The changing brain : neurocognitive development and training of working memory

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Citation

Jolles, D. D. (2011, September 27). *The changing brain : neurocognitive development and training of working memory*. Retrieved from https://hdl.handle.net/1887/17874

Chapter 8

Summary and concluding remarks

8.1 Summary

The goal of this thesis was to study the possibilities of cognitive functioning in children and young adults, and the constraints set by the developing brain. A number of cross-sectional and longitudinal (i.e., training) functional magnetic resonance imaging (fMRI) studies were conducted to examine working memory and resting-state functional connectivity in children (11-13 years old) and young adults (19-25 years old). Prior developmental neuroimaging studies often involved a static assessment (i.e., a single measurement) of age differences on isolated control functions (cf. Crone and Ridderinkhof, 2011). In contrast, the studies in this thesis differentiated between age differences on working memory maintenance and manipulation functions at various difficulty levels, both before and after a 6-week training period. In addition, it was examined whether age differences and training effects could be observed on functional connectivity measures in the absence of a task. In the following sections, the main findings and conclusions of this research are presented. The chapter ends with a number of critical considerations and recommendations for future studies.

Working memory development and training

Different cognitive functions do not always follow the same developmental trajectory. For example, the ability to store and rehearse information in short-term memory develops earlier than the ability to perform complex operations on the information held in mind (i.e., working memory manipulation) (Conklin et al., 2007; Crone et al., 2006; Diamond, 2002). It has been argued that the late development of working memory manipulation functions is related to the protracted structural development of the underlying dorsolateral prefrontal cortex (DLPFC) (e.g., Diamond, 2002). However, an alternative hypothesis argues that manipulation tasks are generally more difficult than maintenance tasks. Therefore, immature performance and brain activation may also be associated with less efficient information processing in general and/or with a reduced amount of practice with manipulation tasks. Thus, there are two questions regarding the development of working memory manipulation versus maintenance functions. First, is the immature DLPFC activation during working memory manipulation tasks function-specific or is it related to task difficulty in general? And second, does the immature neural circuitry prevent children from performing at an adult level or will children show more adult-like performance and activation after extensive practice?

Working memory development: test for specificity

In **Chapter 2**, a cross-sectional study is described which examined whether the under-recruitment of children's DLPFC is function-specific or related to task difficulty. In this study, we examined DLPFC activation during working memory maintenance and manipulation conditions under different levels of task load in children compared with young adults. Behaviorally, we found that both children and adults showed reduced performance for manipulation relative to maintenance of information in working memory, as well as for increasing levels of task load. Consistent with a prior study, right DLPFC showed an interaction between age and condition (specifically at lower working memory loads) (Crone et al., 2006). This interaction was characterized by increased activation for manipulation trials relative to maintenance trials in adults compared to children. In contrast, there was no age-dependent load sensitivity. Moreover, age differences in activation persisted when performance was matched between children and adults. Taken together, these findings suggest that group differences in right DLPFC were function-specific (that is, specific to the manipulation condition) and not related to task difficulty or performance differences per se.

Interestingly, at the highest working memory load the adult group did not show increased activation for manipulation relative to maintenance trials either. This effect was the result of increased activation during maintenance trials, and might be explained by an increased use of strategies to memorize high load sequences, which is also some type of manipulation (Bor and Owen, 2007a; Bunge et al., 2001; Rypma et al., 2002; Rypma et al., 1999; Wendelken et al., 2008). Furthermore, age differences were also examined for other working memory-related regions, such as left DLPFC, left ventrolateral prefrontal cortex (VLPFC) and left superior parietal cortex. In contrary to our expectations, there was no clear evidence of differential developmental activation profiles for these regions. Moreover, statistical tests did not reveal region by age group interactions when left VLPFC and right DLPFC were tested against one another, suggesting that the regions function in a highly connected way.

After establishing that the age differences in DLPFC activation were specific to working memory manipulation, and not related to task difficulty per se, the main question was whether the age effects could be reduced as result of training. However, before investigating training effects in children versus adults (Chapter 5), in Chapter 4 it was first examined how training changes brain activation in adults.

Working memory training: effects of different task demands

The study presented in **Chapter 4** aimed to increase insight in the underlying mechanisms of training effects by examining how training-related changes of brain activation are influenced by different task characteristics. Prior training studies showed inconsistent findings, which might be explained by the nature of the task demands, the difficulty of the task, and the length of the training (Poldrack, 2000). The training paradigm that was used in the present study allowed us to examine the differential effects of different working memory functions (i.e., maintenance versus manipulation) and task difficulty (i.e., increasing load) within a single paradigm. In addition, by including a control group who did not take part in the training sessions, it was possible to differentiate between the effects of task familiarity and training-related activation changes.

