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Development of a superior frontal–intraparietal network for visuo-spatial working memory

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Abstract

Working memory capacity increases throughout childhood and adolescence, which is important for the development of a wide range of cognitive abilities, including complex reasoning. The spatial-span task, in which subjects retain information about the order and position of a number of objects, is a sensitive task to measure development of spatial working memory. This review considers results from previous neuroimaging studies investigating the neural correlates of this development. Older children and adolescents, with higher capacity, have been found to have higher brain activity in the intraparietal cortex and in the posterior part of the superior frontal sulcus, during the performance of working memory tasks. The structural maturation of white matter has been investigated by diffusion tensor magnetic resonance imaging (DTI). This has revealed several regions in the frontal lobes in which white matter maturation is correlated with the development of working memory. Among these is a superior fronto-parietal white matter region, located close to the grey matter regions that are implicated in the development of working memory. Furthermore, the degree of white matter maturation is positively correlated with the degree of cortical activation in the frontal and parietal regions. This suggests that during childhood and adolescence, there is development of networks related to specific cognitive functions, such as visuo-spatial working memory. These networks not only consist of cortical areas but also the white matter tracts connecting them. For visuo-spatial working memory, this network could consist of the superior frontal and intraparietal cortex.

Keywords: Working memory; Child; Development; Frontal; Parietal; Myelination; Functional magnetic resonance imaging; Neuroimaging

1. Development of visuo-spatial working memory

Working memory capacity develops throughout childhood and early adulthood. This can be measured by the increase in the amount of information that can be retained in various types of working memory tasks, such as the span-board task where the subject retains information about the order and position of a number of objects (Gathercole, Pickering, Ambridge, & Wearing, 2004). Although differences in strategy contribute to the improved performance in early childhood (Cowan et al., 1994), the increase in capacity from about 6 years of age seems to be linear (Fry & Hale, 2000; Gathercole et al., 2004) and has been described as a quantitative change in capacity, rather than a change in strategy (Fry & Hale, 2000). Fig. 1 shows the improved performance on a version of the span-board task, where cues are serially presented in a 4 × 4 grid on a computer screen and then recalled by indicating the positions in the correct order (Westerberg, Hirvikoski, Forssberg, & Klingberg, 2004). The development is well described as a linear increase that continues to at least 16 years of age.

Working memory processes can be divided into two categories, one being passive storage and the other being a more active process related to "executive control" (Baddeley & Hitch, 1974), or "controlled attention" (Engle, Kane, & Tuholski, 1999). Tasks requiring more controlled attention are more highly correlated with reasoning ability and intelligence (Conway, Kane, & Engle, 2003). The demand for controlled attention can be increased in many ways, for example by requiring the subjects to manipulate the stored information, by introducing a dual-task requirement (Conway et al., 2003; Engle et al., 1999), or by including distractions or interference (Gray, Chabris, & Braver, 2003).

At a superficial level, the forward spatial-span task does not seem to require any manipulation of the retained information, nor any dual-task requirements. Yet, the correlation to performance on complex reasoning tasks such as the Raven's

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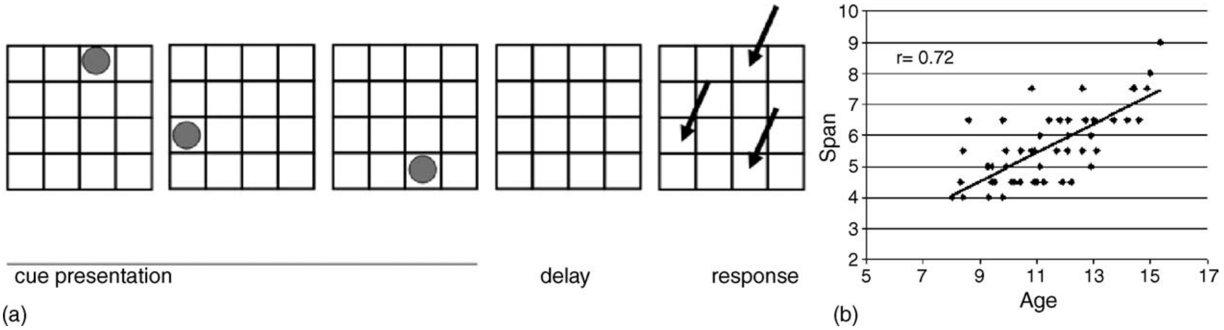

Fig. 1. (a) The visuo-spatial working memory task. Cues are presented one at a time in a 4 × 4 grid and the subject then responds by indicating the correct positions in the correct order on the screen. The testing starts with only two cues, and the number of items are then gradually increased. The subject is given two attempts on each level and the testing is terminated when the subject fails on both attempts at a specific level. The total score is calculated as the total number of correctly remembered cues. (b) Correlation between age and performance on the visuo-spatial working memory task (from Westerberg et al., 2004).

