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Load-related brain activation predicts spatial working memory performance in youth aged 9–12 and is associated with executive function at earlier ages

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ABSTRACT

Spatial working memory is a central cognitive process that matures through adolescence in conjunction with major changes in brain function and anatomy. Here we focused on late childhood and early adolescence to more closely examine the neural correlates of performance variability during this important transition period. Using a modified spatial 1-back task with two memory load conditions in an fMRI study, we examined the relationship between load-dependent neural responses and task performance in a sample of 39 youth aged 9–12 years. Our data revealed that between-subject differences in task performance was predicted by load-dependent deactivation in default network regions, including the ventral anterior cingulate cortex (vACC) and posterior cingulate cortex (PCC). Although load-dependent increases in activation in prefrontal and posterior parietal regions were only weakly correlated with performance, increased prefrontal–parietal coupling was associated with better performance. Furthermore, behavioral measures of executive function from as early as age 3 predicted current load-dependent deactivation in vACC and PCC. These findings suggest that both task positive and task negative brain activation during spatial working memory contributed to successful task performance in late childhood/early adolescence. This may serve as a good model for studying executive control deficits in developmental disorders.

1. Introduction

As a central form of executive function, working memory is required for the optimal performance of goal directed behaviors. Spatial working memory refers to the temporary maintenance of object location and the ability to manipulate this information (Logie, 1995). Neuroimaging studies have shown that the neural architecture of spatial working memory in young adults involves a group of frontal and parietal regions including the dorsolateral prefrontal cortex (DLPFC), frontal eye fields (FEF), pre-supplementary motor area (pre-SMA), superior (SPL) and inferior parietal lobules (IPL) and intraparietal sulcus (IPS) (Courtney et al., 1997; Leung et al., 2004). Similar frontal and parietal regions are found to be involved in spatial working memory in children and adolescents (Geier et al., 2009; Nelson et al., 2000; Thomas et al., 1999), though younger individuals (aged 9–12) appeared to show weaker neural responses to increased memory load compared to older individuals (aged 13–18) (Klingberg et al., 2002) and even weaker in comparison to adults (aged 20–29) (Thomason et al., 2009). This weaker load-related activation is thought to be related to lower working memory capacity and immature fronto-parietal function in youth (Giedd and Rapoport, 2010; Klingberg et al., 2002; Scherf et al., 2006).

Several cross-sectional neuroimaging studies have examined the relationship between frontal and parietal activation and spatial working memory performance in youth, but yielded mixed findings. An earlier study showed that activations in the left superior frontal sulcus and left posterior parietal cortex (PPC) during spatial delayed recognition were associated with better working memory capacity, measured outside the scanner, in a group of 9–18 year olds (Klingberg et al., 2002). Greater activation in the left PPC was also associated with better performance on a spatial 1-back task during fMRI in a group of youth aged 12–17, with the inferior parietal areas further associated with better executive function measured outside of the scanner using the Trail Making Task (Nagel et al., 2005). However, the same study found a positive correlation between ventral anterior cingulate cortex (vACC) activation and working memory

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performance (measured by a backward digit span and an arithmetic task outside the scanner), while many other frontal areas including the medial superior frontal gyrus and bilateral inferior frontal gyri showed a negative correlation. In contrast, Olesen and colleagues (2007) found no significant correlation between spatial working memory performance and activation in the prefrontal or parietal areas in a group of 13 year olds, though a significant positive correlation between performance and parietal activation was found when adults (mean age 22.8) were included in the sample. These previous studies showed some evidence that better spatial working memory performance is associated with greater frontal and parietal activation in samples with a wider age range or in older individuals, though this may not extend to a narrower age range or younger individuals. Thus, the relationship between neuropsychological measures of working memory and executive function with frontal and parietal activation during working memory remains unclear.