It was demonstrated that 6 weeks of training was beneficial for working memory performance, both in terms of accuracy and response times. Training-related performance improvements lasted up to 6 months after the training period, and were larger than the improvements of control participants. This indicates that the observed performance improvements were not simply caused by familiarity with the task. There was no evidence of generalization of training effects to untrained executive function tasks, suggesting that the improvements were task-specific and not related to a general improvement of working memory functions or intelligence.

Neuroimaging results indicated that training-related changes in working memory manipulation and maintenance processes were supported by different underlying mechanisms. Whereas maintenance trials showed increased activation (i.e., less deactivation) in regions known to be part of the *default mode network* (Buckner et al., 2008; Raichle et al., 2001), manipulation trials showed increased activation in the striatum. Besides, training effects were influenced by the level of task difficulty. That is, left VLPFC, bilateral DLPFC, and left superior parietal cortex showed a training-related activation increase for manipulation trials relative to maintenance trials, but only for the highest working memory load. At the lower loads, activation for manipulation relative to maintenance trials was already increased before training, and there was no evidence of training-related activation changes.

Most activation changes were specific to the participants who took part in the training. Yet, the control group showed changes as well, particularly in bilateral DLPFC and left superior parietal cortex. These findings illustrate the effects of task familiarity and point out the importance of controlling for test-retest effects.

Working memory training in children

Chapter 2 showed that 12-year-old children failed to recruit frontoparietal regions (right DLPFC in particular) for manipulation relative to maintenance of information in working memory. Yet, Chapter 4 demonstrated that, at least in young adults, activation in these regions changed after extensive practice. The study presented in **Chapter 5** examined whether training in children would also change frontoparietal activation. More specifically, this study examined whether age-related activation differences on the working memory manipulation task would be reduced as a result of training, or whether children would recruit a different set of regions after training.

It was demonstrated that training resulted in better performance, which lasted at least up to 6 months after the training. Moreover, performance and activation differences between children and adults were considerably reduced after training. That is, after training children recruited similar regions as were seen in adults, including DLPFC, anterior insula, and superior parietal cortex. Children did not rely on any additional, compensatory brain regions. In addition, it was shown that training effects in the DLPFC were largely absent in a group of control participants, suggesting that the results could not be explained by increased familiarity with the task alone. It remains to be determined whether the observed activation changes were related to long-lasting structural changes of the brain regions involved (Lövdén et al., 2010a; Posner and Rothbart, 2005). Alternatively, the training effects could reflect a strategy change that did not affect the underlying brain structure (Lövdén et al., 2010a; Posner and Rothbart, 2005). The absence of transfer to untrained executive function tasks suggested that the training effects were most likely caused by strategic changes specific to the task that was trained. Moreover, it was unlikely that the results were directly caused by changes in grey matter volume (or differences in registration error), because the results were almost unaffected when we included grey matter volume as a voxelwise covariate in the analysis. In summary, this study indicated that age-related activation differences on the working memory manipulation task were reduced as a result of training, arguing against the hypothesis that certain brain structures could not be engaged because of immaturity.

Age- and practice-related changes of functional connectivity

The working memory studies presented in Chapter 2, 4 and 5, described function-specific changes of brain activation related to age and practice. In Chapter 3 and 6, two studies are presented that examined whether age differences and training effects could also be observed in the absence of a task. These studies focused specifically on the temporal coherence of spontaneous blood oxygen level dependent (BOLD) signal fluctuations between brain regions (Fox and Raichle, 2007). Thus, rather than examining the level of activation within different brain regions, these studies examined the pattern of *functional connectivity* between brain regions in the absence of a task.

Functional connectivity differences between children and adults

In **Chapter 3**, a cross-sectional study is described examining age differences in functional connectivity between 12-year-old children and young adults. In contrast to prior studies, the study presented in Chapter 3 used a whole brain independent component analysis-based approach to study a range of functional networks, including visual, auditory and sensory-motor networks, the default-mode network, and several networks associated with higher cognitive functions. In addition, it was examined to what extent age differences in functional connectivity could be explained by differences in grey matter volume (or possible misregistrations) in the same regions.