Progressive matrices is high (Fry & Hale, 1996), and in our own data this correlation is $r = 0.45$ in 8–12-year-old children (Klingberg et al., 2005). This is comparable to the 0.32 correlation between performance of the Raven's tasks and performance of working memory dual-tasks such as reading span and operation span (Engle et al., 1999). It is likely that other factors, in addition to manipulation and dual-task requirements, demand controlled attention in a working memory task. Active rehearsal of the spatial sequence might be one such factor. In pure passive storage of visuo-spatial information, the capacity limit is about four items (Cowan, 2001). In span tasks the limit is typically seven to eight items, which is presumably due to the active rehearsal of the information. The serial presentation and response in the spatial-span task also introduces interference and a dual-task requirement because of the interfering effect of later cues on the memory of earlier cues. During the response one has to respond to early cues while simultaneously remembering later cues, which is very similar to the dual-task requirement of the listening span task or the computational span task. The spatial-span task is thus a working memory task requiring active rehearsal and controlled attention, and performance is correlated to complex reasoning abilities. The capacity measured with this task develops throughout childhood and early adulthood, and task performance is also a sensitive measure of the cognitive deficits in attention deficit hyperactivity disorder (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Westerberg et al., 2004). What then, are the neural correlates of the development of the spatial-span task?

2. Development of working memory and changes in brain activity

Non-invasive methods such as functional MRI (fMRI), have opened the possibilities to image brain activity in children. In two previous studies, using overlapping samples of subjects, fMRI was used to measure changes in brain activity associated with the development of spatial-span performance (Klingberg, Forssberg, & Westerberg, 2002a; Olesen, Nagy, Westerberg, & Klingberg, 2003). The first study (Klingberg et al., 2002a) included 13 children (age 9–18, mean age 13.4, 9 boys). This sample was later extended to 23 children (age 8–18, mean age 11.9, 14 boys). Children were scanned while performing a visuo-spatial working memory task and a baseline task. The working memory task was similar to that described in Fig. 1, except that the response was made by indicating whether a probe was located in the same position as any of the remembered cues (a yes/no response). In order to avoid differences in accuracy between older and younger subjects we only required subjects to remember a small number of cues (three or five) in order to achieve ceiling effects. Outside the scanner, a spatial-span task (Fig. 1) and a different testing procedure was used to measure the maximum capacity of each participant.

A subtraction of brain activity recorded during the control task from that recorded during the working memory task resulted in a measurement of working memory related activity. We then explored where in the brain the score on the spatial-span task correlated with activity. Brain activity in the posterior part of the superior frontal sulcus (−26, 8, 56) and intra- and inferior parietal cortex (−36, −50, 56) correlated positively with span. The first study included 14 children (Klingberg et al., 2002a). When the number of participants was increased to 23, we also found a significant, positive correlation in the head of the caudate nucleus in the left hemisphere (Olesen et al., 2003). The results are consistent with a previous study of working memory performance in children and adults, which found both dorsal frontal and parietal activations in both groups, and concluded that the areas activated were similar (Nelson et al., 2000; Thomas et al., 1999). The results were also confirmed in a later developmental study of visuo-spatial working memory (Kwon, Reiss, & Menon, 2002).

3. Development of white matter

There are several structural maturational processes that coincide in time with the increase in working memory capacity, most importantly the myelination of axons (Yakovlev & Lecours, 1967) and synaptic remodelling, including strengthening of connections and pruning. Myelination continues at least until 20 years of age and can be measured from T1-weighted MR images as an increase in white matter volume (Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; De Bellis et al., 2001; Giedd et al., 1999; Paus et al., 1999; Pfefferbaum et al., 1994; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). The microstructural properties of white matter can be investigated in vivo by diffusion tensor MR imaging (DTI). This technique is based on the fact that the diffusion of water in the white matter of the brain is anisotropic (Moseley et al., 1990), so that it is faster along the axons than perpendicular to them. The axonal membrane itself induces some of this directional preference even without myelin (Gulani, Webb, Duncan, & Lauterbur, 2001; Wimberger et al., 1995). However, myelination of the axons further increases the anisotropy, as shown in studies comparing anisotropy with histological findings (Wimberger et al., 1995), comparing anisotropy in normal mice with that of knock-out mice lacking myelin (Gulani et al., 2001), as well as in human studies of demyelination (Werring, Clark, Barker, Thomson, & Miller, 1999). The degree of anisotropy can be quantified as fractional anisotropy (FA), which ranges from 0, corresponding to free diffusion, to 1, which is the hypothetical case of diffusion along a single line. Although FA can be affected by microstructural properties, such as how densely the axons are packed, and how regular their arrangement, these factors do not increase with age in a normal sample of children. Increase in FA during childhood and adolescence can therefore be attributed to myelination and thickening of axons.