Along with increases in fronto-parietal activation, task-related decreases are frequently seen in a set of regions including the vACC and posterior cingulate cortex (PCC) commonly known as the default network (Greicius and Menon, 2004; Greicius et al., 2003; Raichle and MacLeod, 2001; Shulman et al., 1997). Previous neuroimaging studies showed that the magnitude of vACC and PCC deactivation increases with increasing task demand as compared to rest/baseline conditions (Li et al., 2007; McKiernan et al., 2003; Thomason et al., 2008), though both task-positive and task-negative networks are based on contrasts relative to baseline. While the specific role of vACC and PCC in working memory remains unclear, it has been suggested that their deactivation is related to the ability to ignore task irrelevant information (Chadick and Gazzaley, 2011). Few studies have examined the role of default network regions in spatial working memory performance, though positive correlations between the degree of deactivation in default network regions and performance during non-spatial working memory tasks have been observed in adults (Anticevic et al., 2010; Prakash et al., 2012). It is less clear whether similar deactivation patterns exist in younger individuals. The default network is known to undergo functional and structural changes through adolescence (Fair et al., 2008; Supekar et al., 2010; for review see Power et al., 2010). In a recent fMRI study with a large group of youth (ages 8–21) it was found that greater task-related deactivation in default network regions predicted better performance on a non-spatial n-back task with fractal visual stimuli (Satterthwaite et al., 2013). However, an earlier fMRI study of spatial working memory in youth (age 12–17) reported both positive and negative correlations between performance and deactivation of different default network regions (Nagel et al., 2005). The mixed findings could be due to parameter differences across studies and in participant age ranges. Thus, studying task-related deactivation during working memory in comparison with task-related activation with a more restricted age range would extend our understanding of their contribution to performance variability in youth.

Our goal in this study was to examine the relationship between spatial working memory and activation of the fronto-parietal and default network regions during late childhood and early adolescence, as working memory ability varies widely across individuals in this age range (Farrell Pagulayan et al., 2006; Gathercole et al., 2004) and large variability in the development of various cortical systems have been reported (Giedd and Rapoport, 2010). We used a modified spatial 1-back task with two load conditions to investigate the relationship between neural responses to spatial working memory load and performance variability in a sample of youth with a narrow age range (9–12). We used whole brain multiple regression, regions of interest (ROI), and functional connectivity to analyze the data.

It is well recognized that pronounced individual differences in working memory performance exist throughout childhood and adolescence. Previous longitudinal studies suggested that frontal and parietal activity predicts cognitive abilities later in development (Darki and Klingberg, 2014; Dumontheil and Klingberg, 2012; Ullman et al., 2014), it is therefore plausible that executive function abilities at earlier stages of development predict performance and brain activation during a later stage. To address this latter issue, we examined whether executive function ability measured at prior time points (ages 3, 6 and 9) predicted current spatial working memory performance and load-related neural activation at time of scanning.

2. Methods

2.1. Participants

Participants were a subsample of a larger sample of 559 subjects enrolled in the Stony Brook Temperament Study. Families were recruited from the community using commercial mailing lists, and participants were evaluated at 3, 6, and 9 years of age. A subgroup of 80 participants were recruited for a neuroimaging study 1–3 years after the age 9 assessment. 68 of these participants (85%) completed the working memory task during fMRI. These participants had no history of major medical conditions and had at least one English speaking biological parent. 29 subjects were excluded from the analyses: 17 had missing behavioral data, 4 appeared to have misunderstood the task instructions (performing the task as a delayed match-to-sample task instead), 4 were behavioral outliers (with accuracy 3 standard deviations below average), and another 4 had excessive head motion during fMRI. Thus, 39 participants (age 9–12 [mean = 11.1 ± 0.7], 43.6% female) were included in the final analysis. The Pubertal Development Scale (PDS) (Petersen et al., 1988) was used to measure puberty score at the time of fMRI. The participants had a mean puberty score of 8.37 ± 2.36; one male participant did not complete the PDS. There was no significant difference in PDS scores between males (8.14 ± 2.13) and females (8.65 ± 2.67) ($t < 1$). Age was not correlated with puberty scores ($r = 0.28$, $p = 0.089$), probably due to the restricted age range. Informed consent was obtained from parents of the participants in accordance with the Stony Brook University Institutional Review Board.

2.2. Spatial working memory task paradigm and behavioral data analysis (current age)

During fMRI, the participants performed a block design 1-back spatial working memory task with two load conditions (Load 1 and Load 3). See Fig. 1 for a schematic of the paradigm. During the Load 1 condition, participants tracked the location of 1 rabbit stimulus and in the Load 3 condition participants tracked the locations of 3 rabbit stimuli.

The two load conditions were presented in blocks of 5 trials. On each trial except the first trial of each block, participants pressed a button to indicate whether any rabbit was in a different location from the previous trial. In the Load 3 condition, only one of the rabbits ever changed location on a trial (the participants were made aware of this). To reduce verbalization, the rabbits were located randomly around an invisible circle with a radius of 5 degrees visual angle. The participants did not report verbalization as a strategy in the post experiment interview, though several reported a shape forming strategy. The rabbits were presented for 200 ms and were an average size of 1° in visual angle. There were 8 possible locations shifted between 5° to 10° from regular clock orientation to prevent verbalization and the locations were