippocampal volume.

Conclusion: This demonstrates that differential developmental effects on memory for short and long periods of time are related to differentially developing brain structures.

PAPER III

Objectives: Two distinctly different maturational processes – cortical thinning and white matter maturation – take place in the brain as we mature from late childhood to adulthood. To what extent does each contribute to the development of complex cognitive functions like working memory? The independent and joint contributions of cortical thickness of regions of the left fronto-parietal network and the diffusion characteristics of the connecting pathway of the left superior longitudinal fasciculus (SLF) in accounting for verbal working memory performance were investigated. It was hypothesized that both of these maturational events may be important contributors to working memory performance.

Methods: 108 healthy participants aged 8-19 years underwent MRI, including anatomical and diffusion tensor imaging (DTI), as well as cognitive testing using a digit span task.

Results: Negative relationships were found between Digit Span Forwards performance and Radial diffusivity of the SLF, as well as cortical thickness of supramarginal gyrus and rostral middle frontal cortex, independently of age. Radial diffusivity of the SLF was also negatively related to Digit Span Backwards. A multi-modal analysis showed that cortical thickness and SLF microstructure were complementary in explaining working memory span. Furthermore, SLF microstructure and cortical thickness had different impact on working memory performance during the developmental period, suggesting a complex developmental interplay.

Conclusion: The importance of cortical thickness of regions and a connecting white matter pathway within the fronto-parietal network for verbal working memory was partly confirmed. The results indicate that cortical and white matter maturation each play unique roles in the development of working memory.

GENEREAL DISCUSSION

What are the relationships between brain maturation and memory?

The diversity of the changing brain

Changes are still taking place in the brains of older children and adolescents, as was shown in Paper I. Gray matter decreases, and white matter increases, in accordance with previous research (Giedd, et al., 2007; Giedd, Snell, et al., 1996; Gogtay, et al., 2004; Gogtay, et al., 2006; Mackie, et al., 2007; Shaw, et al., 2008; Sowell & Jernigan, 1998; Sowell, et al., 1999; Sowell, et al., 2004; Sowell, et al., 2002) (Ashtari, Cervellione, et al., 2007; Barnea-Goraly, et al., 2005; Elizabeth R Sowell, 2002; Giorgio, et al., 2008; Gong, et al., 2008; Guo, et al., 2007; Jernigan, et al., 2001; Lebel, et al., 2008; Li & Noseworthy, 2002; Liu, et al., 2003; Nagy, et al., 2004; Paus, et al., 1999; Reiss, et al., 1996; Schmithorst, et al., 2005; Sowell, et al., 2002). When looking at brain development in greater detail, the diversity among structures emerges as a prominent feature of brain development. Some regions are affected by age to a greater extent than others, and some regions seem to follow different trajectories than other regions. This was evident both when considering the non-linearity of age trajectories in some regions as compared to others, and when (informally) comparing the estimated time of peak development calculated from the non-linear analyses. The general notion that frontal and temporal cortices mature later than posterior (parietal and occipital) cortical regions, was confirmed in these results, when considering the timing estimate. Low timing estimates were found for occipital and parietal lobes, and these regions showed a clear curvilinear relationship with an early rapid decline in volume and thickness of the cortex, whereas frontal and temporal lobes were estimated high in timing, and showed a steady decline throughout adolescence. Since the publication of Paper I, a number of studies have confirmed these patterns of cortical development. In studies of young participants, age effects on cortex are seen in parietal and occipital lobes (Muftuler et al., 2011; Pangelinan et al., 2011), while a study with adolescent participants finds age effects in frontal and temporal regions (Sullivan et al., 2011). A recent, large-scale study by the Brain Development Cooperative Group (2011) also confirms the findings of most prominent age effects in parietal and occipital lobes, in the age span 4-18 years. Also, the general notion of cortical volume increase in early childhood followed by reduction through late childhood and adolescence, and white matter increase, has been yet again confirmed in a large (> 600 participants) sample of children, adolescents and

young adults aged 3-30 years (Raznahan et al., 2011). In this study, the different nature of surface area and cortical thickness in terms of development is also shown, which is in accordance with the finding of Paper I.

Diversity of grey matter maturation and long-term memory

In the case of subcortical structures, great variability between various structures was seen, with the amygdala and hippocampus standing out from the rest of grey matter structures with their slight increase in volume. Especially the hippocampus has received attention in the brain developmental literature, where different results have been found in different studies (Giedd, Vaituzis, et al., 1996; Gogtay, et al., 2006; Guo, et al., 2007; Toga, Thompson, & Sowell, 2006). Clearly, the developmental trajectory of the hippocampus is important to establish, in order to understand its role in memory development. The results of the present study thus contribute to an increasing amount of available data describing the hippocampus in development. In the present data, the hippocampus seems to increase in volume from 8 to 30 years, with a slight difference in rate of change early in the age span as compared to older adolescents and adults where the age-curve levels off. It is therefore tempting to conclude that our data show an early development of hippocampal volume. Caution is warranted though, as the interindividual variability, independently of age, was formidable, and the ―true‖ effect of age might not appear until a longitudinal mapping of its volume change is available. Also, this pattern was not confirmed when analyzing only the children and adolescents in the study of Paper II. The number of participants and the age range used is therefore likely to be important when searching for this pattern in future studies.

Since the completion of this study, other researchers have contributed with data showing the development of hippocampus through late childhood and adolescence. Even though studies are still scarce on this matter, one study of children with schizophrenia and their non-affected siblings, as well as normal controls, showed no age effect from 10 to 29 years of age, and if anything, a decline in all three groups (Mattai et al., 2011). Another recent study found evidence for sex differences in developmental trajectories, offset by entry into puberty (Bramen et al., 2011), where onset of puberty was related to smaller hippocampal volume in girls and bigger volumes in boys. In a 7-month longitudinal study of adolescents, Sullivan et al. (2011) found a tendency for an increase in both hippocampus and amygdala. The quest of finding the developmental trajectory of the hippocampus thus continues on.

While the exact nature of hippocampal development is still under debate, it is beyond doubt that its trajectory is different from that of cortical regions, where age effects are more pronounced. But what is the impact of these developmental events on long-term memory? The results presented in paper II were interpreted in the direction that different aspects of remembering may be separable by different developmental trajectories, and that these differences are associated with developmental differences between brain structures. While recall performance continued to increase during adolescence, the relative saving of information across a week's delay did not change in the 8-19 age span. It has been suggested that consolidation processes undergo developmental changes during preschool years (Bauer, 2008), and this might fit into the picture drawn here, of an early development of retention, which has possibly reached a plateau some time before the beginning of the present age range. The adolescent increase in recall performance is mirrored in the developmental changes still taking place in adolescents' brains during the same period. The finding that recall was related to thinning of orbitofrontal cortex fits with this observation, pointing to the possibility that executive functioning during encoding or retrieval processes are at play. The orbitofrontal cortex has been found to be involved in memory encoding and retrieval also in adults, and an account of this is given by Petrides (2007). The orbitofrontal cortex may be employed in monitoring relevance for moment-to-moment goals, and hence control attention given to stimuli at encoding. During retrieval, the orbitofrontal cortex may evaluate the relevance of items retrieved from long-term memory in order to decide which item to bring back from memory. These processes may seem basic, but even basic aspects of executive functioning are likely to develop during adolescence (Huizinga, Dolan, & van der Molen, 2006). Retentional abilities, on the other hand, were related to hippocampal volume in our data. Even though it is too early to say whether this is reflective of smaller developmental effects in both of these measures, it shows that heterogeneity in brain development translates to heterogeneity in cognitive development. An implication of these results is that different aspects of remembering must be taken into account when trying to understand children and adolescents' memory skills. The results showing a relationship between long-term retention and hippocampal volume, and no relationship with recall, is partly in accordance with previous employment of a long-term retention span in a study from 2004 (Walhovd, et al., 2004), with adult and aging participants. Taken together, that study and the study of Paper II presented here, suggest that when trying to relate hippocampal volume to remembering, a longer time delay is perhaps needed. However, a recent study of young adults (aged 18-20) revealed relationships between hippocampal volume and verbal memory scores after the standard 30

minutes delay (Ashtari et al., 2011), while some studies of normal adults and elderly have found positive relationships between hippocampal volume and verbal recall after the standard 30 minute interval (Van Petten, 2004; Ystad et al., 2009). This issue therefore needs more investigation, preferably using a multitude of materials and testing conditions.

Diversity of brain maturational events and working memory development

The data presented in paper I not only shows the diversity of developmental patterns within grey matter regions, it also illustrates the two major opposing developmental processes: grey matter reduction and white matter increase. There is reason to believe that these two developmental events are reflective of different microbiological maturational processes, which in turn may have different influence on the development of psychological functions. The grey matter reduction could be due to decreases in synaptic density, the so-called pruning of synapses and dendritic branches (Huttenlocher, 1984), but reductions in other classes of neuropil cannot be ruled out. The increase in white matter, as exemplified in Paper I, is thought to be in part caused by increased myelination of axons, whereby action potentials are conducted with increased speed and certainty (Lebel, et al., 2008; Tamnes, Ostby, Fjell, et al., 2010; Yakovlev & Lecours, 1967). At a fundamental level, the biological significance of the opposing age effects as seen on MR images has been debated. On the one hand, the thinning of cerebral cortex could be because of grey-matter-specific maturational processes, but on the other hand, they could be a methodological artifact caused by the analysis tools used. The classification of voxels in an MR image is based on the likelihood of it belonging to one class of tissue or the other. As more axons are myelinated, the contrast at the border between cortex and underlying white matter will change, so that tissue that was formerly classified as cerebral cortex, now becomes classified as white matter, even if it in reality still belongs to the same structural class (as would be apparent if one could have a look at it in a microscope). The two opposing processes could therefore be caused by only one process, i.e. myelination. In a previous part of this project, Tamnes et al. (Tamnes, Ostby, Fjell, et al., 2010) found evidence for different roles played by cortical thinning and white matter increase in development, showing that each were related to age independently of the other, when cortical regions were analyzed together with underlying white matter.

An understanding of the influence of each of these processes on cognitive development is needed. The implication of increased speed of signal transfer could be that more information

can be handled in a shorter time period, freeing up space for other processes to co-occur, and that distant brain areas are able to communicate faster and thus cooperate more smoothly in performing memory activities. Working memory constitutes a good example of the working together of brain regions located in different parts of the brain, through communication via white matter pathways. Thus, by studying the influence of white matter properties and cortical thickness of regions within a predefined network of the brain, different roles of different brain developmental processes could be identified. The results point to a unique role played by white matter development and cortical thickness reduction in working memory development. This could mean that in addition to the maturation of brain regions thought to subserve different aspects of working memory, like subvocal rehearsal, and control of attentional resources, the speed of processing, and/or the integration of different parts of the network, could also be an important factor in working memory development. The results of the present study raise some questions about working memory development. For instance, in the field of working memory development, debate has been going on about the importance of processing speed in facilitating working memory development (Bayliss, et al., 2003; Case, Kurland, & Goldberg, 1982; Fry & Hale, 1996). Whereas a direct link between speed of processing and brain development clearly cannot be argued based on the present findings, the importance of white matter pathway development in working memory may encourage further investigations into the link between white matter diffusion properties, processing speed and working memory. Another line of debate concerns the qualitative aspects of the developmental processes of working memory. Gathercole argues that by the age of 7, working memory development is characterized by only continuous increases in capacity and performance (Gathercole, 1998). Looking at the different roles played by different brain maturational processes during age-spans in Paper III, one may wonder in what way different timing of white matter – and cortical influences on working memory relates to the continuous development of working memory on the behavioral level. Functional MRI studies have indicated developmental shifts in activation patterns across the fronto-parietal network, suggesting that a continuous development may be differentiated when taking into account the brain maturational level. The results of the current working memory study could only suggest developmental shifts, as the results could be caused by mere random individual differences, something that the fMRI studies also must take into account.

Frontal cortical involvement in memory functioning

Both working memory and long-term memory recall were related to cortical thickness in the frontal lobes. This was expected, based on the knowledge of frontal involvement in working memory (lateral prefrontal regions)(D'Esposito, et al., 1998; Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010; Kwon, Reiss, & Menon, 2002) and executive aspects of memory encoding and retrieval (Dobbins, et al., 2002; Incisa della Rocchetta & Milner, 1993; Petrides, 2007; Simons & Spiers, 2003; Spaniol, et al., 2009). In the long-term memory study, frontal cortical thickness was hypothesized to be predictive of recall performance, based on previous studies that have shown such a relationship (Antshel, et al., 2008; Sowell, et al., 2001), and this was further hypothesized to be caused by the frontal cortical involvement in the employment of strategies. The results did show a relationship between left ventrolateral prefrontal cortex near the frontal pole, and organizational strategy score, but this effect was too small and weak to survive corrections for multiple comparisons. It still remains to be seen whether another measure of organization might be more sensitive. The only effect that remained after correcting for multiple comparisons, was the relationship between lateral orbitofrontal cortex and recall performance, perhaps reflecting this area's importance in motivational aspects of encoding, or control processes in retrieval (Petrides, 2007). In the case of working memory development, the inclusion of frontal regions in a set of regions of interest makes it impossible to say anything beyond the relationships found in the predefined areas. Here, relationships were found between rostral middle frontal cortex, i.e. in dorsolateral prefrontal cortex, and simple storage span, whereas a less certain relationship was found between ventrolateral prefrontal cortex/Brocas area and complex storage span.

In all these instances, relationships where negative, even when controlling for age, suggesting that cortical thinning was still a driving force behind memory development in this sample. A closer look at the developmental processes, either by including an age-interaction-term in the regressions (in the case of long-term recall) or age group comparisons (in the case of working memory), did not reveal a clear pattern of age-related increased involvement of frontal cortex or a difference in frontal maturational trajectory. The Sowell et al. (Sowell, et al., 2001) study argued that the relationships between frontal lobe grey matter and recall performance in children reflects the progression towards mature frontal lobe functioning. Except for the direction of the relationship, adults may show relationships between individual differences in recall performance and individual differences in frontal lobe structure. Therefore, this interpretation must be considered with caution. In the same study, the researchers did not find

as strong relationships between recall and temporal lobe functioning, and this was taken as evidence that early maturation of encoding skills would lead to brain-behavior-relationships becoming less important. In response to this suggestion, our data did find relationships between memory and other regions than the frontal lobes, and therefore, the notion that only variables that show continued development, such as recall scores and frontal cortical thickness, give rise to brain-behavior relationships, must be reconsidered.

How can brain structure inform us about memory development?

A fundamental issue in this thesis regards the question of the relationship between brain structure and memory function, an issue that is important in any endeavor of relating brain structural development to psychological development. This issue can be further divided into more specific questions, which I will elaborate in the following.

The first question concerns how the different levels of analyses are related to each other. In the studies presented here, the macroscopic, structural level is connected with the behavioral level, but the levels in between are only assumed or hypothesized. Roughly, the levels between the size or thickness of grey matter structure and mnemonic behavior could be summarized as the following: 1. Microscopic structural level: size of neurons, number of synapses, presence of glial cells, quality and quantity of myelin sheaths. 2. Neurophysiologic level: action potentials, synaptic activity, oxygen and glucose consumption of neurons. 3. Large-scale neuronal network level: activity within larger populations of neurons within regions and within networks of regions. 4. Memory processes that constitute a memory function, and 5. Memory test scores. On the way along this chain of events, a number of things might happen, that make the direct route between mere structure and memory scores uncertain. All structural differences may not be reflective of neuronal structure change such as synaptic pruning. Further, neuronal activity patterns may not always be influenced directly by the number of synapses and the processes of pruning and myelination. How the brain looks may not be a sole determinant of how it works. Memory processes, such as retrieval, rehearsal, encoding etc are likely represented in the brain's large scale neuronal activity, measurable to a certain degree by functional neuroimaging such as EEG/ERP (event-related potentials) and functional MRI. These memory processes are then hypothesized to be reflective of memory test scores, which in turn may be influenced by a host of other

psychological processes (motivation, attention, fatigue, language and problem solving skills, to name but a few)(Krebs & Roebers, 2010).

When relationships are found on the macroscopic level, such as the relationships reported here, an explanation of these relationships are needed. Although the methods applied in this thesis does not allow for formal testing of hypotheses regarding the levels in between, some speculations are warranted. In the introduction, the importance of synaptic pruning/synapse elimination (Huttenlocher, 1984) in cortical development was elaborated, and it was suggested that a ―pruned" neural network might be more fine-tuned and efficient than a ―bushy" one with excess dendritic branches and synapses. Of course, we do not know enough about the underlying biological processes to conclude on this, or to exclude other neurobiological maturational events such as development of glial cells etc. In the cae of the hippocampus and amygdala, where volume increase was seen, synaptic pruning may not be the underlying force of dvelopment. One possibility is that white matter sections within these structures myelinate sufficiently to cause the increase (Benes, et al., 1994), or that neurogenesis contributes enough new hippocampal neurons to cause a mearurable increase, although this is currently dubious (Snyder & Cameron, 2011). The possibility of neurgenesis being a possible important facet of hippocampal structure and functioning throughout life has inspired efforts to find ways in which new neurons are important in memory processes (Marín-Burgin & Schinder), but much remains before these hypotheses can be applied to the structure-function relationships like the ones presented here. Also, the postulation that myelination, thought to be captured by DTI in the form of FA or RD (Klawiter et al., 2011; Song et al., 2003; Song et al., 2005), has bearings on cognitive development, is appealing. This could be in the form of increased processing speed and hence increased communication between brain regions. Only recently has the quest for an understanding of these implications of white matter development begun in the form of direct investigations of DTI measures and cognitive development.