DTI has been used in order to map the maturation of white matter during childhood (Mukherjee et al., 2001; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Schmithorst, Wilke, Dardzinski, & Holland, 2002; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005). However, these studies could not make any direct connection between structural maturation and behavioral performance. In the study by Nagy, Westerberg, and Klingberg (2004) this was accomplished by measuring two different cognitive functions: visuo-spatial working memory and reading ability, and then correlating the increase in performance over age with fractional anisotropy in the brain. By using two different cognitive functions we were able to demonstrate some specificity of maturation, e.g. that maturation of a white matter region is more associated with development of one function and less with another. We hypothesized that we would find maturational changes in white matter close to the frontal and parietal regions associated with visual–spatial working memory, or in the white matter connecting them.

Development of reading ability is associated with changes in cortical activity in temporo-parietal, temporo-occipital, and ventral frontal regions (Shaywitz et al., 2002; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003). In a previous DTI study, it was found that reading ability, as measured by the word-ID task from the Woodcock test battery, was correlated with white matter integrity in the left temporo-parietal region (Klingberg et al., 2000). In this region, adult subjects with reading disability had impaired integrity of white matter compared to controls. Furthermore, both within the reading impaired group and within the control group there was a positive correlation between reading ability and white matter structure. Given these results, we hypothesized that development of reading ability might be dependent on white matter structure in the temporo-parietal region. If such a developmental trend could be detected, this might also provide insight into the possible mechanisms underlying developmental dyslexia.

In the study by Nagy et al. (2004) DTI was used to estimate diffusion in white matter in 23 children between 8 and 18 years of age (mean age 11.9, S.D. 3.1, 14 boys) and then calculated fractional anisotropy was used as an indicator of white matter maturation, including myelination and thickening of axons. In an exploratory analysis, we searched the brain for voxel in which fractional anisotropy values correlated with working memory and reading scores acresoss individuals. We found that development of working memory capacity was positively correlated with fractional anisotropy in two regions in the left frontal lobe, including a region between the superior frontal and parietal cortices (Nagy et al., 2004; Olesen et al., 2003). Reading ability, on the other hand, was only significantly correlated with fractional anisotropy in the left temporal lobe, in the same white matter region in which adults with reading disability are known to have lower fractional anisotropy (Klingberg et al., 2000). Later studies have also confirmed the positive correlation between fractional anisotropy and reading ability in this white matter region (Beaulieu et al., 2005).

The fact that white matter develops until late in childhood has been shown in previous studies (Caviness et al., 1996; De Bellis et al., 2001; Giedd et al., 1999; Klingberg et al., 1999; Mukherjee et al., 2001; Paus et al., 1999; Pfefferbaum et al., 1994; Reiss et al., 1996; Schmithorst et al., 2002; Sowell et al., 1999). Our results extend these previous findings by showing the regional and functional specificity of this maturation—with maturation of relatively restricted regions that is correlated with specific cognitive functions.

It is tempting to interpret the changes in fronto-parietal myelination seen in Nagy et al. (2004) as structural changes that could cause the changes in brain activity in the frontal and parietal regions demonstrated earlier by Klingberg et al. (2002a). If this is so, one would expect fractional anisotropy and BOLD signal in these regions to be correlated. This was investigated by Olesen et al. (2003). The subjects and the DTI data in the study by Olesen et al. (2003) were identical to those reported by Nagy et al. (2004). We included the fMRI measurements from the study by Klingberg et al. (2002a) plus fMRI measurements from 10 additional subjects. White matter regions that showed a developmental trend were identified by using working memory scores from the children as a covariate, and selecting white matter regions in which there was a positive correlation between working memory scores and FA. In the second step, we extracted the FA values from these regions for each individual. These values were then used as covariates in an exploratory analysis of BOLD activity. Corresponding analyses were also done starting with BOLD response values in grey matter regions that were correlated with FA values. This second analysis (BOLD to FA) was primarily performed in order to confirm findings from the first analysis. A general positive correlation between all measures (age, working memory, FA, BOLD) is to be expected during development. The question was whether we could detect any sign of regional specificity in these data, with some regions showing stronger correlations depending on the functional networks in which they participate.