This study showed that core regions of all functional networks were already present in 12-year-old children. However, there were differences in the size of functional networks, as well as in the strength of functional connectivity in specific areas within these networks. The majority of functional networks showed regional increases of functional connectivity in children compared to adults. In addition, most of these networks showed more diffuse patterns of functional connectivity in children. These results suggest that although the basic configuration of functional networks in the brain has been established by the age of 12, functional networks continue to change during adolescence. Finally, by adding grey matter volume as a voxel-dependent covariate in the analysis, we showed that the majority of functional connectivity differences could not be explained on the basis of grey matter volume alone.

Experience-related changes of functional connectivity

The goal of the study presented in **Chapter 6** was to investigate whether training with a working memory task changes functional connectivity during a resting-state period preceding the task. In addition, because we expected training effects to be different during development, a second goal was to examine whether functional connectivity changes would be different between children and young adults. We focused on two functional networks that were involved in the task: the frontoparietal network and the default mode network, using seed regions in the right middle frontal gyrus (i.e., the DLPFC) and medial prefrontal cortex, respectively.

In agreement with our hypotheses, the adults showed an increase of functional connectivity within the frontoparietal network after the working memory training. More specifically, during the second scan the right middle frontal gyrus was stronger connected with bilateral superior frontal gyrus, paracingulate gyrus, and anterior cingulate cortex. In addition, there was a positive relation between performance increases and frontoparietal connectivity. In contrast, the adults showed reduced functional connectivity between the medial prefrontal cortex and right posterior middle temporal gyrus, and there was a negative relation between performance increases and default mode network connectivity. It remains to be examined whether the training-related connectivity changes were associated with repeated coactivation of brain regions during the training or whether they reflected anticipatory processes concerning the upcoming task (Fox and Raichle, 2007).

There was no evidence of training effects in children, suggesting that training-related changes of functional connectivity are age-dependent. The absence of training effects in children could have been associated with less effective preparation for the upcoming task, since planning abilities are expected to be less pronounced in children of this age group (e.g., Asato et al., 2006; Huizinga et al., 2006). An alternative explanation suggests that working memory training may have less impact on functional connectivity in children because they already experience much practice with working memory in school. Future studies should differentiate between these possibilities, for example by collecting resting-state scans in isolation from task scans.

8.2 Critical considerations and future directions

The studies in this thesis aimed to increase our insight in the interaction between working memory development, brain maturation, and experience by means of neuroimaging methods. General considerations about the interaction between cognitive training and development are described in Chapter 7. In the following section I present conclusions and considerations that are more specific to the experimental studies presented in this thesis.

Age and experience-related effects in working memory development

In Chapter 2 it was demonstrated that immature DLPFC activation during working memory tasks in 12-year-old children is related to working memory manipulation processes rather than less efficient information processing in general. However, Chapter 5 showed that the under-recruitment of DLPFC does not mean that the region is “inaccessible” due to maturational constraints. In fact, age differences in DLPFC activation were reduced as a result of training. Interestingly, both children and adults showed increased frontoparietal activation for manipulation relative to maintenance trials after training (Chapter 4 and 5), although not at the same task load.

Do these findings mean that working memory development is simply a matter of skill acquisition? Probably not. Despite the similarity between developmental and experience-related changes, these processes do not necessarily rely on the same underlying cognitive and neural mechanisms (Galvan, 2010; Klingberg, 2006). Moreover, it is unlikely that training with other tasks or age groups would yield similar results. For example, a prior study showed that attention training in 6-year-olds resulted in event-related potentials (ERPs) that were also found in adult data, but the same training in 4-year-olds did not have this effect (Rueda et al., 2005). Thus, it is to be expected that the training of a particular task requires a certain stage of cognitive and/or structural brain development. Nevertheless, the finding that there is flexibility in children’s brain function serves as a *proof of principle*, demonstrating that immature activation patterns are not necessarily caused by age-dependent maturational constraints. This illustrates the importance of looking at the potential of cognitive functioning during development, rather than examining static age differences.

For an overview of the approaches and possible effects of developmental training studies, I refer to Chapter 7. This chapter also provides a more detailed description of the complex interaction between training and brain development. In short, it was argued that the type of training and the level of (structural) maturation influence the extent to which training accelerates developmental change and/or improves the individual’s *actualized genetic potential*. In addition, it was suggested that the immature brain structure could limit the effects of training, but that in some cases these limitations might also be an advantage.