In addition to these conceptual difficulties along the road from structure to an understanding of memory function, statistical and methodological difficulties are also causing problems with making clear-cut inferences. As mentioned in the Design section of the Methods section, the correlation between brain structure and function in development is made difficult to interpret simply because the effect of age on both variables must be controlled for, thus potentially taking out a lot of the variance to be explained in the other two variables. Still, the approach

taken in this thesis is an important one, making an effort to relate measurable structural changes within living brains to developmental changes in memory processes.

The next big question regards the causal relationship between memory development and brain maturation, and the importance of social and environmental factors. We assume that brain structure causes memory function, because all memories are in some way happening in our brains, and must be the result of firing neurons. When we see the structural changes in brain development, it is reasonable to assume that the biological changes are related to the functional changes. However, the causal relationship could also be the other way around, with increased memory skills causing structural changes during development. Several lines of research now point to the likelihood that cognitive training and specific experience may lead to functional and structural changes in the brain, both in normal adults (Engvig et al., 2010) and children (Hyde et al., 2009). As mentioned in the Methods section, experimenting with children's experiences in order to observe the effect on brain structure is difficult to carry out, due to ethical and practical considerations. One can obviously not interfere with the natural progression through life that is necessary for normal stimulation and hence development of basic functions. Likewise, one cannot purposefully stop development of brain structure to see how it affects memory development. Some studies have however found evidence for the influence of experiences on brain structure and function. In a naturalistic experiment, children were scanned prior to starting musical instrument training, where the initial scans revealed no group differences between soon-to-be young musicians and a control group (Hyde, et al., 2009). A year of practice later, differences in grey matter density (a measure of brain structure) were observed between the groups. In the case of memory functioning, studies of practice effects on the brain are scarce, at least when it comes to development. Focus has however been on working memory training as well as long-term memory training in adults (Engvig, et al., 2010; Klingberg, 2010), where structural and functional effects on the mature and aging brain paves the way for the probability of effects also on the developing brain where the potential for plasticity must be assumed to be even more promising. Clearly, it is of great importance to keep in mind the way the environment shapes development. What we se in the MR images might be the result of joint effects of experience and training on the one hand, and biologically induced maturation on the other hand, and of course a complex interplay between them (R. K. Lenroot & Giedd, 2008). The outcome of such influences and causes, i.e. the present size of structures as we measure them, are in turn likely to be determinants of memory function in the present (although not the sole determinants). Thus, by

postulating that the development that we see through the morphometric analyses is the cause of the functional development does not imply that the other causal direction is not involved. In the context of the present study, suffice it to say that the main focus is on mapping two ongoing developmental trajectories onto each other – the increase in memory function and the maturation of brain structure.

Two examples of one message?

Taken together, the results of the two memory studies show that the brain maturational foundations of two aspects of memory functioning are based upon many brain maturational factors working together, both in terms of different sites (frontal and posterior/subcortical), and in terms of different processes (increasing vs. decreasing structure; grey matter vs. white matter). The message taken from the two memory studies is that brain maturation may shed light on developmental processes within different realms of memory. This message is exemplified in the comparison of subcortical and cortical grey matter within the study of episodic memory, whereas the comparison of cortical and white matter maturation formed the basis of the conclusion of brain maturational diversity in the working memory study. Comparing these two studies raises the inevitable question of what could have been done similarly in these two examples. Could grey and white matter have been compared in relation to long-term memory? At the time of conducting the analyses of Paper II, this seemed beyond the scope the study. However, the involvement of two distant brain regions in aspects of the RCFT warrants investigation of the connecting pathways as well, a task that has been taken on by Mabbott et al (Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009), who found relationships between temporal and parietal white matter diffusion properties and RCFT performance in children and adolescents. Lately, the developmental trajectories of multiple white matter tracts has been investigated longitudinally, showing a late maturation of frontally projecting association tracts (Lebel & Beaulieu, 2011). This also supports the notion of white matter connections between temporal and frontal regions being important for memory development. Future research is needed to elaborate this.

Likewise, could the working memory study have utilized a whole-brain cortical thickness approach? The answer is not so straightforward. Using a whole-brain analysis demands strict corrections for multiple comparisons. So strict, one might argue, that true findings might get overpowered by the threat from randomness. This threat is definitely real, and corrections

using False Discovery Rate or Monte Carlo simulation are ways of securing trust in otherwise uncertain results. By restricting the search to a predefined set of regions, much fewer analyses are performed, and less correction is needed. This search is driven by theory, and sound evidence for the importance of these structures. In a way this means that the opportunity to discover anything *new* is diminished. We already know from the fMRI studies that these regions are involved in working memory. But this also means that these regions can be used to obtain another kind of new information, in this case relationships between memory and structural maturation, and the differential involvement of grey matter and white matter properties during development. The question of which cortical or subcortical regions are ultimately important in working memory development, is not fully answered by only studying pre-selected regions. For these reasons, it must be noted that the two approaches to studying brain-memory relationships taken here, merely represent two *examples* of how memory development may relate to the diversity of brain maturation.

How do the results extend to everyday memory?

After finding a relationship between brain structural development and memory development, the next step is to generalize to real life memory situations. Even if the memory tests themselves are true to the processes they are meant to capture, the relevance to memory at large may be limited. It was stated in the objectives that the tests used here were chosen as examples of memory, as the scope of this study does not allow for memory in its entirety to be related to brain maturation. Some features of the results may still be applicable across domains and levels. For instance, the finding that retention relative to what is recalled is relatively early developed in our sample, could mean that encoding and retrieval abilities are what makes a difference in the development of memory for life events and facts as well. And in a related way, the improvement in frontal lobe maturation which might mediate executive aspects of encoding and retrieval, related or not as they may be to the employment of strategies, would likely also be related to the way real-life events are encoded and retrieved, but the elements of self-relevance, motivation and life-story organization might cause the brain-behavior relationship to be more complex. Mixed results have come from studies linking laboratory measures with everyday ratings of working memory and long-term memory in children (Gonzales et al., 2008; Mahone, Martin, Kates, Hay, & Horska, 2009), and this topic is clearly of relevance for future research.

Methodological considerations

How do we measure memory across age-spans?

A problem that hampers developmental studies over wide age ranges is the question of whether the construct that we are seeking to investigate, is really being measured in the same way in all age groups. In the case of the RCFT, this is especially relevant, as it is a test with multiple facets to it. For instance, the developmental increase in copy accuracy shows that the initial encoding of the figure into memory may be quite different in the youngest participants as compared to the oldest ones. Struggling to get the proportions and the lines right, while having trouble organizing it surely must have consequences for the ability to encode it into memory, and hence the possibility of retrieving information from it. Measures were taken in order to control for this in the analyses. Copy performance was controlled for in the GLM with cortical thickness and recall performance, which only partly altered the results. Also, the participants' approach to structuring the material was measured while they were copying the figure. Controlling for this measure, which also increased with age, also showed mainly the same effect in the orbitofrontal region, thus indicating that the relationship between orbitofrontal cortex and recall performance was not caused by developmental differences in copy or organizational strategy performance. This conclusion is however only based on the measures of encoding opportunities available to us at the time of the data acquisition. Notably, the encoding of the figure is not equal to the drawing skills, and the drawing skills are not necessarily fully reflective of organizational skills.

In the case of working memory performance, the underlying processes might be different at different ages. This may especially be so for the Digit Span Backwards test, where anecdotal evidence from the test situation might suggest that children differ in the degree to which they employ a mnemonic strategy of rehearsing the digits in the right order, or at least paying close attention to them, before proceeding to reversing them. Even though subvocal rehearsal is in place by the age at which the participants were recruited from, the effortful use of such strategies might vary with age. Any complete account of the different constructs involved in the memory measures at different ages is impossible to achieve, but care must be taken to approach this problem, both methodologically and when interpreting results.

The matter of different constructs or tasks being tested at different times during development has become increasingly evident within the functional MR literature. For instance, activation patterns might show up in different places for children as compared to adults. Memory

development as investigated using fMRI has often been characterized in terms of different activation patterns in children as compared to adults or older adolescents. For instance, encoding into long-term memory seems to tax hippocampal resources to a larger degree in younger children as compared to older adolescents, where frontal activation patterns are more pronounced (Menon, et al., 2005). In the realm of working memory, too, several studies suggest differences in the balance between parts of the working memory network, or difference in regional extent of activation, or different activation response to increasing working memory load (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Finn, et al., 2010; Geier, Garver, Terwilliger, & Luna, 2009; O'Hare, Lu, Houston, Bookheimer, & Sowell, 2008; Scherf, Sweeney, & Luna, 2006; Schweinsburg, Nagel, & Tapert, 2005; Thomason et al., 2009). These differences might mean that the physiological foundations change during development for the same function, but the possibility of the differences being due to differences at the functional level should always be kept in mind.

Brain measurements

In parallel with the questions raised above, one can also question whether brain measurements are actually capturing the same underlying constructs, i.e. grey matter and white matter, FA and RD, in all age groups. One factor that could potentially bias these measures is the fact that children have more difficulty lying still in the scanner. In all three papers, the largest proportion of participants with only one scan was in the 8-11-year age-group. The main reason for only using one scan was that the other scan (or sometimes more than one other) was too disturbed by movement artefacts. All in all, most participants had two scans, but the possibility that age differences in scan quality might have influenced the results cannot be fully ruled out. However, by inspecting all scans and making sure that only good quality scans were included, the threat of such an age effect should be minimized.

Another methodological concern is related to all age groups, and has to do with the construct validity of the brain measures in the face of movement artefacts (regardless of age), segmentation errors and manual editing of segmentations and reconstructions. As was described in the Methods section, there is good reason to believe that what we get from the MR images is fairly representative of the bran tissue in question, as both manual labelling and post mortem studies report a great extent of overlap (Fischl, et al., 2002; Rosas et al., 2002; Tae, et al., 2008). These imaging techniques are, after all, the best available means of getting

a glimpse into the developing brains of healthy children and adolescents, with their skulls intact.

Selection of participants.

The selection of participants in this study could potentially be biased, causing problems with interpretation of results, in two ways. The first problem arises when the characteristics of participants are not similar across age cohorts. For instance, there could be an imbalance of genders that is not evenly distributed across ages, or there could be a recruitment bias of families with high or low socio-economic status in one end of the age span. This could cause ―false" age effects on brain or memory measures. In the present cohort, the gender distribution was fairly even across ages, as was the distribution of general intellectual abilities. In a recent study, the Brain Developmental Cooperative Group (2011) took a closer look at recruitment biases and socio-economic status in relation to MRI brain measures. They found that socio-economic status is not related to brain variables in development. Further, even though they attempted to recruit participants based on demographic diversity, there seemed to be an overrepresentation of families within the above-average socio-economic status segment of the population. This could be in line with the results of the non-randomized and non-stratified recruitment employed in the present study, where the sample is of above average intellectual abilities. The second problem concerns the description of developmental patterns as related to different cognitive performance levels, as mentioned in the methods section as well: there is some evidence that different maturational trajectories is related to different cognitive outcome (Shaw, et al., 2006), and by only sampling from the above-average group, a part of the picture might simply get lost. In any case, this should be kept in mind when comparing the results with those of for instance clinical studies, where the demographic composition might be different.

Implications and thoughts on the future

Practical and clinical implications

The study of memory development has presumably great implications for education, where the enhancement of learning, and hence transfer of knowledge from the classroom to long-

term memory, perhaps through the use of working memory, is one of the main goals. The results of the study bears optimism regarding children and adolescents' ability to keep what has been initially learned, while the late maturation of frontal lobes might be indicative of some biological restrictions on children's memory abilities. Also within the working memory realm, children may be restricted by their maturing brains when it comes to their abilities to keep track of the information presented to them in the classroom. One way of using this information is to acknowledge these limitations and take measures to adjusting to it, for instance by presenting tasks in a way that does not exceed working memory capacity, and to strive for optimizing encoding and retrieval opportunities. One should however take care not to take brain developmental results too literally when using them in the classroom, as James Byrnes (2007) points out. One should not be too deterministic in the view of how brain development is a prerequisite to learning. On the contrary, making tasks that are challenging to working memory and long-term memory retrieval may actually be what developing brains need in order to help their maturing brains move forward. Another issue is the way children and adolescents may benefit from learning about memory processes, in order to become skilled in the use of memory strategies, thus not being solely dependent on the passive unfolding of memory networks in their brains to take advantage of learning.

Clinically, the findings from the present study are important mostly in two ways. The first is related to the findings from Paper I, where great variability was found in development, both between people, and between different parts of the brain. When mapping the brain developmental abnormalities associated with clinical conditions such as autism spectrum disorders (ASD) (Brambilla et al., 2003; Estes et al., 2011; Verhoeven, De Cock, Lagae, & Sunaert, 2010), attention deficit/hyperactivity disorder (ADHD) (Krain & Castellanos, 2006; Semrud-Clikeman, Pliszka, Lancaster, & Liotti, 2006), dyslexia (Niogi & McCandliss, 2006) and schizophrenia (Ashtari, Cottone, et al., 2007; Giedd et al., 2008), this variability must be kept in mind. Typically, small groups are compared in clinical studies, increasing the risk of attributing random individual differences to clinically important group differences. As the discussion of the findings from normal brain development makes clear, there are still controversies regarding developmental trajectories of normal development, which need to be reconciled before making strong inferences about abnormal development. In this sense, the present study makes a contribution to the general understanding of brain development, necessary for the further understanding of abnormal patterns of development. The linking together of brain structure and memory function in normal development is also of importance

for clinical research. For instance, our results suggest that a relationship between hippocampal volume and memory function is best captured when using retention over extended delays. Thus, when seeking to explore subtle effects of abnormal hippocampal development, using a long delay retention test might be better suited if effects on memory are to be detected.

Directions for future research

This thesis seeks to explore the relationships between structural brain maturation and memory in normal development. Although the results are among the first in this endeavor, and as such contribute greatly to a growing field of research, there are restrictions that apply to the generalizability of the results. Therefore, a future line of research, building upon the present findings, should seek to replicate these results, both in terms of the structural development and the memory results, preferably using memory material of same and different modalities (verbal and visuo-spatial). Also, the lack of developmental effects on retention in the present age range calls for the study of retentional abilities in younger children as well using similar testing conditions, to possibly confirm the hypothesized early development in this memory function. There is still dispute in the field of brain development at the level of precision presented here, thus the future may hold the conclusions about these matters. Next, the findings should be investigated further using a longitudinal design. That way, the importance of a measurable increase or decrease in brain structure could be related to a measurable increase in memory function. This could potentially capture developmental brain-memory-relationships that are obscured by inter-individual differences on the cross-sectional level. Yet another turn this line of research may take in the future is to relate basic memory functions to higher-order memory functioning and everyday use of working memory and long-term memory. The way brain maturation may contribute to different facets of personal episodic memories, and in turn autobiographical memory during late childhood and adolescence, is important to acknowledge for a full understanding of the remembering brain in development. A look into the future may also reveal a focus on the relationship between remembering and future thinking, as these two domains have been linked behaviorally in children and adults (D'Argembeau & Van der Linden, 2004; Suddendorf, 2010), as well as on a neural level in adults (Addis, Wong, & Schacter, 2007). Finally, the extension of the present findings to relevant clinical populations could be a valuable approach that may shed light on

developmental disorders where working memory or long-term memory may be at risk
(Gathercole & Alloway, 2006; Salmond et al., 2005).

Conclusion

The results of the three studies presented here together shed light on the heterogeneity of the
developing brain, and how diversity in brain developmental properties may relate to different
aspects of memory functioning. After the first study of this thesis, knowledge of the diversity
of brain developmental paths is strengthened, as the hypotheses of increaseing white matter
and decreasing grey matter (cortical and subcortical) were confirmed. Much research still
remains in order to get a complete picture of the true developmental paths of the various
subcortical structures. While medial temporal lobes structures, hippocampus and amygdala,
showed a slight increase in the present results, divergent findings have been reported by
others since the release of the first paper. Also, the developmental trajectories of basal
ganglia, thalamus and cerebellum, all of which showed linear decreases as compared to the
non-linear decrease of cortical grey matter, need to be further investigated. The results
nevertheless give a picture of diversity in brain maturation, a complexity that shows us that
late childhood and adolescence is more than a mere waiting period in between early childhood
and adulthood. The consequences of these complexities for cognitive development were
shown here in the realm of memory.

Investigating the role of hippocampal volume for episodic long-term memory has proven
difficult by previous researchers, but the results of Paper II indicates that such a relationship
may be dependent upon the length of the retention interval. Early maturation of long term
retention of visual material, interpreted as an index of memory consolidation, was related to
the volume of hippocampus. In contrast, development of recall was accompanied by a
relationship with thickness of left orbitofrontal cortex. This confirms the hypothesis of
frontal cortical involvement in recall during development, although the exact location within
frontal cortex was not foreseen specifically. The hypothesized mediating role of
organizational strategy was not confirmed in the present results.

In the case of working memory development, as investigated in Paper III, results showed that
both cortical thickness and microstructural properties of the superior longitudinal fasciculus,
connecting frontal and parietal regions, accounted for working memory performance

independently of age, confirming the main hypothesis of Paper III. The unique contribution of the cortical and white matter variables in explaining working memory indicates that working memory development results from the joint contribution of different neurobiological maturational events. It was further suggested that these brain maturational contributions could have different timing during the developmental period from 8 to 19 years.