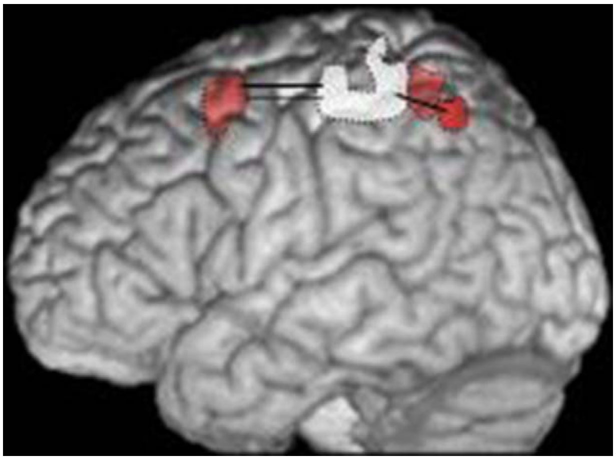

Fig. 2. Summary of the superior frontal–intraparietal network involved in the development of visuo-spatial working memory (from Klingberg et al., 2002a,b; Nagy et al., 2004; Olesen et al., 2003). Regions showing a correlation between brain activity and the development of capacity are shown in red. Regions showing a correlation between white matter maturation and development are shown in white. The regions that showed a significant correlation in the analysis of BOLD response vectors on FA maps, are shown with thin lines. Thick lines indicate regions that showed a significant correlation when FA was used as covariates in the BOLD analysis.

It was found that FA values in fronto-parietal white matter were positively correlated with the BOLD response in closely located grey matter in the superior frontal sulcus ($x = -26$, $y = 6$, $z = 56$) and intraparietal cortex ($x = -34$, $y = -68$, $z = 52$), areas that could form a functional network underlying working memory function (Fig. 2) (Olesen et al., 2003). The correlation of FA values in fronto-parietal white matter with the BOLD response in the superior frontal sulcus was confirmed in the converse analysis, where BOLD response values were used as covariates on FA maps. This correlation is primarily explained by age-related maturation of white and grey matter since working memory score did not correlate with FA values or the BOLD response in these regions when age-related variance was removed.

Taken together, these studies (Klingberg et al., 2002a; Nagy et al., 2004; Olesen et al., 2003; Westerberg et al., 2004) have identified a superior frontal–intraparietal network where brain activity, myelination and development of visuo-spatial working memory capacity are related during childhood and early adulthood.

4. The superior frontal region

The cortex in the posterior part of the superior frontal sulcus (possibly Brodman area 8) is consistently activated during performance of visuo-spatial working memory tasks (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Curtis, Rao, & D'Esposito, 2004; Jonides et al., 1993; Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002; Postle & D'Esposito, 1999; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Smith et al., 1995; Sweeney et al., 1996). However, activation of this region is also evident in non-spatial working memory tasks (Cohen et al., 1997; Klingberg, 1998; Postle & D'Esposito, 1999). Furthermore, this area exhibits sustained activity during the delay-period, when information is held in working memory (Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997; Curtis et al., 2004; Pessoa et al., 2002; Rowe et al., 2000). The sustained activity thus resembles the sustained activity observed during delay periods in electrophysiological studies of working memory in macaques (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971).

Several tasks involving 'top-down', or 'voluntary control' of attention have found activation at an almost identical superior frontal site as in visuo-spatial working memory tasks (Corbetta et al., 1998; Hopfinger, Buonocore, & Mangun, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). In these tasks, the subject is cued about the location of a future target, or searches for a particular known target. The subject thus needs to keep a representation of the target, or its location, in working memory, in a similar way to that in which information is kept on-line during working memory tasks. Top-down attention and working memory could thus be overlapping concepts, with overlaps in the underlying brain activity, as has also been suggested previously (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). Interestingly, a positive correlation between activity in the superior frontal sulcus and developmental improvement in performance was also found in a study using the Stroop task (Adleman et al., 2002). This task is not generally thought of as requiring working memory, and the function here is presumably related to the demand for top-down control of attention.

