The changing brain : neurocognitive development and training of working memory

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Chapter 1

Introduction

1.1 Scope

It is well known that complex mental abilities develop at least until late adolescence (Bunge and Crone, 2009; Diamond, 2002). Why is it then that many teenagers do not have any difficulties keeping up-to-date with the latest technology, while their parents cannot even install a new "app" on their cell phone? It seems that there are limitations on children's performance, but there are also skills that children master perfectly, sometimes even better than adults. Why is it that? Is there an explanation in the different trajectories of the underlying brain mechanisms? Or does it have to do with task difficulty or the amount of experience with a particular task? Both the functions that children do not yet master and the (increased) possibilities of children might be explained in the context of the developing brain. Prior studies in developmental cognitive neuroscience already argued that the immature neural circuitry may prevent children from performing a specific task (e.g., Diamond, 2002), but there is now also a growing interest in the potential of the developing brain to learn new cognitive skills (Diamond et al., 2007; Karbach and Kray, 2009; Klingberg et al., 2002b; Mackey et al., 2011; Posner and Rothbart, 2005). A better understanding of the possibilities of the developing brain, as well as the functions it does not yet master, is warranted and could eventually be used to tailor education programs or interventions for children with developmental disabilities.

When studying the mechanisms of neurocognitive development, it is important to consider the interaction between prespecified biological maturation (i.e., biological development that is driven by genetic predispositions and unrelated to the context in which a child is raised) and learning (i.e., the influence of experience on cognitive or neural processes). Although it seems that the acquisition of some abilities mainly depends on prespecified biological changes, and that other skills are largely driven by learning, it is impossible to separate biological inheritance and learning-related processes completely (e.g., Stiles, 2008). Development is always a combination of both. That is, maturational changes in the brain's physiology, morphology, and connectivity may allow for more efficient and specialized cognitive functioning. Yet, experience is necessary to specifically drive these changes. At the same time, it is expected that experience-related changes depend on the maturity of the structural system in which the changes take place (Galvan, 2010; Kolb et al., 2010; Munakata et al., 2004). In other words, *the changing brain* influences the possibilities for *changing the brain* with training or other experiences.

The goal of this thesis was to learn more about the possibilities of cognitive functioning in children and young adults, and the constraints set by the developing brain. We used a developmental training paradigm in combination with innovative neuroimaging techniques, such as task-related functional magnetic resonance imaging (fMRI), resting-state fMRI, and structural MRI. This allowed us to examine both age- and experience-related effects during functional brain development. More specifically, we studied age differences on task performance and brain activation during a cognitive task with varying demands and difficulty levels, both before and after an extended period of training. In addition, to learn more about the interaction between different brain regions, we also examined age differences and training effects on functional connectivity during resting-state. Before describing the specific objectives of the different studies that are presented in this thesis, a short overview of the theoretical background is given.

1.2 Background

Developmental cognitive neuroscience

Classic developmental theories already emphasized the importance of both brain maturation and experience on cognitive development (e.g., Case, 1992; Piaget and Inhelder, 1974). However, until recently it was not possible to directly relate these factors with one another when studying cognitive or behavioral change. Now, in the advancing field of developmental cognitive neuroscience, neuroimaging methods provide us with the opportunity to examine more directly the interrelations between cognitive development, brain maturation, and environmental experiences. Johnson (2001; 2011) has distinguished three different viewpoints in this field. The first viewpoint suggests that cognitive functions develop when the underlying brain regions reach maturity. This *maturational account* has been adopted by many traditional developmental neuroimaging studies and it predicts that the repertoire and efficiency of children's cognitive abilities are limited by their immature neural circuitry. In contrast, the second viewpoint, the *skill learning account*, emphasizes the influence of experience in shaping functional brain development. This account points out that the brain regions that are involved when children learn a new skill are sometimes similar to those involved in skill acquisition in adults. Finally, the *interactive specialization account* suggests that the specialization of a particular brain region is a consequence of its interaction and competition with other brain regions over the course of development. In agreement with the *probabilistic epigenesis* view of development (Gottlieb, 2007), this account suggests that developmental changes are a consequence of the dynamic interaction between genes, brain, and behavior.

Working memory development

During late childhood and adolescence, individuals become increasingly proficient at complex tasks that involve planning towards long-term goals, performing mental operations, or ignoring irrelevant information (Best et al., 2009; Bunge and Crone, 2009; Diamond, 2002; Huizinga et al., 2006; Luna et al., 2009). One of the most important functions to develop is the ability to hold information in mind and to work with it. This function, which has been labeled *working memory* (Baddeley, 1992; Baddeley, 2003), has often been conceptualized as a driving force behind the development of cognitive control (Case, 1992; Hitch, 2002; Pascual-Leone, 1995), and is a key factor to understand children's improvements in school performance (Gathercole, 2004).