These results, although limited by the restriction of memory processes sampled and the methodological difficulties inherent in correlational and cross-sectional designs, constitute a step towards integrating our understanding of brain maturation and its relationship with memory development.

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PAPERS I-III

I

Development/Plasticity/Repair

Heterogeneity in Subcortical Brain Development: A Structural Magnetic Resonance Imaging Study of Brain Maturation from 8 to 30 Years

Ylva Østby,[1] **Christian K. Tamnes,**[1] **Anders M. Fjell,**[1,2] **Lars T. Westlye,**[1] **Paulina Due-Tønnessen,**[3] **and Kristine B. Walhovd**[1,2]

[1]Center for the Study of Human Cognition, Department of Psychology, University of Oslo, N-0317 Oslo, Norway, [2]Department of Neuropsychology, Ullevaal University Hospital, N-0407 Oslo, Norway, and [3]Department of Radiology, Rikshospitalet University Hospital, N-0027 Oslo, Norway

Brain development during late childhood and adolescence is characterized by decreases in gray matter (GM) and increases in white matter (WM) and ventricular volume. The dynamic nature of development across different structures is, however, not well understood, and the present magnetic resonance imaging study took advantage of a whole-brain segmentation approach to describe the developmental trajectories of 16 neuroanatomical volumes in the same sample of children, adolescents, and young adults ($n = 171$; range, 8–30 years). The cerebral cortex, cerebral WM, caudate, putamen, pallidum, accumbens area, hippocampus, amygdala, thalamus, brainstem, cerebellar GM, cerebellar WM, lateral ventricles, inferior lateral ventricles, third ventricle, and fourth ventricle were studied. The cerebral cortex was further analyzed in terms of lobar thickness and surface area. The results revealed substantial heterogeneity in developmental trajectories. GM decreased nonlinearly in the cerebral cortex and linearly in the caudate, putamen, pallidum, accumbens, and cerebellar GM, whereas the amygdala and hippocampus showed slight, nonlinear increases in GM volume. WM increased nonlinearly in both the cerebrum and cerebellum, with an earlier maturation in cerebellar WM. In addition to similarities in developmental trajectories within subcortical regions, our results also point to differences between structures within the same regions: among the basal ganglia, the caudate showed a weaker relationship with age than the putamen and pallidum, and in the cerebellum, differences were found between GM and WM development. These results emphasize the importance of studying a wide range of structural variables in the same sample, for a broader understanding of brain developmental principles.

Introduction

Subcortical structures are important in developmental disorders (Krain and Castellanos, 2006), and we need a better understanding of the dynamics of differential subcortical brain development. However, few magnetic resonance imaging (MRI) studies cover normal brain development in multiple subcortical regions in childhood and adolescence. The aim of the present study was to describe and compare the developmental trajectories of several subcortical structures in the same sample of participants, thereby shedding light on the dynamic interplay between different brain structures in development.

It is generally acknowledged that gray matter (GM) volume increases in early childhood and decreases during adolescence (Jernigan et al., 1991; Reiss et al., 1996; Giedd et al., 1999; Sowell et al., 1999, 2002; Lenroot et al., 2007; Wilke et al., 2007; Shaw et

al., 2008). This may, in part, reflect early synaptic arborization and later pruning (Huttenlocher, 1990). Results indicate that subcortical GM structures show differential developmental trajectories (Giedd et al., 1996b; Sowell et al., 2002; Toga et al., 2006). Because most studies have quantified only one or a few structures, the relative development of the subcortical structures is still unclear, however. For instance, different emphasis has been put on either the caudate or lenticular nuclei in development in various reports, sometimes because of methodological constraints (Jernigan et al., 1991; Giedd et al., 1996a; Sowell et al., 1999, 2002; Wilke et al., 2007). There has been some focus on structural development of the cerebellum (Sowell et al., 2002; Liu et al., 2003; Mackie et al., 2007) and accumbens (Sowell et al., 2002), but cerebellar development is still not characterized in terms of separate WM and GM development. Furthermore, there is a need for a broader understanding of the development of hippocampus and amygdala, as these structures often appear to increase during development, although discrepancies exist (Giedd et al., 1996b; Sowell et al., 2002; Gogtay et al., 2006; Toga et al., 2006; Guo et al., 2007). It is not clear how this is to be understood within a (proposed) framework of arborization/pruning as general principles of GM development. White matter (WM) volume has been shown to increase, often linearly, probably driven by increased myelination during adolescence and early adulthood (Reiss et al., 1996; Giedd et al., 1999; Sowell et al., 2002;

Table 1. Age and sex distribution of the sample

Age group	Sex		
	Female	Male	Total
8–11	17	21	38
12–15	19	18	37
16–19	19	17	36
20–23	17	16	33
24–31	15	12	27
Total	87	84	171

Lenroot et al., 2007). However, developmental trajectories for WM in the cerebrum versus cerebellum have not been compared.

In the current study, maturational changes were described and compared across volume estimates for the caudate, putamen, pallidum, accumbens area, amygdala, hippocampus, thalamus, cerebellar cortex and WM, brainstem, cerebral cortex and WM, and ventricles (lateral ventricles, inferior lateral ventricles, third ventricle, fourth ventricle), along with volume, thickness, and surface area estimates of the cortical lobes. Especially, it was investigated how subcortical structures develop compared with the cerebral cortex, how the basal ganglia/striatal structures compare in development, how the amygdala and hippocampus develop, and how cerebellar development can be described in terms of separate GM and WM volume.

Materials and Methods

Sample. One hundred seventy-one children and young adults (87 females and 84 males) were included. The age and sex distributions are shown in Table 1. Pearson's χ^2 test revealed no differences in gender distribution for the age groups shown in Table 1 (Pearson's $\chi^2 = 0.870$; $p = 0.93$). Children and adolescents between 8 and 19 years of age were recruited through newspaper advertisements, and local schools and workplaces. Adult participants were recruited through newspaper advertisements and among university students. The project was approved by the Regional Ethical Committee of South Norway. Written informed consent was obtained from all participants from 12 years of age and from the parent/guardian for participants <18 years. Oral informed consent was given by participants <12 years of age. Participants had no self- or parent-reported history of neurological or psychiatric disorders, chronic illness, premature birth, learning disabilities, or use of medicines known to affect nervous system functioning. They were required to be right handed, as reported in a structured interview (performed with participants ≥12 years and with parents of participants aged 8–19), to speak Norwegian fluently, to have normal or corrected-to-normal hearing and vision, and to have no MRI contraindications. Participants were tested using the WASI (Wechsler Abbreviated Scale of Intelligence) (Wechsler, 1999), and all participants scored above 80 on full-scale intelligence quotient [IQ; M (mean), 110.27; SD, 9.96]. There was no difference in IQ between males (M, 111.8; SD, 10.5) and females (M, 109.2; SD, 9.2; $t_{(168)} = -1.697$; $p = 0.10$). Among the 176 children and adolescents who met inclusion criteria, 4 had no useable MRI scans because of movement artifacts. All participants' scans were examined by a neuroradiologist, which led to the exclusion of one additional participant, reducing the total number of participants to 171.

MRI acquisition and analysis. Imaging data were collected using a 12-channel head coil on a 1.5 tesla Siemens Avanto scanner (Siemens Medical Solutions). The pulse sequences used for the morphometric analyses were two three-dimensional, T1-weighted [magnetization prepared rapid gradient echo (MP-RAGE)] scans, with the following parameters: repetition time, 2400 ms; echo time, 3.61 ms; inversion time, 1000 ms; flip angle, 8°; matrix, 192 × 192; field of view, 192. Each scan took 7 min, 42 s. Each volume consisted of 160 sagittal slices with voxel sizes of 1.25 × 1.25 × 1.20 mm. Each MP-RAGE was visually inspected, and only scans deemed to have no or minimal movement artifacts were included in analyses. The two MP-RAGEs were averaged to increase the signal-to-noise-ratio. Where there were problems achieving two high-quality scans

attributable to motion artifacts, etc., only one scan was used in the analysis. This was the case for 15.2% of the participants, of whom most (73%) were <12 years of age.

All datasets were processed and analyzed at the Neuroimaging Analysis Lab, Center for the Study of Human Cognition, University of Oslo, with additional use of computing resources from the Titan High Performance Computing facilities (http://hpc.uio.no/index.php/Titan) at the University of Oslo. Volumes of the caudate, putamen, pallidum, accumbens, thalamus, hippocampus, amygdala, cerebellum cortex, cerebellum WM, ventricles, and total cerebral WM were calculated using FreeSurfer 4.0.5. (http://surfer.nmr.mgh.harvard.edu/fswiki). The automated segmentation procedure was described previously (Fischl et al., 2002) and automatically assigns a neuroanatomical label to each voxel in a MR volume based on probabilistic information automatically estimated from a manually labeled training set. The segmentation puts constraints on allowable locations of structures in relation to each other based on the training set (e.g., hippocampus is never anterior to amygdala). The automated segmentations have been found to be statistically indistinguishable from manual labeling (Fischl et al., 2002), and correlations between FreeSurfer segmentation and manual labeling of hippocampal volume reached 0.85 in a study by Tae et al. (2008). Reproducibility errors between scan sessions have been shown to be up to 2.3% in young adults, with higher error estimates for the smallest structures (Jovicich et al., 2009). The segmentations were visually inspected for accuracy, and none were discarded. The segmentation is exemplified in Figures 1 and 2. As can be seen in Figure 2, the ventricles are only partly segmented, particularly the third ventricle and the inferior lateral ventricle. This should be kept in mind when considering the results. Although the brainstem is not segmented further into separate WM and GM volumes, it is considered together with WM volumes in this study.

Cortical volume, thickness, and area. Regional cortical thickness was estimated using FreeSurfer 4.1 (http://surfer.nmr.mgh.harvard.edu/fswiki) by means of an automated surface reconstruction procedure described previously (Dale et al., 1999; Fischl et al., 1999a,b, 2001; Fischl and Dale, 2000; Segonne et al., 2004). Briefly, a representation of the GM/WM boundary was reconstructed (Dale et al., 1999), using intensity and continuity information from the entire MR volume in segmentation and deformation procedures. Minor manual editing of vessels and dura was routinely performed, according to FreeSurfer guidelines (see http://surfer.nmr.mgh.harvard.edu/fswiki). The cortical surface was automatically parcellated based on (1) the probability of each label at each location in a surface-based atlas space, based on a manually parcellated training set; (2) local curvature information; and (3) contextual information, encoding spatial neighborhood relationships between labels (conditional probability distributions derived from the manual training set) resulting in 33 neuroanatomical regions (Fischl et al., 2004; Desikan et al., 2006). All resulting labels were manually inspected for accuracy. The results of these regional analyses of the 33 parcels were presented previously (Tamnes et al., 2009). In the present study, the mean lobar thickness (frontal, parietal, temporal, and occipital lobe) is reported, based on bilateral combinations of parcels, as well as total cortical mean thickness. The surface-based analysis also yielded estimates of the regional cortical (pial) area of each of the 33 parcels, which in turn were combined into a bilateral lobar area (frontal, parietal, temporal, and occipital) and a total cortical area. Cortical volume was calculated by multiplying cortical surface area with mean cortical thickness. Parcels were combined into bilateral lobar volumes. The surface-based (thickness) analyses have been shown to be comparable to postmortem pathological analyses, with agreement between pathological measurements and automated thickness estimation within 0.20 mm (Rosas et al., 2002). Test–retest variability in cortical thickness measurements across weeks and across scanner platforms has been shown to be within 0.20 mm in most of the cerebral cortex (Han et al., 2006), and correlations between cortical thickness and cognitive performance were shown by Dickerson et al. (2008) to be comparable across scan sessions, scanner platforms, and field strengths.

Total brain volume (TBV) was calculated based on all GM and WM volumes and ventricular volumes.
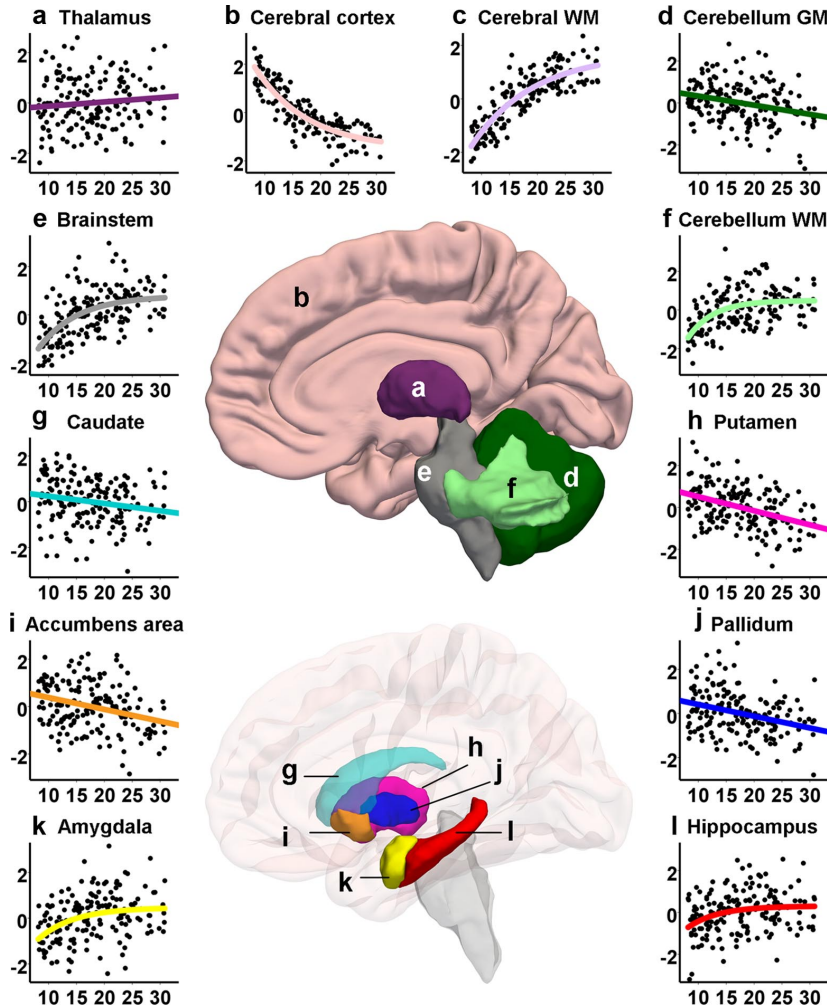
Figure 1. Regression plots showing the relationship between age and bilateral volumes of thalamus (***a***), cerebral cortex (***b***), cerebral WM (***c***), cerebellum GM (***d***), brainstem (***e***), cerebellum WM (***f***), caudate (***g***), putamen (***h***), the accumbens area (***i***), pallidum (***j***), amygdala (***k***), and hippocampus (***l***), with age on the horizontal axis and TBV-corrected volume in z-scores on the vertical axis. Also displayed are samples of the segmentation (cerebral WM not shown), based on the group mean.

Statistical analysis. Regression analyses were performed on three sets of volumetric variables: raw volumes, residual volumes after correcting for TBV (the sum of all 16 brain and ventricular volumes) by regression analyses, and proportional volumes of TBV. The choice of these types of variables is based on the assumption that each measure may be useful in its particular way, elucidating different aspects of development. On the one hand, the actual increase and decrease in each volume needs to be taken into account, and hence the raw volumes were analyzed and displayed in regression plots (see Table 3 and supplemental Fig. 1, available at www.jneurosci.org as supplemental material). On the other hand, there is substantial individual variance in brain size, which is bound to affect individual brain volumes both within and across age groups. This variance is, among other things, related to physical parameters such as height (Peters et al., 1998) and sex (Giedd et al., 1997; Sowell et al., 2007), which may create noise in the data that can obscure the unique effects of age. Several approaches to correcting for individual differences in brain volumes exist, including correcting for intracranial volume (ICV) (Walhovd et al., 2005) and TBV, with or without ventricles (Sowell et

al., 2002; Wilke et al., 2007). Since ICV correlated positively with age in our sample ($r = 0.37$; $p < 0.001$), correcting for this variable would also take out some of the effects of age. TBV did not correlate significantly with age ($r = -0.09$; $p = 0.26$), thus being better suited to control for individual differences without removing the effect of age. Brain development is characterized by a complex interplay between regressive and progressive events, and this should be taken into consideration in the interpretation of TBV-corrected results. How each volume relates to the rest of the brain throughout development may be conceptualized as each volume's proportion of the TBV (Jernigan et al., 1991; Sowell et al., 2002), and hence this measure was also used in the analyses. Cortical thickness and surface area variables were analyzed without TBV correction, as thickness analyses are often done without such correction (Sowell et al., 2004; Shaw et al., 2008; Tamnes et al., 2009), and we wanted to be able to compare thickness and surface area as aspects of cortical development. The matter of correction in the case of surface area is less straight forward, though (Panizzon et al., 2009). Regression analyses were performed with all measures separately as criterion variables and age as the
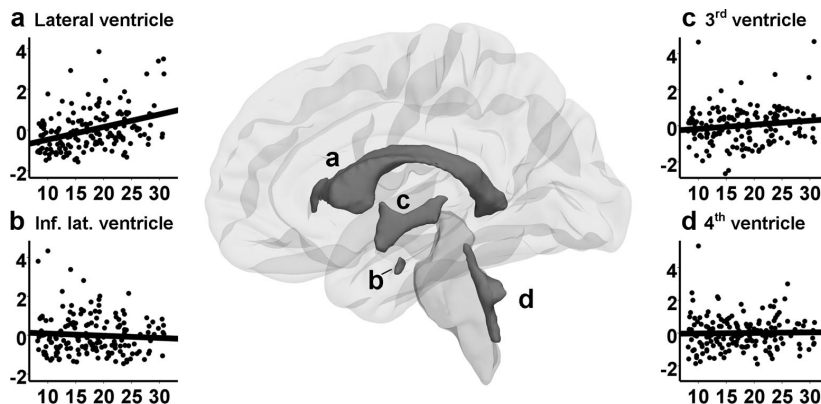
Figure 2. Regression plots showing the relationship between age and bilateral volumes of the lateral ventricles (*a*), the inferior lateral ventricles (*b*), the third ventricles (*c*), and the fourth ventricles (*d*), with age on the horizontal axis and TBV-corrected volume in *z*-scores on the vertical axis, shown together with samples of the segmentation, based on the group mean.

