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

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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, were 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). Separating working memory tasks into simple storage capacity and complex working memory manipulation is thought to be reflective of the divide between the basic level "slave-systems" of the phonological loop/visuo-spatial sketch pad and the central executive component (Groeger, Field, & Hammond, 1999; Lezak, 1995; Wager & Smith, 2003). FMRI studies show different activity within the fronto-parietal network depending on the involvement

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of the central executive, typically with more activity in frontal regions (Wager & Smith, 2003). However, activations in parietal areas during complex working memory tasks, as well as activations in frontal regions during simple storage tasks (Wager & Smith, 2003) make it difficult to pinpoint an independent location of each of these processes within the fronto-parietal network.

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). The thinning of the cortex may be partly caused by pruning of synapses (Huttenlocher, 1984; Rakic, Bourgeois, & Goldman-Rakic, 1994), and this elimination of abundant synapses may lead to more efficient information processing. Increase in working memory capacity as seen during childhood and adolescence, has been hypothesized to be linked to the late cortical 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). Histological studies have shown that myelination is a developmental characteristic within human white matter (Yakovlev & Lecours, 1967). DTI indices may be reflective of myelination, as well as other properties of fiber organization, as suggested by histological studies in both humans and animals (Bockhorst et al., 2008; Klawiter et al., 2011; Song et al., 2003, 2005). Furthermore, diffusion parameters have been 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 maturation, and vice versa. Answering this will help increasing our understanding of the principles of neurocognitive development, disentangling the contributions of two partly separable neurodevelopmental events 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 verbal working memory (simple and complex digit span) performance and (a) cortical thickness within 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. Based on previous results from a partly overlapping sample (Ostby, Tamnes, Fjell, & Walhovd, 2011; Tamnes et al., 2011; Tamnes, Ostby, Walhovd et al., 2010), we expected the correlations with cortical thickness and RD to be negative, while correlations with FA would be positive. Further, we hypothesized that cortical maturation and fiber tract development would contribute uniquely to working memory performance, as they are likely reflective of two distinct neurodevelopmental processes. Both of these processes may have a bearing on working memory development through more mature cortical processing, and speeded and efficient communication between frontal and parietal areas. Dividing the sample into age groups was done in order to investigate the changing patterns of white matter versus cortical contributions to working memory performance across development. At least two developmental patterns could potentially be revealed through this analysis: 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 providing increased speed of communication between relatively more mature cortical regions, thus primarily 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 8–19 years (*M* = 13.89, SD = 3.46) participated in the study. The distribution of sex and age in three age groups is shown