Neuroimaging studies in adults have repeatedly demonstrated that working memory demands are associated with activation of a frontoparietal network, including (dorso-) lateral prefrontal cortex, and superior parietal cortex (Owen et al., 2005; Wager and Smith, 2003). In addition, the majority of working memory studies that have been conducted in children showed that these regions become increasingly engaged as development progresses (Klingberg et al., 2002a; Kwon et al., 2002; Olesen et al., 2007; Scherf et al., 2006). It has been suggested that developmental changes are most dramatic when participants need to manipulate, or work with information held in working memory (Conklin et al., 2007; Crone et al., 2006; Diamond, 2002). For example, when 8-to 12-year-old children were asked to maintain a sequence of objects in short-term memory, they showed a similar activation pattern as adults. However, when they were asked to reverse the sequence of objects, they showed less activation than adults, specifically in dorsolateral prefrontal cortex and superior parietal cortex (Crone et al., 2006). These findings indicate that there are different developmental trajectories for different subcomponents of working memory. However, an alternative hypothesis suggests that the observed age differences were related to less efficient information processing in general, which specifically affected the more difficult manipulation task. Thus, a central issue in current research on working memory development is whether there are different neurodevelopmental trajectories for different subcomponents of working memory. A second issue involves the extent to which age differences in working memory-related brain activation can be influenced by practice and how practice-related changes depend on the maturation of the underlying brain structure (Bunge and Crone, 2009).

Brain maturation: the changing brain

Structural brain maturation involves a multitude of different processes that are manifest at various levels of organization. For example, at a micro scale, postmortem histological research has described that development during late childhood and adolescence is characterized by a reorganization of synapses (Bourgeois et al., 1994; Bourgeois and Rakic, 1993; Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997), and an increase of the myelination of white matter tracts (Benes et al., 1994; Yakovlev and Lecours, 1967). These processes may enhance the specificity and efficiency of information processing, and increase the speed of signal transmission across neural networks (Changeux and Danchin, 1976; Chechik et al., 1998; Fields, 2008; Goldman-Rakic, 1987; Paus, 2010). In addition, the efficiency of communication across neural networks might be modulated further by the protracted development of neurotransmitter systems (Benes, 2001; Kostovic, 1990).

At a much larger scale, MRI-based anatomical methods have demonstrated large-scale changes in grey- and white matter structure. It has been suggested that grey matter volume follows a nonlinear, region-specific developmental trajectory, reaching a peak during childhood, followed by a decline continuing during adulthood (Giedd, 2004; Gogtay et al., 2004; Sowell et al., 2003; Sowell et al., 2001b). In contrast, white matter maturation follows a more linear trajectory, both in volume (Giedd et al., 1999; Giorgio et al., 2010), and in directional organization (i.e., reflected in the degree of diffusion anisotropy; Barnea-Goraly et al., 2005; Giorgio et al., 2010; Snook et al., 2005). It should be noted that there is not yet agreement on the exact processes underlying the changes of grey- and white matter as observed with MRI methods. It has been suggested that the decline of grey matter volume might be attributed to synaptic pruning, vascular changes, and/or increasing intracortical myelination (Gogtay et al., 2004; Paus, 2005; Paus et al., 2008). In addition, the changes of white matter structure are thought to be associated with myelination and/or maturation of axons (Paus, 2010; Paus et al., 1999).

Structural changes show a large variation across regions. Interestingly, it has been demonstrated that regions involved in working memory manipulation, such as the dorsolateral prefrontal cortex and superior parietal cortex are among the latest regions to mature (Giedd et al., 2009). Moreover, some studies have described a correlation between frontoparietal grey matter maturation, neural activation, and/or cognitive functioning (Lu et al., 2009; Sowell et al., 2001a). In addition, a comparison of fMRI data and diffusion tensor imaging data has revealed that frontoparietal activation and cognitive performance are related to the increasing strength of frontoparietal white matter connectivity (Olesen et al., 2003). Thus, it seems that there is a relation between cognitive development and the maturation of the underlying brain structure. However, it is important to note that these findings do not automatically imply causality, nor do they imply that cognitive functions are strictly dependent on preprogrammed changes in brain structure (e.g., Casey et al., 2005). It has been argued that there is a bidirectional relation between cognitive- and brain development, such that experience-related processes influence structural brain maturation and vice versa (Changeux and Danchin, 1976; Fields, 2008; Gottlieb, 2007; Greenough et al., 1987).

