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Structural brain correlates of executive engagement in working memory: Children's inter-individual differences are reflected in the anterior insular cortex

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ABSTRACT

Although the development of executive functions has been extensively investigated at a neurofunctional level, studies of the structural relationships between executive functions and brain anatomy are still scarce. Based on our previous meta-analysis of functional neuroimaging studies examining executive functions in children (Houdé, Rossi, Lubin, and Joliot, (2010). *Developmental Science*, *13*, 876–885), we investigated six a priori regions of interest: the left anterior insular cortex (AIC), the left and the right supplementary motor areas, the right middle and superior frontal gyri, and the left precentral gyrus. Structural magnetic resonance imaging scans were acquired from 22 to 10-year-old children. Local gray matter volumes, assessed automatically using a standard voxel-based morphometry approach, were correlated with executive and storage working memory capacities evaluated using backward and forward digit span tasks, respectively. We found an association between smaller gray matter volume – i.e., an index of neural maturation – in the left AIC and high backward memory span while gray matter volumes in the a priori selected regions of interest were not linked with forward memory span. These results were corroborated by a whole-brain a priori free analysis that revealed a significant negative correlation in the frontal and prefrontal regions, including the left AIC, with the backward memory span, and in the right inferior parietal lobe, with the forward memory span. Taken together, these results suggest a distinct and specific association between regional gray matter volume and the executive component *vs.* the storage component of working memory. Moreover, they support a key role for the AIC in the executive network of children.

1. Introduction

Executive functions (EFs) refer to high-level cognitive control processes that underlie goal-directed behavior, such as inhibition (resisting habits, temptations, or distractions), switching (adjusting to change), and working memory (mentally holding and manipulating information or instructions). Although the development of EFs has been extensively investigated at a neurofunctional level in children, studies of how this development relates to brain anatomy are still scarce. One relevant method is to use inter-individual differences to link behavior to brain anatomy (Kanai & Rees, 2011). Behavior performances in an EFs task measured outside the magnetic resonance imaging (MRI) scanner can be linked to anatomical data from brain regions known to be functionally engaged in EFs. Here, we investigated a possible link between performances observed on tasks that varied in the degree to which they engage the executive functioning component of working memory and gray matter (GM) brain volume in typically developing children. Six regions of interest (the left anterior insular cortex, the left and the right supplementary motor areas, the right middle and superior frontal gyri, and the left precentral gyrus) revealed by our previous meta-analysis of functional MRI studies examining EFs in children (Houdé, Rossi, Lubin, & Joliot, 2010) were chosen to test this hypothesis.

EFs emerge early in development, probably around the end of the first year of life (Diamond, 2006; Houdé, 2000) and continue to develop throughout childhood and adolescence, with peak

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performance in adulthood (Zelazo & Müller, 2011). EFs are typically associated with several regions in the prefrontal cortex (Fuster, 2008; Koechlin, Ody, & Kouneiher, 2003; Miller & Cohen, 2001), depending on the specific EFs components engaged. Using a meta-analysis, we recently demonstrated that bilateral prefrontal areas were strongly involved during cognitive control in children and adolescents (Houdé et al., 2010). In particular, the dorsolateral and inferior prefrontal cortices extending to the anterior insular cortex (AIC) exhibit reliable activity across functional neuroimaging studies involving inhibition, switching, and working memory tasks. Moreover, a developmental comparison between children (mean $\pm$ SD age, 9.5 $\pm$ 2 years) and adolescents (14.3 $\pm$ 2.8 years) demonstrates a key role for the AIC in EFs, with additional involvement of the right AIC in adolescents.

Structural MRI studies have revealed an inverted U-shape GM volume trajectory; GM volume increases in early childhood and then decreases during late childhood and adolescence (Giedd et al., 1999; Østby et al., 2009; Sowell et al., 2003, 2004). The prefrontal cortex, which supports EFs, is one of the last regions losing GM toward the end of adolescence (Gogtay et al., 2004). These studies suggest that the slow development of EFs could be attributed to a protracted maturation of the prefrontal cortex (Diamond, 2002). Tamnes et al. (2010) related cortical thickness to behavioral measures of updating, shifting, and inhibition in children and adolescents (8–19 years), observing negative associations in the frontal and prefrontal regions. The aim of the present study was to investigate structural properties of prefrontal regions that we have revealed to be common to a set of neurodevelopmental functional MRI studies of EFs (Houdé et al., 2010). We chose to link GM volumes and cognitive performances observed in children on tasks that engage different degrees of executive processing in working memory.

We focused on the digit span (DS) task because it contains two subtests varying in the degree to which they require executive functioning: the forward DS and the backward DS. According to Gathercole, Pickering, Ambridge, and Wearing (2004), and in line with the model of Baddeley (2003), a simple working memory task such as the forward DS requires little input from the central executive; instead, it relies solely on information storage in the phonological loop. Conversely, the backward DS requires central executive intervention to coordinate multiple processes in order to manipulate the information. This distinction between the executive and storage processes engaged in working memory was clearly demonstrated with the DS task in typically developing children (St Clair-Thompson, 2010).