Table 2. Raw volumes of brain structures and ventricles

	Age groups					
	8–11 (*n* = 38)	12–15 (*n* = 37)	16–19 (*n* = 36)	20–23 (*n* = 33)	24–31 (*n* = 27)	Total (*n* = 171)
Cerebral cortex	576,253 (47,504)	560,231 (53,479)	509,614 (48,172)	492,307 (32,649)	487,303 (49,454)	528,512 (58,970)
WM	423,665 (50,171)	479,170 (47,799)	469,127 (57,028)	491,376 (49,735)	504,704 (70,491)	471,109 (60,860)
Hippocampus	8535 (802)	8995 (648)	8824 (828)	8922 (690)	8874 (787)	8824 (763)
Amygdala	3478 (324)	3750 (395)	3660 (440)	3722 (465)	3741 (461)	3664 (424)
Caudate	8261 (993)	8216 (862)	7848 (815)	7765 (704)	7765 (909)	7990 (882)
Putamen	12,805 (1352)	12,747 (982)	12,297 (1208)	11,697 (1023)	11,635 (1207)	12,287 (1250)
Pallidum	3721 (358)	3837 (372)	3582 (389)	3463 (257)	3486 (400)	3630 (382)
Accumbens	1467 (145)	1467 (180)	1409 (163)	1393 (178)	1309 (203)	1415 (180)
Thalamus	14,294 (1238)	14,947 (1006)	14,104 (1251)	14,365 (892)	14,498 (1373)	14,441 (1181)
Cerebellum GM	121,069 (9770)	124,302 (12,420)	116,799 (10356)	11,7831 (13,254)	114,138 (12,023)	119,150 (11,950)
Cerebellum WM	26,135 (2538)	29,241 (3766)	28,658 (2784)	29,831 (3399)	29,727 (2347)	28,619 (3311)
Brainstem	19,046 (1741)	21,166 (2346)	20,521 (1928)	21,558 (2281)	21,741 (1856)	20,725 (2253)
Lateral ventricle	8909 (4195)	11,043 (6526)	12,926 (7269)	12,509 (6163)	16,105 (8682)	12,048 (6903)
Inferior lateral ventricle	571 (341)	625 (306)	650 (297)	539 (225)	526 (245)	586 (290)
Third ventricles	906 (213)	967 (199)	904 (213)	921 (205)	1019 (270)	940 (220)
Fourth ventricles	1641 (680)	1669 (470)	1582 (369)	1604 (530)	1692 (558)	1636 (527)
Total brain volume	1,218,700 (102,670)	1,268,100 (101,391)	1,196,400 (112,006)	1,204,200 (91,544)	1,208,900 (129,920)	1,220,400 (109,094)

Mean (SD) number of voxels in each raw volume measured (summed across hemispheres), for each age group and for the total sample. One voxel equals 1 mm^3.

predictor variable. The analyses were repeated with age^2 as an additional predictor to assess possible quadratic components, and again with age^3 as a third predictor, to assess possible cubic components. Regression analyses were then performed with all measures separately as the criterion variable and TBV, age, and (where the previous analyses had shown a nonlinear component) age^2 as the simultaneous predictor variables, to show the relative contributions of each variable on the brain volumes. For volumes in which age^2 gave a significant contribution, exponential curves were calculated. The data points were fitted iteratively to exponential functions of the form $f(x) = b_1 + b_2 \times e^{(-\text{age}/t)}$, where b_1 is the estimated value at the asymptote, b_2 is the difference between b_1 and the estimated value of x at age zero, and t is a time constant reflecting rate of development. The effect size of each exponential curve fit is indicated by R^2. For both the exponential and linear fits, absolute and relative change in volume from 8 to 30 years was calculated. The relative change of nonlinearly developing volumes was calculated from the exponential function. As correlations between the different brain structures were expected, Bonferroni corrections for multiple comparisons should be considered overly conservative. Still, Bonferroni-corrected results are also reported, with a *p* value threshold of 0.003 in the volumetric analysis (based on 16 volumes) and a threshold of 0.006 in the regional cortical analyses (based on four lobes × two variables, thickness and surface area, whereas total cortical volume is Bonferroni corrected in the volumetric

analysis and the regional volumes are dependent on the thickness and surface areas). Within designated regions, the differences in relationships with age were tested statistically using *t* tests of Fisher's *z*-transformed correlations. This was done to statistically compare age trajectories where it was deemed theoretically and statistically appropriate. Two regions were selected for this analysis based on proximity and apparent similarities in trajectories: the basal ganglia (caudate, putamen, and pallidum) and the medial temporal lobe subcortical structures (hippocampus and amygdala).

Results

Descriptive analyses

ANOVA with 13 bilateral brain volumes and two hemispheres as within-subjects factors and age as the between-subject factor showed no significant hemisphere × age interaction effects ($F_{(124,46)} = 1.104$; $p = 0.36$). This analysis was repeated for four bilateral regional (cortical lobe) variables, yielding no significant hemisphere × age interaction effects for volume ($F_{(124,46)} = 0.885$; $p = 0.706$), thickness ($F_{(124,46)} = 1.269$; $p = 0.179$), or surface area ($F_{(124,46)} = 1.092$; $p = 0.375$). Thus, the sum of right- and left-hemisphere volumes was used in all analyses. As expected, males had larger TBVs than females as evidenced by an

Table 3. Results from regression analyses with raw volumes

	Regression with age				Regression with age and age^2			
	β	F	p	R^2	F	p	R^2	p age^{2a}
Cerebral cortex	−0.60	95.42	3.78E-18	0.36	51.91	2.79E-18	**0.38**	0.018
Cerebral WM	0.41	34.93	1.84E-8	0.17	20.84	8.25E-9	**0.20**	0.018
Hippocampus	0.12	2.35	0.127	0.01	3.11	0.047	0.04	0.052
Amygdala	0.16	4.32	0.039	0.03	3.97	0.021	0.05	0.061
Caudate	−0.21	8.13	0.005	0.05	4.56	0.012	0.05	0.324
Putamen	−0.38	28.12	3.54E-7	0.14	13.98	2.43E-6	0.14	0.956
Pallidum	−0.32	18.66	2.65E-5	0.10	9.42	1.33E-4	0.10	0.612
Accumbens	−0.30	16.90	6.15E-5	0.09	9.88	8.82E-5	0.11	0.103
Thalamus	−0.02	0.04	0.849	2.16E-4	0.08	0.925	0.001	0.731
Cerebellum GM	−0.26	11.89	0.001	0.07	7.01	0.001	0.08	0.154
Cerebellum WM	0.35	23.48	2.84E-6	0.12	18.37	6.12E-8	**0.18**	0.001
Brainstem	0.37	26.55	7.09E-7	0.14	17.67	1.08E-7	**0.17**	0.006
Lateral ventricle	0.34	21.56	6.87E-6	0.11	10.99	3.28E-5	0.12	0.489
Inferior lateral ventricle	−0.07	0.94	0.335	0.01	0.47	0.628	0.01	0.955
Third ventricle	0.09	1.38	0.241	0.01	1.76	0.176	0.02	0.147
Fourth ventricle	−9.52E-4	1.53E-4	0.990	9.06E-7	0.01	0.988	1.38E-4	0.880

Results shown are from two separate regression analyses with raw volumes, one with only age as the predictor variable and the other with both age and age^2 as predictor variables. Bold characters for R^2 indicate a statistically significant quadratic age relationship.

[a]The p value for the unique contribution of age^2 to the explained variance in brain volume.

Table 4. Results from regression analyses with TBV-corrected volumes

	Regression with age				Regression with age and age^2			
	β	F	p	R^2	F	p	R^2	p age^{2a}
Cortex volume	−0.83	384.98	1.98E-45	0.70	276.27	7.64E-54	**0.77**	1.94E-11
Cerebral WM	0.82	356.03	1.87E-43	0.68	230.68	6.59E-49	**0.73**	2.15E-8
Hippocampus	0.24	9.85	0.002	0.06	7.62	6.81E-4	**0.08**	0.025
Amygdala	0.34	21.64	6.62E-6	0.11	14.18	2.05E-6	**0.14**	0.015
Caudate	−0.20	6.74	0.010	0.04	4.26	0.016	0.05	0.188
Putamen	−0.41	34.55	2.16E-8	0.17	17.23	1.56E-7	0.17	0.754
Pallidum	−0.33	20.03	1.40E-5	0.11	10.00	7.87E-5	0.11	0.773
Accumbens	−0.31	17.44	4.75E-5	0.09	10.20	6.60E-5	0.11	0.097
Thalamus	0.10	1.83	0.177	0.01	0.91	0.403	0.01	0.963
Cerebellum GM	−0.27	13.03	4.04E-4	0.07	7.73	0.001	0.08	0.13
Cerebellum WM	0.45	41.66	1.10E-9	0.20	29.86	8.03E-12	**0.26**	1.79E-4
Brainstem	0.55	72.68	8.21E-15	0.30	45.43	1.70E-16	**0.35**	4.09E-4
Lateral ventricle	0.38	28.09	3.58E-7	0.14	14.42	1.67E-6	0.15	0.379
Inferior lateral ventricle	−0.07	0.82	0.367	0.01	0.410	0.664	0.01	0.936
Third ventricle	0.14	3.31	0.071	0.02	3.33	0.038	0.04	0.070
Fourth ventricle	0.02	0.07	0.796	3.96E-4	0.07	0.934	0.001	0.793

Results shown are from two separate regression analyses with TBV-corrected volumes, one with only age as the predictor variable and the other with both age and age^2 as predictor variables. Bold characters for R^2 indicate a statistically significant quadratic age relationship.

[a]The p value for the unique contribution of age^2 to the explained variance in brain volume.

independent-samples t test (males: 1,290,900 mm^3; SD, 87,897; females: 1,152,300 mm^3; SD, 80,731; $t_{(169)} = -10.75$; $p = 0.0001$). Also, as can be seen from Table 2, the variance was high within the age groups. Analysis of covariance with 16 TBV-corrected brain volumes as the within-subjects factor, sex as the between-subjects factor, and age as a covariate showed no sex × age interaction effects ($F_{(22,23)} = 0.68$; $p = 0.82$) or sex × age × structure effects ($F_{(182.737,191.043)} = 1.141$; $p = 0.183$). This analysis was also performed with the regional cortical variables, revealing no significant sex × age effects in thickness ($F_{(22,23)} = 0.876$; $p = 0.743$), surface area ($F_{(22,23)} = 0.867$; $p = 0.630$), or TBV-corrected volumes ($F_{(22,23)} = 0.852$; $p = 0.645$) or sex × age × structure effects for thickness ($F_{(53.864,56.312)} = 0.963$; $p = 0.554$), surface area ($F_{(44.832,46.869)} = 0.823$; $p = 743$), or TBV-corrected volumes ($F_{(42.731,44.673)} = 0.881$; $p = 0.660$). There may still be sex effects of interest in select structures. However, since no interaction effect of sex and age was shown in this overall analysis, and sex is not the primary focus of the present study, additional analyses were performed on males and females together.

Relationships between age and brain volumes
The volume for each brain structure in each of five age groups is displayed in Table 2. The volume, thickness, and surface area of each cortical lobe and total cerebral cortex are displayed in supplemental Table 1 (available at www.jneurosci.org as supplemental material). The results of the regression analyses with subcortical brain volumes are shown in Tables 3 and 4, whereas Table 5 shows the results of the regression analyses with cortical variables (volume, thickness, and surface area). In the raw volume analyses, all GM volumes, except hippocampus, amygdala, and thalamus, showed a negative relationship with age ($p < 0.05$). Amygdala and hippocampus showed a slight positive relationship with age, but only the amygdala increase was significant. The cerebral cortex was the only GM structure that showed a curvilinear relationship with age. This pattern was seen in the parietal and occipital lobe volumes in the regional cortical analysis, whereas the frontal and temporal lobes were best described by linear age relationships. In the cortical thickness analysis, the frontal, parietal, and occipital lobes showed quadratic age relationships, and the temporal lobe showed a linear age relationship.

Table 5. Regression analyses with cortical lobe volumes, thickness, and surface area

	Regression with age				Regression with age and age^2			
	β	F	p	R^2	F	p	R^2	p age^{2a}
Volume								
Total cortex	−0.83	384.98	1.98E-45	0.36	276.27	7.64E-54	**0.38**	1.94E-11
Frontal	−0.58	85.14	1.12E-16	0.34	43.42	6.29E-16	0.34	0.227
Parietal	−0.67	135.72	2.12E-23	0.45	87.36	9.81E-27	**0.51**	5.43E-06
Temporal	−0.41	34.86	1.89E-08	0.17	17.69	1.07E-07	0.17	0.442
Occipital	−49	54.47	6.83E-12	0.24	32.34	1.31E-12	**0.28**	0.005
TBV-corrected volume								
Total cortex	−0.83	384.98	1.98E-45	0.70	276.27	7.64E-54	**0.77**	1.94E-11
Frontal	−0.77	238.48	4.02E-34	0.59	130.30	6.80E-35	**0.61**	0.002
Parietal	−0.79	281.04	8.81E-38	0.62	253.31	1.93E-51	**0.75**	1.09E-16
Temporal	−0.61	98.02	1.64E-18	0.37	53.37	1.14E-18	**0.39**	0.016
Occipital	−0.55	72.65	8.31E-15	0.30	48.41	2.51E-17	**0.37**	5.33E-05
Thickness								
Total cortex	−0.81	314.81	1.91E-40	0.65	181.89	9.22E-43a	**0.68**	4.09E-5
Frontal	−0.76	233.44	1.16E-33	0.58	129.26	1.03E-34	**0.61**	0.001
Parietal	−0.82	345.42	2.42E-43	0.68	225.70	2.52E-48	**0.73**	6.54E-8
Temporal	−0.53	66.10	8.74E-14	0.28	33.62	5.24E-13	0.29	0.297
Occipital	−0.77	239.56	3.21E-34	0.59	157.29	3.21E-39	**0.65**	7.68E-8
Surface area								
Total cortex	−0.32	18.80	2.49E-5	0.10	10.23	6.42E-5	0.11	0.208
Frontal	−0.33	21.18	8.18E-6	0.11	10.76	4.02E-5	0.11	0.525
Parietal	−0.35	24.27	1.98E-6	0.13	16.40	3.12E-7	**0.16**	0.007
Temporal	−0.22	8.34	0.004	0.05	4.20	0.017	0.05	0.759
Occipital	−0.18	5.73	0.018	0.03	3.64	0.028	0.04	0.218

Results shown are from two separate regression analyses with both raw and TBV-corrected lobar volumes, thickness, and surface area, one with only age as the predictor variable and the other with both age and age^2 as predictor variables. Bold characters for R^2 indicate a statistically significant quadratic age relationship.

^{a}The p value for the unique contribution of age^2 to the explained variance in brain volume.

All lobar surface areas showed statistically significant age relationships, and the parietal lobe surface area also showed a quadratic relationship with age ($p < 0.05$). All WM volumes (cerebral WM, cerebellar WM, brainstem) showed a quadratic relationship with age ($p < 0.05$). The lateral ventricles increased linearly with age, whereas the inferior lateral ventricles and the third and fourth ventricles showed no significant relationship with age. With Bonferroni corrections, the amygdala and caudate age relationships no longer reached significance in the volumetric analysis, whereas the additional contribution of age^2 to the explained variance in the parietal surface area disappeared. When introducing age^3 as a third regressor, an additional unique variance ($p < 0.05$) was explained in only one structure, the pallidum, for which R^2 increased from 0.10 to 0.13 ($p = 0.02$) (not displayed in the tables). The regression plots for the raw volumes are displayed in supplemental Figure 1 (available at www.jneurosci.org as supplemental material). The regression plots for the regional cortical variables (thickness and surface area) are displayed in Figure 3.

When the analyses were repeated with the TBV-corrected volumes as the dependent variables (Tables 4, 5), the finding that most GM volumes decreased with age while the WM volumes increased was replicated. However, hippocampus showed a significant positive relationship with age, and both the hippocampus and the amygdala showed a nonlinear increase in volume. The regional cortical analysis revealed statistically significant contributions of age^2 in all four cortical lobes. As in the analyses with the raw volumes, an additional unique variance ($p < 0.05$) was explained in only the pallidum when introducing age^3 as a third regressor, with R^2 increasing from 0.11 to 0.13 ($p = 0.048$) (not displayed in the tables). The amount of variance explained by age tended to increase for the cerebral cortex and WM, cerebellum WM, brainstem, amygdala, putamen, lateral ventricles, and hippocampus when TBV-corrected volumes were analyzed

compared with the raw volumes. When the results were Bonferroni corrected, the TBV-corrected caudate age relationship no longer reached statistical significance, and the contribution of age^2 to hippocampus, amygdala, and temporal lobe also disappeared, as did the cubic component in the regression with pallidum. Regression analyses were also performed with TBV, age, and age^2 in the model, to enable evaluation of these separate components, and the results are shown supplemental Table 2 (available at www.jneurosci.org as supplemental material). Generally, TBV showed a profound effect on individual brain variables. The TBV-corrected cerebral cortex (frontal and parietal lobes more than temporal and occipital lobes), cerebral WM, brainstem, cerebellar WM, and amygdala showed the greatest impact of age in terms of explained variance, whereas the hippocampus, the cerebellum cortex, and the caudate showed the least impact of age in this analysis. The regression plots for TBV-corrected GM and WM volumes and ventricles are displayed in Figures 1 and 2. The regression plots for the TBV-corrected regional cortical volumes are displayed in Figure 3.