Cognitive development and functional connectivity

In addition to task-related age differences, it was demonstrated that there were differences between children and adults in the patterns of functional connectivity between brain regions. In the majority of functional networks, children showed regional increases of functional connectivity and for these networks functional connectivity was often more widespread. Interestingly, in both functional connectivity studies (Chapter 3 and 6), there were no age differences in the core regions of the frontoparietal networks, which stands in contrast with the task fMRI studies that showed age-related activation differences that were specific to these frontoparietal regions (e.g., Chapter 2 and Crone et al., 2006). Thus it seems that, at the age of 12, dorsal frontal and parietal regions are functionally connected within relatively mature frontoparietal networks, but during cognitive control tasks children do not always recruit these networks to the same extent as adults. In addition, the finding that children show more mature activation in the frontoparietal network after 6 weeks of practice with a working memory task (Chapter 5), without showing changes in the interregional interactions (Chapter 6), suggests that the training effects reflect the learning of a skill that results in increased engagement of the frontoparietal network, rather than a change in the underlying functional network architecture (Posner and Rothbart, 2005). Alternatively, it should be noted that the sample of children was small, and it is possible that the study was underpowered for the discovery of functional connectivity changes after training.

Future studies should further examine how cognitive development is related to changes in the underlying functional network architecture, using large samples of resting-state fMRI data that are combined with measures of cognitive performance in various domains. In addition, it is important to examine how regions interact during task performance, for example using effective connectivity measures (Friston, 1994). Finally, to investigate the relation between the development of functional or effective connectivity and changes in the underlying brain structure, these measures could also be combined with structural measures, such as diffusion tensor imaging (see for example Hagmann et al., 2010; Supekar et al., 2010).

The dynamics of functional connectivity

It has been demonstrated that networks of functional connectivity are relatively consistent across different subjects (Damoiseaux et al., 2006; Smith et al., 2009), task conditions (Fransson, 2006; Kelly et al., 2008), sleep (Fukunaga et al., 2006; Horovitz et al., 2008; Larson-Prior et al., 2009), and even anesthesia (Greicius et al., 2008; Vincent et al., 2007). However, the overlap between individuals is not perfect and functional connectivity patterns exhibit small changes between one context and the next. For example, it has been demonstrated that functional connectivity of the default mode network is attenuated during a working memory task (Fransson, 2006), conscious sedation (Greicius et al., 2008), and deep sleep (Horovitz et al., 2009). Moreover, in Chapter 6, we demonstrated that functional connectivity at rest might also change after repeated practice with a working memory task. Thus it seems that although the core pattern of intrinsic connectivity is relatively stable, the strength of particular functional connections dynamically changes due to different task contexts and experiences. One important future direction is to determine to what extent the context- and experience-related changes reflect a true reorganization of functional connectivity (possibly even related to long-lasting structural changes) or whether they are due to a superposition of spontaneous BOLD fluctuations and task-related activity (Fox and Raichle, 2007).

Generalization of training effects

The training effects that were presented in this thesis most likely reflected the improvement of task specific skills, rather than a general improvement of working memory functions (Chapter 4 and 5). It is still not entirely clear what the optimal training procedures are that promote transfer to other cognitive tasks, or real-life situations. Yet, it has been suggested that process-based training paradigms are more effective than strategy-based training programs because strategy-based programs focus more on domain-specific processes (Klingberg, 2010; Morrison and Chein, 2010). In addition, has been suggested that complex tasks should be used that train several different processes at once (Buschkuehl and Jaeggi, 2010; Green and Bavelier, 2008), and that it is most effective to vary the tasks and stimuli during the training period (Sanders et al., 2002; Schmidt and Bjork, 1992). Finally, it has been argued that the difficulty level of the trained task(s) should be adapted to the participants' level of performance to keep the participant motivated and to prevent automaticity (Buschkuehl and Jaeggi, 2010; Holmes et al., 2009; Klingberg et al., 2005). However, these recommendations are not necessarily effective for all participants (Karbach and Kray, 2009; Sanders et al., 2002; Van der Molen et al., 2010). For example, Karbach and Kray (2009) showed that there were age differences in the type of training that was most effective. That is, transfer of task-switching training was improved in adults, but impaired in children when training tasks were variable. Moreover, there seems to be a trade-off between maximizing the effectiveness of training and maximizing our understanding of the mechanisms underlying training effects (see also Chapter 7). One solution might be to *reverse engineer* the training program (Bavelier et al., 2010). That is, one could select a successful training program and then gradually determine what the combination of factors is that make the training successful.

Familiarity, expectancy, and motivation

It was demonstrated that performance improvements and (most) changes of brain activation were larger in the trained participants than in participants of a passive control group, who only participated in the scanning sessions before and after practice (Chapter 4 and 5). These findings are important since they suggest that training effects could not simply be attributed to familiarity with the task. However, it should be noted that the inclusion of a passive control group does not take into account expectancy effects or effects of motivation. For example, it is possible that participants in the training group improved more than participants in the control group simply because the training had increased their confidence in task performance or because they put in more effort after training. To rule out the effects of expectancy and motivation, future studies should consider including an active control group, which receives a *placebo treatment* similar to the training program (e.g., Klingberg, 2010; Morrison and Chein, 2010).