5. Function of the parietal cortex and fronto-parietal networks

The inferior and intraparietal cortex shares many functional characteristics with the superior frontal cortex: it is active during visuo-spatial working memory tasks (Courtney et al., 1998; Jonides et al., 1993; Postle and D'Esposito, 1999; Rowe et al., 2000; Smith et al., 1995; Sweeney et al., 1996) and shows sustained activity during the delays in the working memory tasks (Cohen et al., 1997; Rowe et al., 2000). The intraparietal cortex is also active in tasks demanding voluntary control of visual attention (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Hopfinger et al., 2000; Kastner et al., 1999) and has sustained activity during the cue period in such tasks (Corbetta et al., 2000; Hopfinger et al., 2000; Kastner et al., 1999). Although the functional parcellation of the intra- and inferior parietal cortex is unclear at this point, this intra/inferior parietal region can be separated from an area at the temporo-parietal junction (about 15 mm above the AC–PC line) which is not involved in top-down control but is involved in orienting (Corbetta & Shulman, 2002; Corbetta et al., 2000; Downar, Crawley, Mikulis, & Davis, 2000) and arousal (Coull, Nobre, & Frith, 2001).

The activity in the frontal and parietal regions is higher during correct trials than incorrect trials (Pessoa et al., 2002). Several recent studies have also shown a correlation between inter-individual differences in working memory capacity and activity in the intraparietal cortex (Todd & Marois, 2004; Vogel & Machizawa, 2004), which is in line with the correlation between parietal activity and capacity found in the developmental studies.

The intraparietal and superior frontal areas seem to constitute a functional unit, and the functionality of this unit is dependent on the connections between them. Electrophysiological data suggest that the character of the neuronal activity in the parietal area i.p. and frontal area 8a is very similar (Chafee & Goldman-Rakic, 1998). However, it is also possible that there are slight differences in the computations done by the frontal and parietal regions. It could, for example, be that the parietal region stores the spatial representation of the sensory cues, and that the role of the frontal region is to maintain this representation by activity similar to that associated with covert eye movements (Courtney et al., 1998; Curtis & D'Esposito, 2003). It is also likely that this network needs to be extended with additional prefrontal regions in some circumstances, such as when distracters are present during the trial (Sakai, Rowe, & Passingham, 2002).

6. The influence of experience on working memory capacity and brain activity

One way of interpreting the maturation of the fronto-parietal network, is to assume a genetically programmed maturation of white matter which affects the neural activity in the frontal and parietal regions, and in turn determines the capacity and the BOLD response. However, it is important to keep in mind the correlational nature of the studies, and the possible direct effect of experience on neural activity and capacity.

Except for the changes in capacity that occur during development and aging, it has previously generally been assumed that working memory capacity is a fixed trait. Recent studies, however, have suggested that practice of working memory tasks can result in improved performance, not only for the trained tasks, but also for non-trained working memory tasks, given that the practice is done daily, intensively, with adaptive algorithms and during several weeks (Klingberg, Forssberg, & Westerberg, 2002b; Klingberg et al., 2005). In addition, this effect generalizes to improved performance on the Raven's progressive matrices (Klingberg et al., 2002b, 2005). In a subsequent study, fMRI was used to measure changes in brain activity induced by practice of working memory in young healthy adults. Several weeks of daily practice increased the working memory related activity in the intraparietal cortex and middle frontal gyrus (Olesen, Westerberg, & Klingberg, 2004). This suggests that the neural systems underlying working memory are plastic and formed by experience, and that the effect of experience must be considered even when evaluating such basic cognitive functions as working memory capacity. Moreover, the part of intraparietal cortex that is affected by training overlaps with the regions in which a developmental change is present. This suggests that the neural bases of development and practice have some similarities, and that it is possible that the developmental changes we have observed are the results of experience and practice in every day life during development. However, the fact that similar regions are involved, and that increases in BOLD are observed in both cases, does not necessarily mean that the same mechanisms underlie the two processes. It is possible that there are different neuronal mechanisms that result in an identical behavioral change, as well as a similar change in the BOLD signal. For example, development might rely on a genetically programmed maturation of fronto-parietal connections, while training results in strengthening of local excitatory connections. Both processes could result in improved working memory capacity and higher BOLD activity in the intraparietal cortex. In order to resolve these questions we need a deeper understanding of the relationships between cellular mechanisms, the BOLD signal and information processing in the brain.

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