The results of the regression analyses with proportional volumes of TBV are displayed in supplemental Table 3 (available at www.jneurosci.org as supplemental material), and the results primarily mirrored the results of the regressions with the standardized residuals after correcting for TBV. Additional analyses were therefore not performed with the proportional measures as dependent variables. The regression plots for proportional volumes are shown in supplemental Figure 2 (available at www.jneurosci.org as supplemental material).

Characteristics of the rate of change of nonlinearly developing structures

When age^2 was a significant predictor independent of age, nonlinear regression analyses were run. Relative differential nonlinear trajectories were found for the cerebral cortex, cerebral WM,

brainstem, and cerebellum WM in the raw volume analyses, and additionally for the amygdala and hippocampus in the analysis with the TBV-corrected volumes. The time constant values are shown in Table 6. Cerebellar WM, amygdala, and hippocampus appeared to undergo a relatively rapid change early in the studied age span, whereas the cerebral WM, cerebral cortex, and brainstem showed less steep changes in the earliest part of the age span. Within the cerebral cortex, the frontal and temporal lobes appeared to approach the peak in volume reduction later than the parietal and occipital lobes, as seen in Table 7. Time constant estimates were derived from the exponential fitting analysis of frontal, parietal, and occipital thickness, showing earlier thinning in the occipital lobes. Only the parietal lobe surface area showed a nonlinear age relationship, making it difficult to compare the time constant estimate with the trajectories of the remaining lobar areas.

Estimated percentage change

From the raw volumes, percentage change from 8 to 30 years was estimated, and the results are shown in Table 6. For the structures with nonlinear age relationships, the nonlinear analysis equation was used to estimate the percentage change. The lateral ventricular volume changed the most, with a near 100% increase during this age range. Also, the WM volumes (in cerebrum, cerebellum, and brainstem) showed high percentage increases in volume. As can be seen in Figure 3, the cerebral cortex, followed by the putamen, accumbens, and pallidum, showed the greatest percentage decrease, whereas the amygdala, hippocampus, and thalamus were the structures that appeared to change the least from 8 to 30 years of age. Within the cerebral cortex, thickness changed by 8.3–19.4%, with the greatest change in parietal and occipital lobes. Surface area changed by 7.0–20.9%, with the greatest change observed in the frontal lobes, whereas lobar volumes changed 15.0–28.5%, with the greatest change observed in parietal lobes, as seen in Table 7.

Differential age relationships within subcortical regions

To explore whether differential age relationships between adjacent subcortical structures can be observed, statistical comparisons were made within the basal ganglia and within the temporal lobe subcortical structures. Within the basal ganglia, the putamen showed a stronger relationship with age than the caudate (TBV-corrected volumes), as there was a significant difference between the age correlations of -0.19 for the caudate and -0.40 for the putamen ($t_{(168)} = 2.37$; $p < 0.05$). The difference in age correlations between the caudate and the pallidum (-0.31) was not significant ($t_{(168)} = 1.56$; $p > 0.05$). There was no significant difference between the age correla-
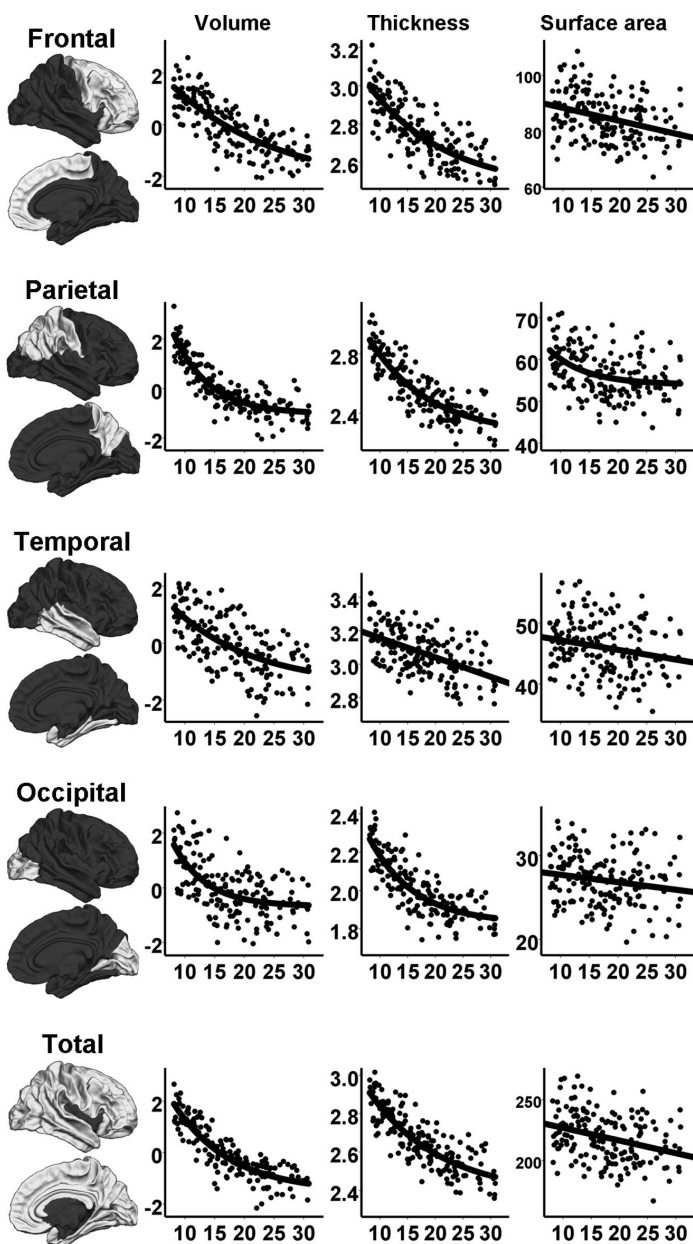
Figure 3. Regression plots showing the relationship between age and bilateral cortical volume (TBV corrected), thickness, and surface area for each cortical lobe and for the total cerebral cortex, with age on the horizontal axes. The measurements are standardized residuals (volumes), in millimeters (thickness), and in square millimeters (surface area) on the vertical axes. The parcellation of the cortical lobes are displayed in the left column.

tion of 0.26 for the hippocampus and 0.36 for the amygdala ($t_{(168)} = 1.29$; $p > 0.05$).

Discussion

The results of the present study confirmed the general notion that GM decreases while WM and lateral ventricular volumes increase

Table 6. Age effects in terms of explained variance (R^2), time constant (t), absolute change, and percentage change

	TBV-corrected volumes		Raw volumes			
	R^2	t	R^2	t	Absolute change	Percentage change
Cerebral cortex	0.77	9.47	0.38	14.88	129,206	−21.5
Cerebral WM	0.73	11.06	0.21	5.33	103,314	26.1
Hippocampus	0.08	5.51	0.01		322	3.7
Amygdala	0.14	6.42	0.03		241	6.8
Caudate	0.04		0.05		682	−8.2
Putamen	0.17		0.14		1703	−13.1
Pallidum	0.11		0.10		434	−11.4
Accumbens	0.09		0.09		195	−13.0
Thalamus	0.01		2.16E-4		63	0.4
Cerebellum GM	0.07		0.07		11,047	−8.9
Cerebellum WM	0.27	4.54	0.20	2.87	6347	27.3
Brainstem	0.35	7.03	0.19	3.69	3893	22.1
Lateral ventricle	0.14		0.11		8372	99.8
Inferior lateral ventricle	0.01		0.01		78	12.5
Third ventricle	0.02		0.01		72	7.9
Fourth ventricle	3.96E-4		9.06E-7		2	0.1

R^2 is from the nonlinear regression analysis. Time constant (t) indicates the rate of development, calculated from the 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 and b_2 is the difference between the b_1 value and the estimated value at age zero. Lower values indicate a faster developmental course. When no value of t is presented, a linear fit best described the data, and R^2 is from the linear regression. Absolute and percentage change is calculated from the estimated mean values for 8 year olds and 30 year olds.

Table 7. Age effects in terms of explained variance (R^2), time constant (t), absolute change, and percentage change in cortical volume, thickness, and surface area

	TBV-corrected volumes		Raw volumes/variables			
	R^2	t	R^2	t	Absolute change	Percentage change
Cortex volume	0.77	9.47	0.38	14.88	129,206	−21.5
Frontal volume	0.61	17.72	0.34		46,196	−20.0
Parietal volume	0.76	6.00	0.51	8.29	46,550	−28.5
Temporal volume	0.39	13.57	0.17		20,170	−15.0
Occipital volume	0.38	5.57	0.28	8.34	14,901	−23.0
Mean thickness			0.69	12.93	0.44	−15.1
Frontal thickness			0.61	14.08	0.43	−14.3
Parietal thickness			0.73	10.72	0.56	−19.4
Temporal thickness			0.28		0.26	−8.3
Occipital thickness			0.66	8.14	0.42	−18.4
Cortex area			0.10		22,898	−10.0
Frontal area			0.11		18,642	−20.9
Parietal area			0.16	6.30	5595	−9.4
Temporal area			0.05		3486	−7.3
Occipital area			0.03		1965	−7.0

R^2 is from the nonlinear regression analysis. Time constant (t) indicates the rate of development, calculated from the 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 and b_2 is the difference between the b_1 value and the estimated value at age zero. Lower values indicate a faster developmental course. When no value of t is presented, a linear fit best described the data, and R^2 is from the linear regression. Absolute and percentage change is calculated from the estimated mean values for 8 year olds and 30 year olds.

during late childhood and adolescence (Jernigan et al., 1991; Giedd et al., 1996b, 1999; Reiss et al., 1996; Sowell et al., 1999, 2002; Gogtay et al., 2004; Lenroot et al., 2007; Shaw et al., 2008), while simultaneously pointing to important nuances in subcortical development. Volume reductions were not observed in all GM structures; there were no age effects on thalamic volume, and the hippocampus and amygdala showed volume increases. Overall, the results were characterized by substantial heterogeneity. Unless specified otherwise, the remainder of the discussion will deal with the results of the TBV-corrected analyses.

Heterogeneous age effects
The reduction in cortical volume was driven by both a reduction in thickness and a slight reduction in surface area, seen in all lobar regions. The cerebral cortex, and the cortical lobe volumes, differed from subcortical GM volumes by showing a stronger relationship with age (37–77% vs 4–16% explained variance of age; 15–28.5% vs 3–13% change from 8 to 30 years) and by showing a nonlinear relationship with age, whereas linear age relationships

were found in most subcortical structures. Proportionally stronger age effects in frontal cortical GM compared with subcortical structures have also been reported by Sowell et al. (2002). Lobar cortical thickness was characterized by strong age effects but less percentage change than cortical volumes [see Tamnes et al. (2009) for voxel-wise and regional thickness analyses]. Cortical surface area showed less developmental effects, comparable to effects seen for subcortical raw and TBV-corrected volumes. Differential properties of thickness and surface area have also been pointed out by Panizzon et al. (2009) using an adult sample.

WM volumes changed more than cortical and subcortical GM, which is in line with previous literature (Sowell et al., 2002), up to 27%. All WM volumes showed decelerating nonlinear increases during development. However, different rates of development were revealed by looking at the time constants from the nonlinear regression analyses. The increase in WM volume of the brainstem and cerebellum approached the asymptote earlier than what was the case for cerebral WM.

Basal ganglia and the accumbens area

Basal ganglia structures and the accumbens area showed similarities in development as they all were moderately and linearly related to age. These structures changed relatively little compared with cortical and frontal cortical GM. Sowell et al. (2002) have previously pointed out the similarities in development between different basal ganglia structures. However, the differences may also be noteworthy, as there has been a focus on only the caudate in many reports (Lenroot et al., 2007; Wilke et al., 2007; Giedd, 2008), and few studies, with the exception of Sowell et al. (2002) and Jernigan et al. (1991), have tried to disentangle maturational effects on different parts of the basal ganglia. In the present study, the caudate showed the weakest relationship with age (nonsignificant with Bonferroni correction) and changed the least compared with lenticular nuclei. The statistical analyses of the basal ganglia structures' different relationships with age also confirmed this point. This seems to be in line with previous reports in which both the caudate and lenticular nuclei have been studied in the same sample (Jernigan et al., 1991; Sowell et al., 2002).

Cerebellum

Differential developmental properties were also discovered for GM and WM within the cerebellum. A general cerebellar volume increase has been observed (Sowell et al., 2002; Mackie et al., 2007), along with a nonlinear decrease in cerebellar GM volume (Mackie et al., 2007). Our results confirmed a general tendency of cerebellar GM reduction, although linear. Giedd et al. (2007) commented on the cerebellum as being among the latest structures to reach peak volume. Interestingly, our cerebellar WM analysis indicates an early development, as the time constant derived from the nonlinear equation was low, especially compared with cerebral WM. Although our data could not pinpoint the exact timing of cerebellar GM development (because of the linear fitting of data), the results for cerebellar WM indicate differential developmental trajectories in GM and WM in the cerebellum. This needs to be confirmed by future studies.

Temporal lobe subcortical GM

Hippocampus and amygdala diverge from the other GM volumes in their slight increase with age during development. Our data are in line with some of the previous studies and reviews (Giedd et al., 1996b; Toga et al., 2006; Guo et al., 2007), but discrepancies exist (Giedd et al., 1996b; Sowell et al., 2002; Gogtay et al., 2006). It must be noted that the observed age effect in the hippocampus was weak, appearing only when correcting for TBV (without Bonferroni correction), although a tendency was also visible for the raw volumes. Gogtay et al. (2006) argued that the weak and diverging developmental effects in the hippocampus may be attributable to opposing effects in subregions of the hippocampus. However, the relatively more robust effect in the nearby amygdala supports the finding of a volume increase. Caution must be taken, as the contribution of age^2 to these two volumes did not reach statistical significance when correcting for multiple comparisons.

GM reduction and WM increase in light of developmental principles

Myelination has been shown to constitute a major developmental principle during late childhood and through adolescence, supported by recent diffusion tensor imaging studies (Giedd et al., 1999; Paus et al., 2001; Sowell et al., 2002; Giedd, 2004; Barnea-Goraly et al., 2005; Ashtari et al., 2007; Giorgio et al., 2008; Lebel et al., 2008). GM reduction is thought to, in part,

reflect synaptic pruning (Huttenlocher, 1990). However, it is also possible that GM reductions are attributable to increased myelination, pushing the border between segmented GM and WM in favor of WM volume (Sowell et al., 2004; Shaw et al., 2008). This would likely be the case also for subcortical structures, surrounded by myelinated, long-distance axonal projections of neurons. The temporal lobe structures show a different developmental pattern than the other GM structures, making it possible that other neurobiological mechanisms are responsible for the maturational changes observed. Although the present results do not directly explain neurobiological mechanisms in development, the pattern of increases and decreases observed here represents valuable developmental information and points to the need for a better understanding of the biological mechanisms in brain development.

These developmental principles must be considered together with cognitive development, to disentangle the relationships between the dynamics of volumetric changes and cognitive performance throughout childhood and adolescence. The nonlinear and dynamic nature of brain development makes this especially important, as the differential trajectories may have different cognitive implications. For instance, there is some evidence from functional MRI studies to suggest that subcortical structures and cortical areas may play different roles at different times during cognitive development (Menon et al., 2005; Ciesielski et al., 2006; Galvan et al., 2006). However, it remains elusive how this relates to differential regional structural neurodevelopment.

Limitations and conclusions

Future investigations are needed to confirm the results in a longitudinal design. This has the advantage of being more sensitive to individual differences in developmental trajectories, thus potentially capturing developmental peaks early in the age span, as has been found by Giedd et al. (1999). Studying children and adults in the same sample also raises some methodological problems. For instance, the scans of younger children may be more prone to movement artifacts, which could lead to erroneous estimations of brain measures. Our data were characterized by a greater reliance on only one scan among the younger participants. However, negligible differences have been found between using one versus two averaged scans (Han et al., 2006). Children may have smaller neuroanatomical volumes, and hence biases may be introduced when comparing neuroanatomical segmentations across children and adults. For instance, child scan segmentations may suffer from greater partial volume effects. However, the TBV of 8 year olds is probably comparable to that of adults (Reiss et al., 1996), and the classification technique used employs a registration procedure that is especially well suited to account for varying anatomies (Fischl et al., 2004). Also, by visual inspection of the segmentations, the techniques used were deemed to yield accurate results in children of the present age. Another limitation of the present study is that brain development was only studied from 8 years of age and up. Clearly, dramatic changes take place much earlier in development (Giedd et al., 1996a; Gogtay et al., 2004; Gogtay et al., 2006; Knickmeyer et al., 2008). Still, our cross-sectional data from the present age range yielded results that shed new light on brain development seen as a whole. GM decreases in cerebral cortex, basal ganglia/accumbens, and cerebellum were confirmed, as were GM increases in hippocampus and amygdala and WM and ventricular increases. Especially noteworthy are the nuances in developmental differences observed, as shown by the differential age effects within the basal ganglia, between cortex and subcortical structures, and the

patterns of cerebellar WM development compared with both cerebellar GM and cerebral WM.