The time window of training effects

In Chapter 5, the main analysis of training effects in children only included the lowest task loads. However, in a separate analysis we also examined training-related changes for the highest load. For this load, children showed improved performance after training, but there was no evidence of increased activation for manipulation relative to maintenance. These findings might suggest that there were constraints on the effects of training in this age group. However, it is important to note that performance did not yet reach asymptote, and from the present results it is not clear whether children would demonstrate activation changes if they practiced for a longer time. The same notion applies to the training-related activation changes during the highest load in adults. Although the activation difference between manipulation and maintenance trials increased after training, the level of activation during high load maintenance trials did not yet reach the level of activation during lower load maintenance trials. In future studies, it is important to study the entire time window of training-related changes (Kelly and Garavan, 2005; Poldrack, 2000).

Neurocognitive development and functional connectivity across the lifespan

The studies in this thesis are based on only two age groups: 12-year-old children and young adults. Therefore, it is not possible to make any direct conclusions about the *trajectories* of different working memory functions or networks of functional connectivity during development. Moreover, the children – who should actually be called *early adolescents* – are already in a relatively advanced stage of development, when several large structural and functional changes have already occurred (e.g., Diamond, 2002; Hagmann et al., 2010; Uylings, 2006; Welsh et al., 1991). It is expected that different effects would be obtained in much younger children for whom the basic architecture of the structural system is still undergoing great changes. At the same time, (most of) the young adults are actually in a late stage of adolescence, when there are still several maturational processes taking place, both structurally (e.g., Shaw et al., 2008; Tamnes et al., 2009) and functionally (e.g., Adleman et al., 2002). Thus, the results that were found in the young adults might also differ from results in adults who are several years older. Future studies should examine age- and experience-related changes of neural activation and functional connectivity in larger samples across a wider age range.

Variability and group size

Several studies have pointed out that inter- and intraindividual variability in anatomy, physiological fluctuations, motion, or cognitive strategies has a large impact on the reliability and sensitivity of the fMRI data (cf. Thirion et al., 2007). Moreover, these types of variability may actually be larger in children than in adults. For example, it has been demonstrated that the variability in cortical surface anatomy is higher in children than in adults (Sowell et al., 2002a) and children may show larger inter- and intraindividual differences in performance and/or brain activation during cognitive tasks (Bunge et al., 2002; Williams et al., 2005). A high variability reduces the power to detect activation changes, which is particularly problematic in small samples such as the ones used in this thesis (Desmond and Glover, 2002; Thirion et al., 2007). Although we performed some additional analyses to examine the possible effects of the small sample size, it is nevertheless important to validate the results in a larger number of participants.

In addition, rather than controlling for interindividual variability, it may actually be informative to explore the relation between individual differences in brain activation and individual differences in performance and/or brain structure. For example, it might be valuable to investigate whether or not better performing children (or children with more mature brain structure) show more adult-like patterns of activation (Bunge et al., 2002). In addition, individual differences in brain structure (Erickson et al., 2010; Golestani et al., 2002) or cognitive functioning (Neubauer et al., 2004) might be critical factors in predicting training effects. The investigation of individual differences is an important direction for future research.

8.3 Conclusion

In this thesis an fMRI training approach was used to examine age- and experience-related effects in the development of working memory and resting-state functional connectivity. It was described that although the late development of working memory manipulation was not an effect of task difficulty per se, performance could be improved as a result of training, both in children and adults. Moreover, we found training-related changes of neural activation, with children demonstrating more mature frontoparietal activation after training. In adults there was even a change of resting-state functional connectivity. These findings emphasize the additional value of developmental training studies relative to static assessment, because they can tell us something about possibilities of cognitive functioning, and the constraints set by the developing brain. In other words, training studies may be used to study the *potential* of cognitive functioning at a certain age.

A better understanding of the potential of cognitive functioning does not only have value to the scientific community, but it could also be of great importance to the educational service. By understanding the possibilities of children's brain systems, we will be able to demonstrate what can and cannot be expected of children across school-aged development. Knowledge about children's abilities to learn from experience is also critical to aid in the understanding of cases of abnormal cognitive development, as seen in children with learning disorders, Attention Deficit Hyperactivity Disorder, or traumatic brain injury, and it might be used to build intervention programs.