It is known that working memory recruits a fronto-parietal network in adults (Wager & Smith, 2003). In children, this effect appears less clear-cut. The majority of functional MRI studies have employed visuo-spatial working memory tasks (Klingberg, 2006; Kwon, Reiss, & Menon, 2002; Nelson Monk, Lin, Carver, Thomas, & Truwit, 2000; Thomas et al., 1999) and reported that children recruit frontal and parietal regions, an adult-like pattern of activations. Verbal working memory studies are fewer in number but suggest that the fronto-parietal network is less functionally developed in children (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006). An increasing activation with age was observed in parietal and cerebellar regions that are engaged in phonological processing in response to increasing working memory load (O'Hare, Lu, Houston, Bookheimer, & Sowell, 2008).

The cortical thickness of predefined regions of interest (ROIs) in the left parietal and lateral prefrontal regions was recently investigated with respect to working memory performance as assessed using forward and backward DS in a sample of participants who were aged 8–19 years (Østby, Tamnes, Fjell & Walhovd, 2011). Negative relationships were observed between forward DS and cortical thickness in the supramarginal gyrus and the rostral middle frontal cortex, and this effect was independent of age. Regression analyses performed with each of the three age groups revealed no significant association for the youngest and the middle age groups (8–11 and 12–15 years of age, respectively) and a significant negative relationship for the oldest age group (16–19 years of age). Backward DS was negatively associated with cortical thickness of the rostral middle frontal cortex pars triangularis independently of age, albeit only at an uncorrected significance level. These results suggested that structural development of fronto-parietal regions is related to working memory performance and is age-dependent.

We examined local GM volumes using the standard, fully automated voxel-based morphometry approach (Ashburner, 2009). GM volumes were correlated with executive and storage working memory capacities. Based on our previous meta-analysis of functional MRI studies on EFs in children (Houdé et al., 2010), we a priori examined local GM volumes in six regions of interest: the left anterior insular cortex, the left and the right supplementary motor areas, the middle and superior frontal gyri, and the left precentral gyrus. Two supplementary posterior regions were highlighted in our meta-analysis: the left middle occipital gyrus and the right fusiform gyrus. Because these regions are known to be not engaged in the fronto-parietal working memory network, they were considered as control ROIs in the present work. Consequently, we expect to found no significant results in these two posterior ROIs. We then conducted a whole-brain a priori-free analysis to explore regions, such as parietal regions, that are likely to be engaged in the working memory network. Brain maturation is characterized by GM loss with age (Giedd et al., 1999; Østby et al., 2009; Sowell et al., 2003, 2004), and normal cortical maturation in childhood and adolescence is negatively correlated with executive performance (Tamnes et al., 2010). In line with these results, we expected to observe a negative association between GM volumes of prefrontal regions and executive engagement as evaluated using the backward DS. Measurements of storage capacities evaluated using forward DS scores, which were used as a control condition, require fewer executive demands and should not be linked with GM volumes in prefrontal regions.

2. Material and methods

2.1. Participants

Twenty-two children with a mean age of 10 $\pm$ 0.6 years (11 girls, 19 right-handed) were recruited from schools in Caen (Calvados, France). The participants had no history of neurological disease and no cerebral abnormalities as assessed by a T1-weighted MRI. The local ethics committee (No. ID RCB 2007—A00442-51, CPP Nord-Ouest III, France) approved the study. Written consent was obtained from the parents and the children themselves after detailed discussion and explanations.

2.2. Assessment of working memory

All children were administered cognitive assessments based on the Wechsler Intelligence Scale for Children (fourth edition WISC-IV; Wechsler, 2003). Children completed the DS task. The DS task is a validated test that is widely used with child populations and represents a well-established measure of working memory using verbal material (Best & Miller, 2010). Repetition of a dictated series of digits of increasing complexity allows the DS task to obtain a measure of digit memory span. Two subtests were presented: the forward DS and the backward DS. During the forward DS, a series of digits were read aloud to the children, and the children were asked to repeat the digit sequence in the same order that it was originally presented. The series began at two digits in length and continued until it comprised nine digits, with two sequences at each length. Series were delivered until a child made two consecutive errors in a same length series. The backward DS was administered in a similar manner; however, the participants were asked to repeat the series in reverse order. The number of repeated digits at the last trial determined the forward and backward memory spans. Maximum scores were 9 for the forward DS and 8 for the backward DS.

2.3. MRI acquisition

All children were familiarized with the MRI scanner before MRI acquisition by individual participation in a half-hour-long session at school the day before the scan. Particular efforts were made to desensitize children to the sights and sounds