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Supplementary table 1. Raw volumes, thickness and surface area of cortical lobes and total cortex

	8-11 (n=38)	12-15 (n=37)	16-19 (n=36)	20-23 (n=33)	24-31 (n=27)	Total (n=171)
			Age groups			
Volume						
Cortex volume	576253 (47504)	560231 (53479)	509614 (48172)	492307 (32649)	487303 (49454)	528512 (58970)
Frontal volume	225159 (19634)	223692 (21697)	202558 (19178)	195607 (14648)	191393 (19921)	209049 (23634)
Parietal volume	152364 (14589)	141478 (14503)	125647 (13156)	121701 (8291)	120150 (13602)	133380 (18152)
Temporal volume	132454 (11320)	131970 (13412)	124273 (13638)	118444 (10555)	119766 (12198)	125920 (13526)
Occipital volume	61344 (7012)	57877 (7928)	52553 (6200)	51665 (5328)	51384 (7373)	55303 (7861)
Thickness						
Mean thickness	2.84 (.10)	2.72 (.10)	2.63 (.08)	2.54 (.08)	2.51 (.10)	2.66 (.15)
Frontal thickness	2.93 (.12)	2.81 (.11)	2.73 (.09)	2.65 (.09)	2.61 (.11)	2.76 (.15)
Parietal thickness	2.80 (.12)	2.64 (.12)	2.52 (.09)	2.42 (.09)	2.38 (.10)	2.56 (.19)
Temporal thickness	3.17 (.12)	3.09 (.12)	3.07 (.10)	3.00 (.11)	2.98 (.13)	3.07 (.13)
Occipital thickness	2.18 (.11)	2.06 (.11)	1.96 (.09)	1.90 (.08)	1.89 (.07)	2.01 (.14)
Surface area						
Total surface area	226789 (18456)	227728 (20175)	212921 (18309)	212265 (16427)	212158 (21167)	218960 (20071)
Frontal area	87606 (8013)	89228 (8604)	82557 (7255)	82043 (6924)	81160 (8675)	84803 (8467)
Parietal area	60041 (5369)	58502 (5074)	54436 (5344)	54931 (4320)	54914 (5527)	56733 (5585)
Temporal area	46882 (3791)	47728 (4674)	45394 (4506)	44304 (4202)	45086 (4440)	45971 (4457)
Occipital area	27929 (2818)	27594 (3054)	26271 (2626)	26676 (2797)	26562 (3642)	27050 (3009)

Mean (SD) number of voxels in each raw volume measured (summed across hemispheres), for each age group and for the total sample (1 voxel = 1 mm^3); mean (SD) thickness for each age group and the total sample for each cortical lobes and for the total cortex, in mm; mean surface area for each age group and for the total sample, measured in mm^2.

**Supplementary table 2. Results from regression analyses with TBV, age and age^2 as independent variables**

	Regression		Partial correlation			t			p		
	F	p	TBV	age	age^2	TBV	age	age^2	TBV	age	age^2
Cerebral cortex	537.13	1.63E-85	.77	-.60	-.57	30.53	-10.82	7.18	3.12E-70	5.34E-21	2.23E-11
Frontal cortex	261.74	7.01E-63a	.86	-.40	.23	21.47	-5.68	3.08	6.90E-50	5.97E-8	.002
Parietal cortex	321.67	3.81E-69	.84	-.70	-.62	19.70	-12.51	9.21	2.09E-45	9.41E-26	1.31E-16
Temporal cortex	231.97	2.58E-59	.88	-.30	.18	23.36	-4.03	2.39	1.66E-54	8.57E-5	.018
Occipital cortex	79.64	4.96E-32	.66	-.39	.30	11.23	-5.54	4.12	3.76E-22	1.17E-7	6.06E-5
Cerebral WM	556.37	1.14E-86	.94	.58	-.41	36.11	9.22	-5.85	8.17E-81	1.29E-16	1.29E-16
Hippocampus	53.23	3.38E-24	.69	.21	-.17	12.17	2.75	-2.25	8.60E-25	.007	.025
Amygdala	92.58	2.48E-35	.78	.24	-.19	16.05	3.19	-2.44	1.13E-35	.002	.016
Caudate	24.24	5.63E-10	.43	-.20		6.21	-2.60		4.05E-9	.010	
Putamen	80.13	3.66E-25	.64	-.41		10.65	-5.89		1.45E-20	2.08E-8	
Pallidum	58.40	5.55E-20	.59	-.33		9.41	-4.48		3.81E-17	1.37E-5	
Accumbens	52.47	1.98E-18	.57	-.30		8.95	-4.18		6.33E-16	4.66E-5	
Thalamus	189.60	8.37E-44	.83	.10		19.47	1.36		6.28E-45	.177	
CerebellumGM	82.10	1.34E-25	.68	-.27		11.93	-3.61		3.65E-24	3.98E-4	
CerebellumWM	42.12	2.53E-20	.55	.35	-.28	8.59	4.86	-3.81	6.02E-15	2.64E-6	1.99E-4
Brainstem	88.29	2.85E-34	.73	.36	-.27	13.78	4.99	-3.58	2.48E-29	1.51E-6	4.57E-4
Lateral ventricle	22.98	1.50E-9	.32	.38		4.67	5.31		6.27E-6	3.47E-7	
Inf. lat. ventricle	.67	.512	.05	-.07		.64	-.91		.521	367	
3rd ventricle	19.27	2.93E-8	.42	.14		6.07	1.82		8.22E-9	.071	
4th ventricle	4.85	.009	.23	.02		3.11	.259		.002	.796	

Results of regression analyses with neuroanatomical volumes as dependent variables, and TBV, age and age^2 as independent variables. Where the analyses with TBV-corrected volumes (shown in Table 4) had revealed no significant contribution of age^2, only age was entered in the current analysis. Displayed are F- and p-values from the total expression, partial correlations between volumes and each independent variable, t-statistics and p-values for each independent variable in the regression

Supplementary table 3. Results from regression analyses with proportional volumes.

	Regression with *age*				Regression with *age* and *age²*			
	Beta	F	p	R²	F	p	R²	p age²a)
Cerebral Cortex	-.84	392.24	6.57E-46	.70	287.54	5.74E-55	**.77**	4.24E-12
Frontal	-.77	241.22	2.28E-34	.59	132.38	3.03E-35	**.61**	.002
Parietal	-.79	283.86	5.18E-38	.63	260.87	3.00E-52	**.76**	2.81E-17
Temporal	-.60	95.43	3.77E-18	.36	52.67	1.75E-18	**.39**	.011
Occipital	-.55	72.42	9.01E-15	.30	47.95	3.36E-17	**.36**	6.67E-5
Cerebral WM	.80	302.88	1.59E-39	.64	195.72	1.30E-44	**.70**	5.57E-8
Hippocampus	.26	12.02	.001	.07	7.96	4.98E-4	.09	.056
Amygdala	.34	22.01	5.58E-6	.12	14.42	1.67E-6	**.15**	.014
Caudate	-.15	3.90	.050	.02	2.82	.063	.03	.192
Putamen	-.36	25.01	1.42E-6	.13	12.51	8.64E-6	.13	.721
Pallidum	-.28	14.43	2.03E-4	.08	7.19	.001	.08	.855
Accumbens	-.30	16.39	7.83E-5	.09	9.49	1.24E-4	.10	.119
Thalamus	.14	3.26	.073	.02	1.63	.200	.02	.901
Cerebellum GM	-.23	9.25	.003	.05	5.51	.005	.06	.190
Cerebellum WM	.46	45.24	2.57E-10	.21	30.08	6.83E-12	**.26**	.001
Brainstem	.56	78.77	9.77E-16	.32	47.56	4.31E-17	**.36**	.001
Lateral ventricle	.36	24.95	1.46E-6	.13	12.79	6.75E-6	.13	.411
Inf. lat. vent.	-.06	.56	.455	.003	.31	.736	.004	.813
3rd ventricle	.13	2.82	.095	.02	3.08	.048	.04	.071
4th ventricle	.01	.02	.888	1.18E-4	.10	.908	.001	.677

Results from two separate regression analyses with proportional volumes of TBV, one with only age as the predictor variable, the other with both age and age² as predictor variables. a) The column labelled "p age²" refers to the p value for the unique contribution of *age²* to the explained variance in brain volume. Bold characters for R² indicate a statistically significant quadratic age relationship.
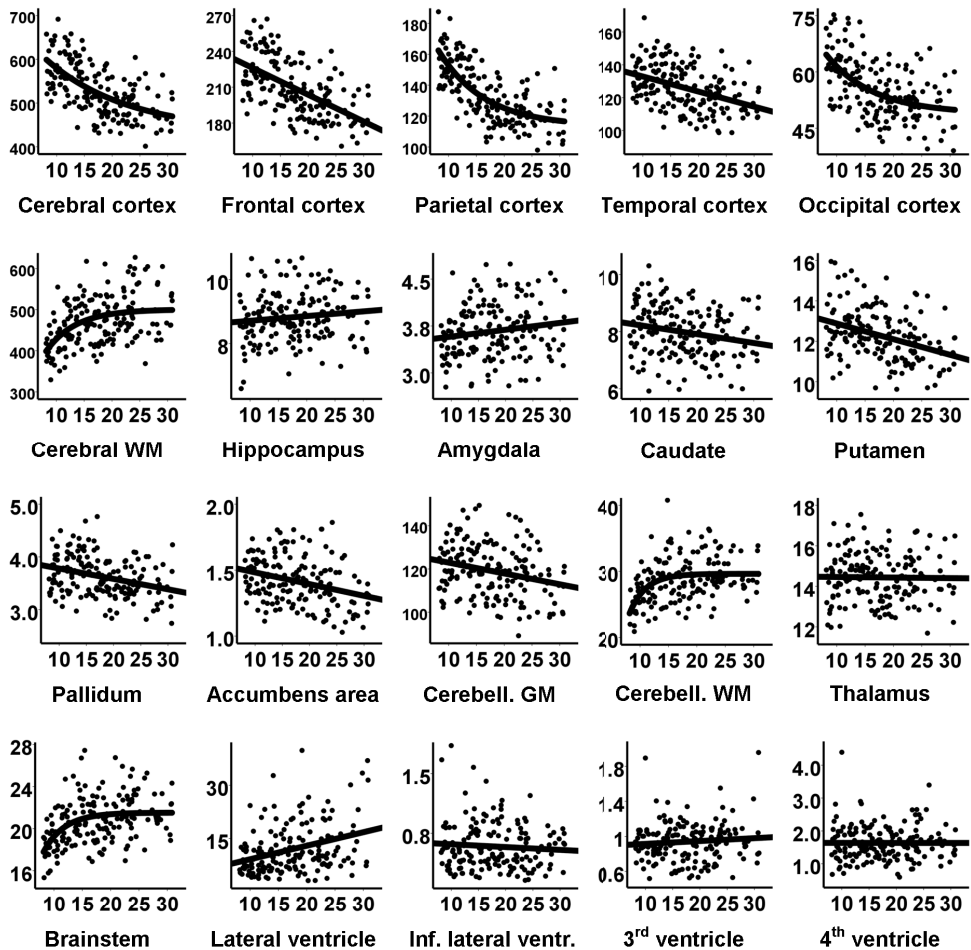
Supplemental figure 1: Regression plots showing the relationship between age and bilateral raw volumes of the cerebral cortex, frontal cortex, parietal cortex, temporal cortex, cerebral white matter, hippocampus, amygdala, the caudate, putamen, pallidum, the accumbens area, cerebellum grey matter, cerebellum white matter, thalamus, the brainstem, the lateral ventricle, the inferior lateral ventricle, 3rd and 4th ventricles, with age on the horizontal axis and volume in cm3 on the vertical axis.
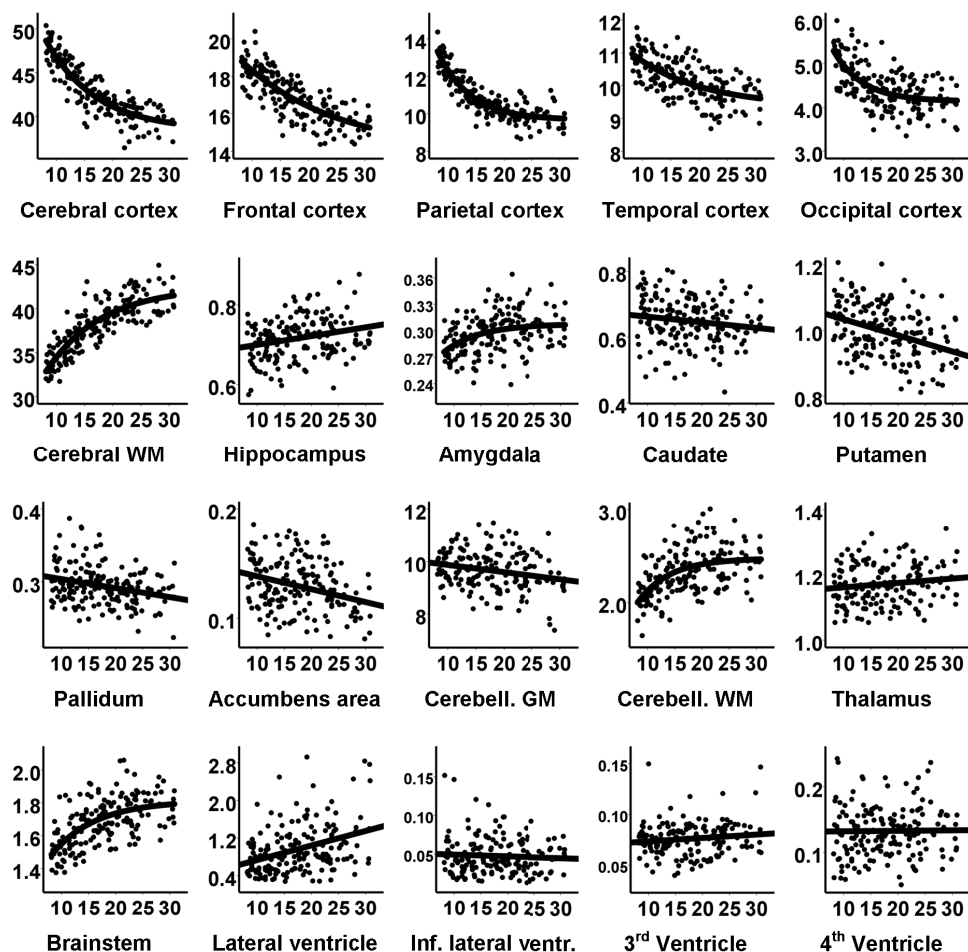
Supplemental figure 2: Regression plots showing the relationship between age and bilateral proportional volumes of the cerebral cortex, frontal cortex, parietal cortex, temporal cortex, cerebral white matter, hippocampus, amygdala, the caudate, putamen, pallidum, the accumbens area, cerebellum grey matter, cerebellum white matter, thalamus, the brainstem, the lateral ventricle, the inferior lateral ventricle, 3rd and 4th ventricles, with age on the horizontal axis and percent of total brain volume on the vertical axis.

II

Morphometry and connectivity of the fronto-parietal verbal working memory network in development

Ylva Østby[1], Christian K. Tamnes[1], Anders M. Fjell[1,2] and Kristine B. Walhovd[1,2]

[1] Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Norway
[2] Department of Physical medicine and rehabilitation, Unit of neuropsychology, Oslo University Hospital, Norway

Corresponding author: Ylva Østby, Department of Psychology, POB 1094 Blindern, 0317 Oslo, Norway
Tel.: +47 22 84 51 08
Fax: +47 22 84 50 01
Email: ylva.ostby@psykologi.uio.no

ABSTRACT: Two distinctly different maturational processes – cortical thinning and white matter maturation – take place in the brain as we mature from late childhood to adulthood. To what extent does each contribute to the development of complex cognitive functions like working memory? The independent and joint contributions of cortical thickness of regions of the left fronto-parietal network and the diffusion characteristics of the connecting pathway of the left superior longitudinal fasciculus (SLF) in accounting for verbal working memory performance were investigated, using a predefined regions of interest-approach. 108 healthy participants aged 8-19 years underwent MRI, including anatomical and diffusion tensor imaging (DTI), as well as cognitive testing using a digit span task. Radial diffusivity of the SLF, as well as cortical thickness of supramarginal gyrus and rostral middle frontal cortex, was negatively related to Digit Span Forwards performance, independently of age. Radial diffusivity of the SLF was also negatively related to Digit Span Backwards. A multi-modal analysis showed that cortical thickness and SLF microstructure were complementary in explaining working memory span. Furthermore, SLF microstructure and cortical thickness had different impact on working memory performance during the developmental period, suggesting a complex developmental interplay. The results indicate that cortical and white matter maturation each play unique roles in the development of working memory.