Changing patterns of functional connectivity

The aforementioned structural changes point out that beyond the maturation of single brain regions, further insight into functional brain development may be gained from studying the patterns of interregional interactions. One way to study such interactions is by analyzing correlations of spontaneous blood oxygen level dependent (BOLD) signal fluctuations between brain regions, which has been called *functional connectivity* (for a review, see Fox and Raichle, 2007). Interestingly, it has been demonstrated that patterns of functional connectivity (i.e., *functional networks*) show close correspondence to task-related activation patterns, even though functional connectivity is often measured in a task-free setting (Biswal et al., 1995;

Biswal et al., 2010; Smith et al., 2009).

Recent progress in the field of functional connectivity has revealed a number of differences between functional connectivity in children and adults. For example, it has been demonstrated that children often have weaker long-range functional connectivity (Fair et al., 2008; Fair et al., 2009; Kelly et al., 2009; Supekar et al., 2009), more widespread functional connectivity (Kelly et al., 2009), and lower levels of hierarchical functional organization (Supekar et al., 2009). Together, these findings indicate that as development progresses, there is more integration within functional networks and more differentiation between these networks (e.g., Fair et al., 2009). It has been suggested that the development of functional connectivity depends on the physical structure of the brain, such as the degree of myelination or the number of synaptic connections (Hagmann et al., 2010; Power et al., 2010). However, functional connectivity is not purely a physiological marker of anatomical connections (cf. Lewis et al., 2009). It has been hypothesized that functional connectivity can be influenced by repeated coactivation between brain regions, depending on collective and individual experiences over the course of development and as a result of training (Fair et al., 2009; Lewis et al., 2009; Power et al., 2010).

Cognitive training: changing the brain

There is much interest in the trainability of cognitive functions by means of practice and/or intentional instruction. Although training studies are often expensive and time consuming, they provide important information about the potential of cognitive functioning in children and adults. Several behavioral training studies have already described that task performance improved after a few weeks of training; in some cases the performance improvements even generalized to untrained cognitive functions (Dahlin et al., 2008b; Jaeggi et al., 2008; Li et al., 2008; Persson and Reuter-Lorenz, 2008; Schmiedek et al., 2010). Now, a growing number of neuroimaging studies, mostly in adults, are trying to relate these behavioral changes to changes in brain function. Yet, the neuroimaging studies that have been conducted so far have reported inconsistent patterns of neural changes. Whereas some studies have found increased activation after training (Kirschen et al., 2005; Olesen et al., 2004), others have demonstrated decreased activation (Beauchamp et al., 2003; Landau et al., 2004; Qin et al., 2003; Sayala et al., 2006), or a redistribution/reorganization of activation (Petersen et al., 1998; Poldrack and Gabrieli, 2001). These findings suggest that training-related performance improvements can have multiple underlying causes. One important focus of current training studies involves the characterization of factors that drive the different activation changes.

The outcome of training is expected to be even more complex in children because training effects interact with maturational processes (Galvan, 2010). On the one hand, the neural architecture in children is less “specialized” than in adults, suggesting that there might be more room for plasticity (Johnson, 2011). On the other hand, there might also be limitations on training effects, depending on the current physical structure of the brain. For example, the degree of grey- and/or white matter development might constrain the speed and efficiency of information transfer, suggesting that children may not be able to reach adult levels on every task (cf. Case et al., 1982). Thus, there might be possibilities, as well as limitations on training effects in children, depending on the current level of structural brain maturation.

Finally, it has been suggested that changes observed during skill acquisition in adults are sometimes similar to the patterns of change observed during development (Casey et al., 2005; Johnson, 2001; Johnson, 2011). These findings point out the need to differentiate between learning and age-related factors in explaining group differences in neural activation (cf. Casey et al., 2005). A training study that involves both children and adults may give us the opportunity to examine whether the immature brain shows the same pattern of neural activity after practice as the mature one (Munakata et al., 2004). In addition, it would make it possible to determine the relative advantages and limitations of cognitive training in children versus adults.

1.3 Objectives and approach

Goal

The main goal of this thesis was to gain insight in the possibilities of cognitive functioning in children and young adults, and the constraints set by the developing brain. We used a working memory training paradigm in children and young adults, which allowed us to examine both developmental differences and training-related changes of brain function. More specifically, using neuroimaging methods we examined age differences and training effects on neural activation during a working memory task and on functional connectivity during a rest period preceding the task.

