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The typical development of posterior medial frontal cortex function and connectivity during task control demands in youth 8–19 years old

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ABSTRACT

To characterize the development of neural substrate for interference processing and task control, this study examined both linear and non-linear effects of age on activation and connectivity during an interference task designed to engage the posterior medial frontal cortex (pMFC). Seventy-two youth, ages 8–19 years, performed the Multi-Source Interference Task (MSIT) during functional magnetic resonance imaging (fMRI). With increasing age, overall performance across high-interference incongruent and low-interference congruent trials became faster and more accurate. Effects of age on activation to interference- (incongruent versus congruent conditions), error- (errors versus correct trials during the incongruent condition) and overall task-processing (incongruent plus congruent conditions, relative to implicit baseline) were tested in whole-brain voxel-wise analyses. Age differentially impacted activation to overall task processing in discrete sub-regions of the pMFC: activation in the pre-supplementary motor area (pre-SMA) decreased with age, whereas activation in the dorsal anterior cingulate cortex (dACC) followed a non-linear (i.e., U-shaped) pattern in relation to age. In addition, connectivity of pre-SMA with anterior insula/frontal operculum (AI/FO) increased with age. These findings suggest differential development of pre-SMA and dACC sub-regions within the pMFC. Moreover, as children age, decreases in pre-SMA activation may couple with increases in pre-SMA–AI/FO connectivity to support gains in processing speed in response to demands for task control.

Introduction

Capacity for selecting appropriate behavior matures through childhood into adolescence. Development of this capacity, broadly defined as task control (Dosenbach et al., 2006), is presumed to underlie age-related improvement in the ability to flexibly adapt behavior so that an individual can produce the response most relevant to achieving task goals (Durston et al., 2006). Task control demands engage the posterior medial frontal cortex (pMFC), encompassing dorsal anterior cingulate cortex (dACC) and pre-supplementary motor cortex (pre-SMA), and are elicited across a range of cognitive tasks, including those designed to elicit cognitive interference, response inhibition, response selection, decision uncertainty, and performance monitoring (Dosenbach et al., 2006; Nee et al., 2007; Ridderinkhof et al., 2004; Rushworth et al., 2007; Stern et al., 2010; Wager et al., 2005). Each of these tasks tap psychologically distinguishable processes, but all require the processing of cognitively salient events known to engage a network defined by pMFC connectivity with bilateral anterior insula/frontal operculum (AI/FO) (Dosenbach et al., 2006; Seeley et al., 2007; Sridharan et al., 2008). Several groups have referred to this pattern of regional correlation as the salience network (although others have distinguished a cingulo-opercular network from a more anterior salience network—e.g., Power et al., 2011), which has been suggested to mediate selection of information from a myriad of internal and external inputs to guide ongoing behavior (Dosenbach et al., 2006; Seeley et al., 2007; Sridharan et al., 2008). Yet, despite age-related improvement in task control capacity, developmental changes in pMFC activation and salience network connectivity during task processing remain poorly understood.

To date, developmental imaging studies of task control function have produced inconsistent results with regard to the role of the pMFC. Typically, this work has employed cognitive interference or response inhibition tasks, both of which are known to reliably engage pMFC in adults (Chambers et al., 2009; Simmonds et al., 2008; Wager et al., 2005). However, studies of age effects on pMFC activation during such tasks have reported increases (Adleman et al., 2002; Fitzgerald et al., 2010; Rubia et al., 2006, 2007), decreases (Durston et al., 2002; Tamm et al., 2002), and no change (Casey et al., 1997; Konrad et al., 2005; Marsh et al., 2006; Rodehacke et al., 2014). The inconsistent findings may derive from differences in specific neuroimaging paradigms (i.e., the use of cognitive interference versus response inhibtion in different studies). However, the critical role of the pMFC for task control *across* various cognitive tasks (Chambers et al., 2009; Dosenbach et al., 2006; Simmonds et al., 2008; Wager et al., 2005) suggests that other factors, besides variation in specific cognitive task probe, may contribute to the inconsistent age effects on pMFC activation in different imaging studies.