1. Introduction

What is happening in the developing brain that enables us to keep increasing amounts of information in mind? Is it the maturation of cortical regions, known to decrease in thickness as a result of processes like synaptic pruning? Or is it the development of white matter fibers in the pathways connecting those regions that ultimately enables us to hold ever increasing loads in mind as we grow older? Working memory, the ability to hold information in memory for short time periods for use in complex tasks (Baddeley, 1998), continues to develop throughout adolescence (Conklin, Luciana, Hooper, & Yarger, 2007; Gathercole, Pickering, Ambridge, & Wearing, 2004). Working memory is considered a tool for both the passive storage of information (short-term memory) and for manipulating and using that information while holding it in mind (Gathercole, et al., 2004). While the working memory model has been mapped to the brain using functional magnetic resonance imaging techniques in numerous studies (D'Esposito et al., 1998), evidence for the relationship between working memory function and the structural development of the brain is lacking.

A fronto-parietal network has been implicated in working memory, in studies using functional magnetic resonance imaging (fMRI), both for adults (D'Esposito, et al., 1998; Salmon et al., 1996; van Asselen et al., 2006; Wager & Smith, 2003) and for children and adolescents (Casey et al., 1995; Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010; Klingberg, 2006; Kwon, Reiss, & Menon, 2002; Nelson et al., 2000; O'Hare, Lu, Houston, Bookheimer, & Sowell, 2008; Thomas et al., 1999; Thomason et al., 2009). This fronto-parietal network includes the dorso- and ventrolateral prefrontal and posterior parietal cortex (D'Esposito, et al., 1998). In verbal working memory, the left supramarginal gyrus has also been implicated, owing to its involvement in phonological processing (Brahmbhatt, McAuley, & Barch, 2008; Crottaz-Herbette, Anagnoson, & Menon, 2004; Paulesu, Frith, & Frackowiak, 1993; Ravizza, Delgado, Chein, Becker, & Fiez, 2004; Rothmayr et al., 2007).

The structural development of the cortical regions in this fronto-parietal network is characterized by thinning of the cortex throughout late childhood and adolescence, with frontal regions approaching adult maturity later than posterior regions (Gogtay et al., 2004; Shaw et al., 2008; Tamnes, Ostby, Fjell, et al., 2010). Increase in working memory capacity as seen during childhood and adolescence, has been hypothesized to be linked to the late maturation of the frontal lobes, and to the development of the pathways connecting these areas (Conklin, et al., 2007; Finn, et al., 2010). The working together of different brain

regions during cognitive tasks, such as working memory tasks, places demands on the communication between brain regions that are quite far apart. This communication, or signal transfer, relies among other properties, on the size, density and myelination of long distance axons. Using diffusion tensor imaging (DTI), studies have shown a development in microstructural properties of white matter (Ashtari et al., 2007; Giorgio et al., 2008; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Tamnes, Ostby, Fjell, et al., 2010), and that diffusion parameters are related to developmental improvements in cognitive functions, including general intellectual abilities (Johansen-Berg, 2010; Nagy, Westerberg, & Klingberg, 2004; Tamnes, Ostby, Walhovd, et al., 2010). Working memory performance is therefore likely to be dependent on white matter microstructural properties of pathways connecting cortical areas within the fronto-parietal network. The superior longitudinal fasciculus (SLF) is the main route connecting parietal and lateral prefrontal cortices (Petrides & Pandya, 2006), and relationships between diffusion parameters in this region and working memory performance have been reported in healthy adults (Burzynska et al., 2011), and in psychiatric disorders such as schizophrenia (Karlsgodt et al., 2008). Verbal and non-verbal working memory tasks have been found to be related to DTI measures in frontal regions and the SLF in development (Niogi & McCandliss, 2006; Olesen, Nagy, Westerberg, & Klingberg, 2003; Vestergaard et al., 2010).

There is a lack of knowledge about the joint contribution of cortical and white matter maturation in explaining age-related improvements in working memory. Temporal synchronicity in the development of cortex and the underlying white matter has been proposed, but recent studies have shown that the developmental patterns are fundamentally different and that the relationship between them in development are modest (Tamnes, Ostby, Fjell, et al., 2010). Thus, a fundamental question is whether white matter maturation contributes to performance independently of cortical grey matter maturation, and vice versa. Answering this will help increasing our understanding of the principles of neurocognitive development. Approaches so far have combined fMRI and DTI (Olesen, et al., 2003), correlating fractional anisotropy (FA), measuring the degree of directionality of water diffusion, with activation in fronto-parietal regions (Olesen, et al., 2003), pointing to the possibility of structural connections being a driving force behind utilization of the working memory network on the cortical level. No working memory studies have so far utilized a combination of measures of morphometry of cortical maturation and microstructural properties of connectivity, in spite of general agreement that structural maturational processes

must have functional consequences. Hence, we investigate whether white matter microstructural properties of the SLF and cortical thickness are important for working memory development independently of each other. Further, we test whether white matter microstructural properties on the one hand, and cortical thinning on the other, play different roles at different times during working memory development. This could give us a unique glimpse into the steps that are taken by developing brains towards adult functioning. Specifically, the objectives of the present study are:

1) In a sample of children and adolescents, to investigate the relationships between working memory (simple and complex digit span) performance and a) cortical thickness within posterior parietal and lateral prefrontal regions within the left hemisphere, b) diffusion parameters (fractional anisotropy (FA) and radial diffusivity (RD)) of the SLF in the left hemisphere and c) the relative contributions of cortical thickness and SLF variables to explaining working memory when seen together in the same analysis.

2) To investigate developmental changes in the relative contributions of DTI measures and cortical thickness in explaining working memory performance, by performing similar analyses as in 1c), separately for three age groups within the 8-19 age span.

We hypothesized that cortical thickness in regions within the left fronto-parietal network (superior parietal, inferior parietal, supramarginal, caudal middle frontal, rostral middle frontal, pars opercularis and pars triangularis) would correlate with working memory performance independently of age, as would microstructural properties (FA and RD) of the SLF. Further, we hypothesized that cortical maturation and fiber tract development would contribute uniquely to working memory performance. Dividing the sample into age groups was done in order to investigate the changing patterns of white matter vs. cortical contributions to working memory performance across development. This has never been presented in any study to our knowledge, so a priori hypotheses are tentative. On the one hand, white matter development is a continuing process throughout late adolescence and early adulthood, and could play a greater part in the oldest adolescents by refining the network. On the other hand, connecting the regions within the fronto-parietal network could be more important earlier in development, in order for the cortical regions to come into play in predicting individual differences in working memory performance.

2. Materials and methods

2.1. Sample

108 children and adolescents (53 males) aged 8 to 19 years (M = 13.89, SD = 3.46) participated in the study. The distribution of sex and age in three age groups is shown in Table 1. The sample was recruited through newspaper advertisements, and local schools and workplaces, and constitutes the first part of an ongoing longitudinal project at the Center for the Study of Human Cognition at the University of Oslo. The study was approved by the Regional Ethical Committee of South Norway. Written informed consent was obtained from all participants older than 12 years of age and from a parent/guardian of volunteers under 18 years of age. Oral informed consent was obtained from all participants under 12 years of age. Participants had no self- or parent-reported history of neurological or psychiatric disorders, chronic illness, premature birth, learning disabilities, or use of medicines known to affect nervous system functioning. They were further required to be right-handed, speak Norwegian fluently and have normal or corrected to normal hearing and vision. Among the initial 116 children and adolescents who met the inclusion criteria, 4 had no useable MRI scans due to movement artifacts. All participants' scans were examined by a neuroradiologist, which led to the exclusion of one additional participant. Of the 111 remaining participants, 3 participants did not complete the DTI sequence, which resulted in a final sample of 108. There was no correlation between sex and age in the current sample (r = -.07, p = .453, females coded as 1, males as 2). Participants were tested using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), and all participants scored above 80 on full scale IQ (M = 108.91, SD = 10.90, range: 82-141). The distribution of WASI full-scale IQ in three age groups is shown in Table 1. There was no difference in IQ between males (M = 110.00, SD = 11.94) and females (M = 107.85, SD = 9.79; t [106] = -1.023, p = .309).

2.2. Working memory assessment

Participants were given the strings of numbers identical to those in the Digit Span subtest of the Norwegian version of WISC-III (Wechsler, 1992) as part of a larger battery of cognitive tests. Participants were orally presented with strings of numbers of increasing length, and were in the first part of the test required to repeat the digits in the same order (digit span forwards, DSF), and in the second part of the task they were asked to repeat them in the reversed order (digit span backwards, DSB). Strings of digits of increasing length were presented. The length of the digit strings were increased after every two strings. The stop criterion was two wrong answers within a pair of equal length. One point was given for each

Table 1. Characteristics of three age groups in terms of sex, WASI IQ scores and Digit Span scores.

	Age groups					
	8-11		12-15		16-19	
N	36 (19M/17F)		37 (18M/19F)		35 (16M/19F)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age	9.91 (1.13)	8.17-11.75	13.90 (1.17)	12.00-15.92	17.97 (1.05)	16.00-19.67
Full scale IQ (WASI)	106.53 (11.00)	82-127	108.16 (10.70)	91-141	112.14 (10.53)	91-132
Digit Span Forwards	7.81 (1.45)	5-12	9.08 (2.14)	5-15	10.00 (2.20)	6-14
Digit Span Backwards	5.1 (1.2)	3-8	5.9 (2.0)	4-12	7.4 (1.5)	5-11

correctly repeated string of digits. The sum scores of DSF and DSB were used in the present study, and the mean scores for three non-overlapping age groups are shown in Table 1.

2.3. MRI acquisition

Imaging data were collected using a 12 channel head coil on a 1.5-Tesla Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). The pulse sequences used for the morphometric analyses were two 3D T1-weighted (MP-RAGE) scans, with the following parameters: TR/TE/TI/FA = 2400 ms/3.61 ms/1000 ms/8°, matrix 192 × 192, field of view = 192. Each scan took 7 min, 42 s. Each volume consisted of 160 sagittal slices with voxel sizes 1.25 × 1.25 × 1.20 mm. Each MP-RAGE was visually inspected, and only scans deemed to have no or minimal movement artefacts were included in analyses. The two MP-RAGEs were averaged to increase the signal-to-noise-ratio. Where there were problems achieving two high quality scans due to motion artifacts, only one scan was used in the analysis. This was the case for 23.1 % of the participants, of whom most (72%) were below 12 years of age. Diffusion-weighted images were acquired using a single-shot twice refocused spin echo planar imaging pulse sequence with 30 diffusion sensitized gradient directions and the following parameters: TR/TE = 8200 ms/82 ms, b value = 700 s/mm2, and voxel size = 2.0 × 2.0 × 2.0 mm, with a total scanning time of 11 min, 21 s. This sequence is optimized to

minimize eddy current- induced image distortions (Reese et al. 2003). The sequence was repeated in 2 successive runs with 10 non-diffusion-weighted images (b = 0) in addition to 30 diffusion-weighted images collected per acquisition. The two acquisitions were averaged during post processing to increase SNR. Each volume consisted of 64 axial slices.

2.4. Morphometric analysis

All datasets were processed and analyzed at the Neuroimaging Analysis Lab, Center for the Study of Human Cognition, University of Oslo, with additional use of computing resources from the Titan High Performance Computing facilities (http://hpc.uio.no/index.php/Titan) at the University of Oslo. Cortical thickness was estimated using FreeSurfer 4.0.5 (http://surfer.nmr.mgh.harvard.edu/fswiki) by means of an automated surface reconstruction procedure (Dale, Fischl, & Sereno, 1999; Fischl, Liu, & Dale, 2001; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Segonne et al., 2004). Briefly, a representation of the gray/white matter boundary was reconstructed (Dale, et al., 1999), using intensity and continuity information from the entire MR volume in segmentation and deformation procedures. Minor manual editing of vessels and dura was routinely performed, according to FreeSurfer guidelines. The cortical maps produced are not restricted to the voxel resolution of the original data and are thus capable of detecting sub millimeter differences between groups (Fischl & Dale, 2000). The 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 approximately 15 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns . This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortions, resulting in a measure of cortical thickness for each person at each point on the reconstructed surface. Using FreeSurfer, each hemisphere was parcellated into 33 brain regions, of which 7 frontal and parietal regions within the left hemisphere were selected as regions of interest (ROI). These were: Superior Parietal Cortex, Inferior Parietal Cortex, Supramarginal Gyrus, Caudal Middle Frontal Cortex, Rostral Middle Frontal Cortex, Pars Opercularis and Pars Triangularis. The cortical ROIs are shown in Figure 2. In accordance with previous findings with largely overlapping samples (Ostby et al., 2009; Tamnes, Ostby, Fjell, et al., 2010; Tamnes, Ostby, Walhovd, et al., 2010), all regions showed age effects, as shown in Supplementary table1.

2.5 Diffusion Data Analysis

DTI analyses were performed using FSL (http://www.fmrib.ox.ac.uk/fsl/index.html) (Smith et al., 2004; Woolrich et al., 2009). The initial steps of the analyses, whereby a common white matter skeleton is derived for use in group analyses, was done with a sample overlapping the present (Tamnes, Ostby, Walhovd, et al., 2010). This sample included the current study's participants, as well as 60 adults aged 20-30 years, described in detail elsewhere (Tamnes, Ostby, Walhovd, et al., 2010). Initially, each DTI volume was affine registered to the T2-weighted $b = 0$ volume using FLIRT (Jenkinson & Smith, 2001). This corrected for motion between scans and residual eddy-current distortions. After averaging of the two acquisitions and removal of nonbrain tissue (Smith, 2002), FA, eigenvector and eigenvalue maps were computed. The FA volumes were then skeletonized and transformed into a common space as employed in TBSS (Smith et al., 2006; Smith et al., 2007). Briefly, all volumes were nonlinearly warped to the FMRIB58_FA template by use of local deformation procedures performed by FNIRT, a nonlinear registration toolkit using a *b*-spline representation of the registration warp field. Next, a mean FA volume of all subjects was generated and thinned to create a mean FA skeleton representing the centers of all common tracts. The mean skeleton was thresholded at FA > 0.25 to reduce the likelihood of partial voluming in the borders between tissue classes, yielding a mask of 108,005 WM voxels. Individual FA values were warped onto this mask by searching perpendicular from the skeleton for maximum FA values. The same steps of analyses were performed, this time using RD (radial diffusion) instead of FA values. In order to obtain DTI measures from white matter tracts, binary masks based on a probabilistic tractography atlas (the Johns Hopkins University (JHU) white-matter tractography atlas) (Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005), as provided in FSL, were created with a probability threshold of 5%. The relatively liberal threshold was chosen to accommodate inter-subject variation in gross WM fiber architecture. Voxels intersecting both the skeleton and the TOIs were used in subsequent regional analyses. The superior longitudinal fasciculus (SLF) was chosen as region of interst, and a 3D-rendeing of this tract is shown in Figure 2. The age effects on SLF RD and FA were as expected based on previously published results with a largely overlapping sample (Tamnes, Ostby, Fjell, et al., 2010), as displayed in Supplementary table 1.

2.6 Statistical analyses

2.6.1. Preliminary analyses: The effects of sex were investigated using multivariate analysis of covariance, with sex as between-subjects factor and age as covariate. These analyses were

completed for each set of variables: working memory test scores (DSF and DSB), cortical thickness ROIs, SLF FA, and SLF RD.

2.6.2. Objective 1 – age-independent relationships between brain morphometry/connectivity and working memory performance: The relationships between brain characteristics and working memory performance were investigated using regression analyses with each of the digit span variables (DSF and DSB) as dependent variables, and cortical thickness ROIs/SLF FA/RD together with age as predictor variables in turn. The significance threshold was Bonferroni-corrected for multiple comparisons in three sets of analyses: analyses with cortical ROIs was corrected for 7 ROIs ($p < .007$), SLF analyses were corrected for 2 DTI measures (FA and RD), and working memory analyses (behavioral only) was corrected for 2 working memory scores (DSF and DSB) ($p < .025$). Where there were statistically significant relationships between brain variables and digit span scores, the regression analyses were repeated with IQ as an additional predictor variable, in order to test whether the relationships were specific to working memory. Further, to investigate cortical and white matter tract contributions to working memory performance relative to each other, regression analyses were performed using working memory scores as dependent variables, and one cortical ROI, SLF diffusion variables and age as simultaneous predictor variables. These analyses where done for cortical ROIs and SLF variables that showed a statistically significant relationship with Digit Span Forwards or Backwards.

2.6.3. Objective 2 – developmental differences in relationships between brain morphometry/connectivity and working memory: The relationships between brain variables and working memory were assessed for three age groups: 8-11 years, 12-15 years and 16-19 years. The IQ and digit spans scores of the three age groups are shown in Table 1. The brain variables that showed Bonferroni-corrected significant relationships with working memory in the analyses in 2.6.2 were chosen for further developmental analyses. Regression analyses were performed using working memory scores as dependent variables, and one cortical ROI, one SLF variable and age as simultaneous predictor variables. Statistical significance testing of these age group differences in brain-behavior relationships was done by computing partial correlations (DSF/DSB with cortical ROIs while partialling out age and SLF FA or RD, and DSF/DSB with SLF FA or RD while partialling out cortical ROI) and testing them pair wise (two age groups at a time) using t-tests of Fisher's z-transformed correlations.

3. Results

3.1. Sex differences

Multivariate analyses of variance where performed with sex as between-group variable, age as covariate, and sets of working memory variables, cortical thickness variables, FA or RD, as dependent variables. These analyses revealed no overall main effect of sex on neither working memory performance (F = .178, p = .837), cortical thickness ROIs (F = 1.078, p = .383), SLF FA (F = .791, p = .376) nor SLF RD (F < .001, p = .998). Sex was therefore not included in further analyses.