Approach

The participants of the studies presented in this thesis were children around the age of 12 and young adults between 19 and 25 years old[1]. We focused specifically on 12-year-olds, because prior research has shown that at this age children perform relatively well on working memory tasks, while there is also still a rapid increase in working memory performance and associated brain activation. In addition, whereas several large structural changes have already occurred earlier in development, there are still great changes in neural efficiency taking place during this age period, particularly in prefrontal and parietal association areas (e.g., Giedd et al., 1999;

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[1] It should be noted that 12-year-olds and 19-to 25-year-olds could also be characterized as *early adolescents* and *late adolescents* respectively. However, to be consistent with most prior studies in this field, they are referred to as children and young adults.

Giedd et al., 2009; Gogtay et al., 2004; Huttenlocher and Dabholkar, 1997). These findings have led to the hypothesis that this period may be well suited for training interventions (e.g., Blakemore and Choudhury, 2006; Giedd et al., 1999), although direct evidence for this suggestion has not yet been given.

The cross-sectional part of the research is presented in the first two chapters, which describe age differences in working memory-related brain activation and resting-state functional connectivity, irrespective of training effects. The second part of the thesis describes the results of working memory training. Children and young adults took part in a 6-week training program, which consisted of extensive practice[2] with a working memory task with several levels of task difficulty. In the first and last week of the training period, participants were scanned using fMRI while they performed the working memory task. On both occasions, resting-state scans were also acquired, as well as high-resolution anatomical scans. In addition, participants completed a battery of cognitive tests to examine whether training generalized to untrained tasks, and results were compared with those of a control group who did not participate in the working memory training. Finally, there was a behavioral follow-up test 6 months after the experiment to examine the durability of performance improvements.

1.4 Outline of the chapters

The first part of the thesis involves two cross-sectional studies, examining age differences in working memory-related activation and resting-state functional connectivity. **Chapter 2** describes a task-related fMRI study, which aimed to better understand the development of different subcomponents of working memory. More specifically, by examining working memory load and manipulation demands in a single design, we were able to show whether immature activation patterns in children were function-specific or whether they were related to less efficient information processing in general.

The study presented in **Chapter 3** investigated age differences in functional network organization. In this study, we examined cross-sectional differences in resting-state functional connectivity; with and without correction for grey matter volume on anatomical MRI scans. In contrast to prior studies, we did not limit our analysis to a priori defined regions or networks of interest. Instead, we used a whole brain *independent component analysis-based approach* to study a range of functional networks, including visual, auditory and sensory-motor networks, the so-called *default mode network*, and several networks associated with higher cognitive functions.

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[2] Because the training involved extensive practice without additional strategy instructions or other forms of guidance, the terms *training* and *practice* will be used interchangeably throughout this thesis.

Chapters 4 to 6 describe training effects on task-related activation and resting-state functional connectivity. We reasoned that the interpretation of training effects in children is very complex because of the interaction between learning and development. Therefore, we first examined the effects of working memory training in adults, which are described in **Chapter 4**. In this study we specifically investigated whether inconsistent (and opposite) patterns of activation changes reported in prior studies could be accounted for by differences in working memory demands. Test-retest effects were excluded using a control group.

The main objective of the study presented in **Chapter 5** was to investigate whether 12-year-old children show reduced frontoparietal activation during working memory manipulation because there are constraints on brain functioning related to the protracted structural maturation of the underlying brain structures, or whether children are able to show increased frontoparietal activation after extensive practice. Therefore, we examined whether performance and activation differences between children and adults would be reduced after working memory training, while taking into account several confounding factors including the number of correct trials and age differences in grey matter volume.

Chapter 6 describes the effects of working memory training on functional connectivity during a rest scan preceding the task. Using a *seed-region approach*, we focused on functional connectivity changes in two task-relevant functional networks: the frontoparietal network and the default mode network. A secondary goal of this study was to examine whether experience-dependent changes of functional connectivity were different in children compared with young adults.

The last two chapters do not describe empirical studies, but they provide some general considerations about learning and development in relation to the studies presented in this thesis. The primary goal of the article presented in **Chapter 7** was to outline a number of conceptual and methodological issues that are important when examining the effects of cognitive training in children from a neuroscientific perspective. Finally, **Chapter 8** (Concluding Remarks) summarizes the empirical studies that were conducted for this thesis and discusses the results in relation to the objectives stated in the introduction.