3.2. Development of working memory

The effect of age on working memory performance is displayed in graphs in Figure 1. Positive age relationships were found for both Digit Span Forwards (F[1,108] = 33.933, p < .001, β = .49, R^2 = .34) and Digit Span Backwards (F[1,108] = 47.330, p < .001, β = .56, R^2 = .31).

3.3. Relationships between brain variables and working memory

3.3.1. Digit Span Forwards

Regression analyses with cortical ROIs and age as predictor variables, and DSF as dependent variable, revealed negative relationships between simple working memory span and thickness of supramarginal gyrus and rostral middle frontal cortex, as shown in Table 2. Inferior parietal cortex and caudal middle frontal cortex showed significant relationships at an uncorrected p < .05, but were not included in further analyses. SLF RD, but not FA, was related to DSF performance (negatively). The ROIs (cortical and SLF) that were significantly related to DSF are indicated in Figure 2a. In order to test the specificity of the results, regression analyses were then performed with DSF performance as dependent variable, and age, IQ and each of the brain variables as predictors. For the cortical ROIs, these analyses revealed mainly the same results: Supramarginal: β = -.32, p = .004; Rostral middle frontal: β = -.29, p = .005. SLF RD showed about the same relationship with DSF performance after correcting for IQ: SLF RD: β = -.24, p = .017.

The independence of cortical ROIs versus SLF microstructure in explaining DSF performance was then tested using regression analyses with each of the two cortical ROIs together with SLF RD and age as predictor variables. One cortical variable was entered together with age and SLF RD in each of the analyses. The results are presented in Table 3. All brain variables

remained significant when tested together in pairs of one cortical thickness variable and SLF
RD (p < .05), and each measure provided comparable predictive power, as shown by partial
standardized βs in the range of -.24 to -.33.

**Table 2. Relationships between brain variables and Digit Span Forwards. Results
of regression analyses with Digit Span Forwards as dependent variable and age
and brain variables (cortical thickness and Superior Longitudinal Fasciculus
fractional anisotropy (FA) and radial diffusivity (RD)) as predictor variables.
Significant relationships (Bonferroni-corrected) in bold.**

	F	p	R^2	β age	p age	β ROI	p ROI
Cortical thickness							
Superior parietal	19.046	<.001	.27	.32	.008	-.23	.068
Inferior parietal	20.012	<.001	.28	.30	.014	-.27	.030
Supramarginal	23.412	<.001	.31	.27	.014	-.34	**.002**
Caudal middle frontal	19.619	<.001	.27	.42	<.001	-.19	.041
Rostral middle frontal	22.707	<.001	.30	.31	.003	-.30	**.003**
Pars opercularis	18.591	<.001	.26	.43	<.001	-.15	.103
Pars triangularis	19.041	<.001	.27	.39	<.001	-.18	.069
White matter diffusion properties							
Superior longitudinal fasciculus FA	19.190	<.001	.27	.41	<.001	.18	.060
Superior longitudinal fasciculus RD	20.996	<.001	.29	.35	.001	-.25	**.013**

3.3.2. Digit Span Backwards

In the regression analyses with DSB as dependent variable, and age and brain variables as
predictor variables, only RD of the SLF showed a significant relationship (standardized
partial β = -.23, p = .018), while thickness of the pars triangularis showed a tendency at
uncorrected p = .019 (standardized partial β = -.24), as shown in Supplementary Table 3 and
Figure 2b. SLF RD was then entered as predictor variable together with age and IQ . This
analysis showed mainly the same result: SLF RD: β = -.23, p = .017.

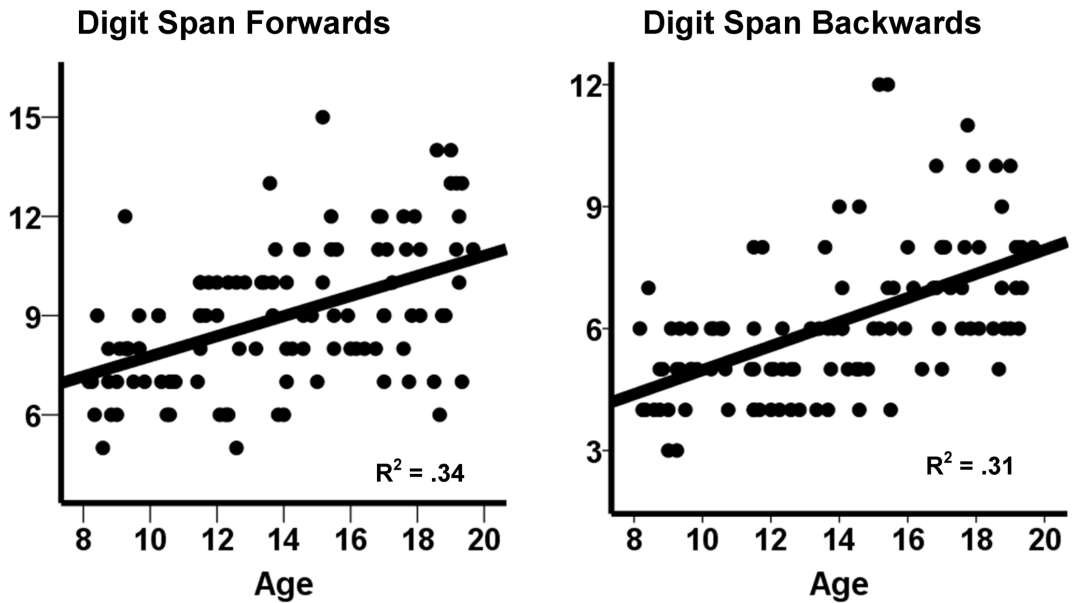**Figure 1.** Scatter plots showing the relationships between age (on the x axes) and Digit Span performance (on the y axes).
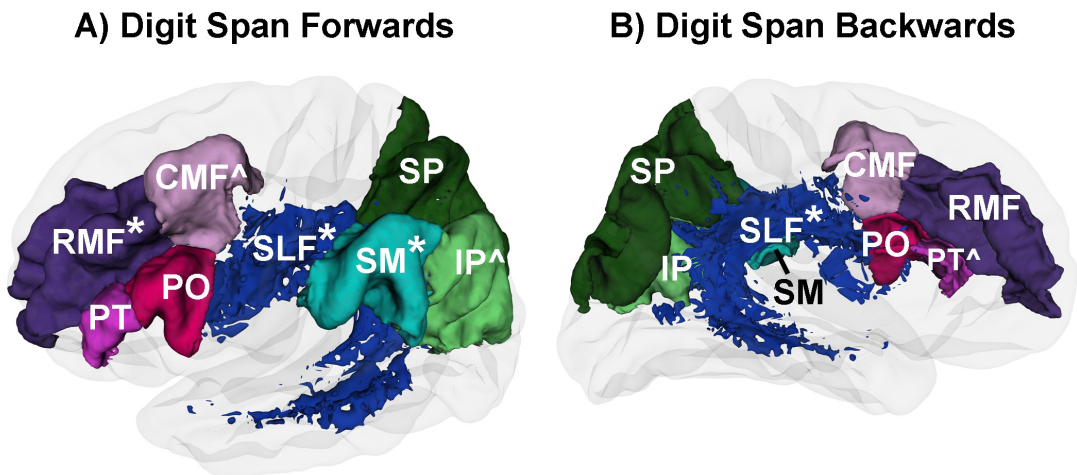

Figure 2. Regions of the fronto-parietal network and superior longitudinal fasciculus. 3D-renderings of Free-Surfer-derived cortical regions of interest and TBSS-derived superior longitudinal fasciculus in the left hemisphere, shown in lateral view in A) and medial view in B). Significant relationships with Digit Span performance are indicated with * (corrected for multiple comparisons) and ^ (uncorrected $p < .05$), for Digit Span Forwards in A) and Digit Span Backwards in B). SP=superior parietal cortex, IP=inferior parietal cortex, SM=supramarginal gyrus, SLF=superior longitudinal fasciculus, CMF=caudal middle frontal cortex, RMF=rostral middle frontal cortex, PT=pars triangularis, PO=pars opercularis.

Table 3. Cortical ROIs and SLF RD and age as simultaneous predictors of Digit Span Forwards. SLF=Superior longitudinal fasciculus. Significant relationships in bold.

	F	p	R2	β age	p age	β cortical ROI	p cortical ROI	β SLF RD	p SLF RD
Digit Span Forwards:									
Supramarginal	18.466	< .001	.35	.14	.241	-.33	**.002**	-.24	**.014**
Rostral Middle Frontal	17.955	< .001	.34	.18	.112	-.29	**.004**	-.24	**.014**

3.3. Age group analyses of brain-behavior relationships

Regression analyses with DSF as dependent variable, and each of the two cortical ROIs, SLF RD and age as predictor variables, were performed with each of the three age-groups (as described in 2.1), and the results are shown in Table 4. For the youngest age group (8-11 years), non of the individual brain variables were significant. In the middle group (12-15 years), only SLF RD was a significant predictor of performance. In the oldest group (16-19 years), only the cortical ROIs were significant predictors of DSF performance. T-tests of Fisher's z-transformed correlations revealed a significant difference between correlations between DSF and SLF of .13 and .18 in the youngest age group and -.40 to -.44 in the middle group. No other differences were significant, although a difference between the youngest age group (r = -.17) and the oldest (r = -.55), of correlations between DSF and thickness of supramarginal thickness showed a tendency towards significance (p = .072).

Table 4. Age group analyses with cortical ROIs and SLF RD. βs from two brain variables from regression analyses performed within each of three age groups, with DSF as dependent variable, and age, one cortical ROI and radial diffusivity (RD) of superior longitudinal fasciculus (SLF) as predictor variables. Only the regressions in the two oldest age groups were significant (p < .05), and significant independent predictors (β) within age groups are shown in bold.

	8-11-year-olds		12-15-year-olds		16-19-year-olds	
	β cortical ROI	β SLF RD	β cortical ROI	β SLF RD	β cortical ROI	β SLF RD
Digit Span Forwards:						
Supramarginal	.12	-.16	-.17	**-.39**	**-.53**	-.16
Rostral Middle Frontal	-.20	.17	-.23	**-.44**	**-.44**	-.18

4. Discussion

There were two novel findings in the present study: 1) verbal working memory (storage and to a lesser extent manipulation) is related to structural properties of regions within the fronto-parietal network and connecting pathways during childhood and adolescence, and 2) regional cortical thickness and SLF microstructure are complementary in explaining working memory performance in childhood and adolescence. The effects were most pronounced for storage capacity (DSF), where the supramarginal gyrus and rostral middle frontal cortex, as well as radial diffusivity in the SLF, were related to performance. Working memory manipulation capacity (DSB) was related to radial diffusivity in the SLF.

4.1 Neurodevelopment of verbal working memory

Both working memory tasks were related to age in our sample, as expected based on age norms (Wechsler, 1992) and previous developmental studies (Gathercole, et al., 2004). Older adolescents could keep longer strings of digits in mind, and could reverse the order of longer digit strings than could younger children. More interestingly, the hypothesized involvement of cortical thinning in regions within the left hemisphere fronto-parietal network in working memory performance was confirmed in the simple storage span condition (DSF). Here, two of the seven predefined regions were predictive of performance, while additionally two regions showed a similar tendency. This confirms that structural cortical development of parietal and lateral prefrontal regions is related to working memory performance, extending the findings from fMRI studies (Casey, et al., 1995; Finn, et al., 2010; Klingberg, 2006; Kwon, et al., 2002; Nelson, et al., 2000; O'Hare, et al., 2008; Thomas, et al., 1999; Thomason, et al., 2009). The supramarginal gyrus was one of the regions most predictive of performance, which is in accordance with this region's role in verbal processing (Brahmbhatt, et al., 2008; Crottaz-Herbette, et al., 2004; Paulesu, et al., 1993; Ravizza, et al., 2004; Rothmayr, et al., 2007).

In the complex span task (DSB), the results were much weaker. One possible reason could be that task performance in the manipulation condition was more vulnerable to effects of extraneous variables such as fatigue, distraction and employment of different strategies, making it a more diverse measure than the purer storage span task. Nevertheless, caution must be taken when concluding on the present results, as the two tasks to varying degrees were related to cortical thickness of fronto-parietal regions. Only one ROI, cortical thickness of the pars triangularis, was related to working memory performance independently of age, and only at an uncorrected significance level, thus making conclusions about its involvement here

uncertain. However, the pars triangularis is part of Brocas area, and fMRI studies have demonstrated the importance of this area in working memory, thought to reflect the articulatory support processes of encoding and rehearsal (Henson, Burgess, & Frith, 2000; Kwon, et al., 2002). This makes it possible that the relationship between DSF and the pars triangularis could be based on the additional use of rehearsal of the digits when preparing for reversing them. Thus, this relationship must await future replications.

Microstructural properties of the SLF was related to of working memory performance in both tasks, confirming the importance of structural connectivity for working memory performance in development. The results are in accordance with previous studies with adults (Burzynska, et al., 2011) as well as children (Vestergaard, et al., 2010). Also in accordance with previous findings (Tamnes, Ostby, Walhovd, et al., 2010; Vestergaard, et al., 2010), radial diffusivity was a stronger predictor of cognitive performance than FA in development. The importance of white matter pathways for efficient working memory performance is thought to reflect the need for speeded communication between the frontal and parietal regions in the network, since these regions are far apart and must work together in close harmony. One of the underlying biological processes in white matter development through adolescence is myelination, whereby axons get insulated and able to conduct action potentials at greater speeds (Lebel, et al., 2008; Yakovlev & Lecours, 1967). Radial diffusivity indexes the degree to which water molecules travel in the direction perpendicular to axon length, and this has been hypothesized to be more reflective of myelination. Support for the role of myelination in the RD measure comes from studies with mouse models (Song et al., 2003; Song et al., 2005), as well as a combined ex vivo DTI and histological study of multiple sclerosis patients where degree of demyelination correlated with radial diffusivity (Klawiter et al., 2011). The idea of the importance of reduced RD, and possibly increased myelination, for cognitive development is compelling. Still, care should be taken when considering underlying biological processes that are not directly measured by DTI or structural MRI. Other processes, such as axonal density and axon circumference (Concha, Livy, Beaulieu, Wheatley, & Gross, 2010) must be kept in mind as well.

As both cortical and white matter maturation are processes that take place in the brains of children and adolescents, the question of their respective impact relative to each other on development of working memory function arises. In the fMRI study by Olesen and colleagues (2003), FA in frontal and parietal white matter regions was correlated with blood oxygenation

level dependent (BOLD) signal in a frontal region, pointing to the possibility of increased structural connectivity being the driving force behind cortical activation. In the present study, white matter microstructural properties and cortical thickness were complementary in accounting for individual differences in working memory performance. This underscores the importance of both cortical and structural connectivity maturational processes within the fronto-parietal network of working memory. This is the first time the question of joint contributions of cortical and white matter properties to working memory function in development has been approached using MRI morphometry and DTI in combination.

4.2 Brain developmental patterns within the fronto-parietal network and working memory performance

The age-group analyses suggested that the importance of white matter microstructure and cortical thickness for working memory performance was different across age: SLF relationships were found mainly in the 12-15 age group, while cortical thickness relationships were found in the oldest age group (16-19). Thus, it may be that the influence of structural connectivity and cortical thickness on working memory performance follows different age trajectories. This remains speculative, though, as statistical comparisons between the age groups yielded few significant differences. This could be because the sample sizes were too small, leaving it an open question whether these group differences are reflective of true developmental patterns or random group differences in brain measures.

The SLF and nearby white matter microstructure has previously been linked to working memory development in other studies (Burzynska, et al., 2011; Karlsgodt, et al., 2008; Olesen, et al., 2003; Vestergaard, et al., 2010), but the study by Niogi and McCandliss (2006) did not find any relationship between SLF microstructure and verbal working memory. Their sample was under 10 years of age, and thus their results are in line with the lack of SLF relationships in the youngest age group in our study. This points to the importance of including wide age ranges in developmental studies, and to consider developmental variability.

4.3 Limitations

The present study was aimed at testing developmental dynamics within a delineated fronto-parietal network of working memory. This network has been established through numerous fMRI studies and lesion studies (Casey, et al., 1995; D'Esposito, et al., 1998; Finn, et al.,

2010; Klingberg, 2006; Muller & Knight, 2006; O'Hare, et al., 2008; Salmon, et al., 1996; van Asselen, et al., 2006; Wager & Smith, 2003). However, other networks and regions are known to be important for working memory as well, including the cerebellum (O'Hare, et al., 2008), the hippocampus (Finn, et al., 2010) and other temporal regions (Geier, Garver, Terwilliger, & Luna, 2009), and basal ganglia (Chang, Crottaz-Herbette, & Menon, 2007; Ciesielski, Lesnik, Savoy, Grant, & Ahlfors, 2006), which were not tested. Also, it must be noted that only the left hemisphere was studied in the present investigation. While right hemisphere regions may also be of interest, this was done in order to limit the number of analyses, and because the left hemisphere has been shown to be more specialized for verbal working memory (D'Esposito, et al., 1998). Last, the current results are cross-sectional, and genuine effects of development may be better captured in a longitudinal design.

4.4 Conclusion

The present study found evidence for the importance of macro- and microstructural brain maturation for working memory performance in children and adolescents. Both cortical thickness and microstructural properties of the superior longitudinal fasciculus connecting frontal and parietal regions accounted for working memory performance independently of age. The unique contribution of the cortical and white matter variables in explaining working memory indicates that working memory development results from the joint sum of different neurobiological maturational events. These findings underscore the importance of considering multiple measures of brain maturation in the effort of understanding the neurobiological basis of cognitive development.

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