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Factors that may have contributed to discrepancies between studies include small sample sizes, variabilty in sample age range, and differences in experimental approach to testing age effects. Small samples sizes in neuroscience yield low reproducibility of results (Button et al., 2013) and may contribute to inconsistencies between developmental neuroimaging studies. In addition, analytic strategies for testing age effects on brain response to task control demands have differed between studies. Some studies compared brain activation between groups, averaging across youth compared to adult participants, which could obscure age differences among youth in whom brain function may vary substantially with each year of age. Other studies treated age continuously, enabling the detection of more subtle age-related variations. Yet, while several such studies have tested for simple linear effects of age (Adleman et al., 2002; Casey et al., 1997; Durston et al., 2002; Fitzgerald et al., 2010; Konrad et al., 2005; Rodehack et al., 2014; Rubia et al., 2006, 2007; Tamm et al., 2002; but see Marsh et al., 2006), none have reported non-linear (e.g., quadratic or U-shaped) effects of age on brain activation in response to task control demands. Given recent evidence suggesting that developmental change in cortical thickness (including in pMFC) follows a non-linear trajectory (Lenroot and Giedd, 2006), it is possible that a non-linear fit may characterize developmental changes in pMFC engagement by task control. If a non-linear, U-shaped curve describes the relationship between age and pMFC activation, then, depending on the ages contained within any given sample, different studies may isolate the decreasing, increasing, or flat part of the developmental trajectory among youth, while studies of youth compared to adults may find greater or lesser activation depending on the exact ages of participants in the youth group.

As noted, the pMFC and the AI/FO exhibit co-variation of low frequency blood oxygenation-level dependent (BOLD) signal fluctuations, part of a putative network for the detection of cognitively salient events (Dosenbach et al., 2006; Seeley et al., 2007; Sridharan et al., 2008). Thus, developmental change of pMFC connectivity, indexed by correlated BOLD fluctuations, with other regions may contribute to age-related improvements in capacity for goal-directed behavior. Consistent with this notion, resting state functional magnetic resonance imaging (fMRI) has been used to demonstrate age-related increase in the strength of functional connectivity between pMFC and AI/FO (Fair et al., 2007). These resting state fMRI correlations between pMFC–AI/FO suggest a history of co-activation that may define a canonical network for task control (Fair et al., 2007). However, little is known on the developmental change of pMFC–AI/FO connectivity during cognitive information processing, when these brain regions are actually engaged.

To address these gaps in the literature, the current study tested both linear and non-linear (i.e., quadratic) effects of age on whole-brain activation and connectivity in a large sample of youth performing a child-friendly cognitive interference task, previously found to engage the pMFC (Bush and Shin, 2006). The task allowed for testing of activation associated with three cognitive processes: cognitive interference, error processing, and general task control (i.e., across high and low interference conditions). Accordingly, developmental effects on task-specific cognitive processes (interference, errors) *and* more general cognitive task processing were tested. Given discrepant findings on age-related change in task-based pMFC activation in prior work, both linear and non-linear changes in pMFC activation with age were hypothesized. In addition, given previous literature showing positive effects of age on salience network connectivity during rest, positive effects of age on pMFC–AI/FO connectivity during task were predicted.

Materials and methods

Participants

Seventy-six healthy children and adolescents were recruited from the community. Participants' ages ranged from 8 to 19 years (36 female, mean age = 13.9 ± 3.3). Of these, 2 participants were excluded due to unusable fMRI data (see "Motion control" for details), one participant was excluded due to low accuracy (55% overall) and one participant was excluded due to lack of behavioral data for technical reason. Demographic data on the remaining participants ($n = 72$) is described in Table 1. Participants were evaluated using the Kiddie-Schedule for Affective Disorders—Present and Lifetime (Kaufman et al., 1997) to rule out the presence of any current or past psychiatric illness. Serious medical/neurological illness, head trauma, and mental retardation were excluded. Written informed assent was obtained from pediatric participants (<18 years) and consent from their parents. For participants older than 18 years, written consent was obtained from the participants alone. The study was approved by the University of Michigan Medical School Institutional Review Board.

fMRI task

Participants performed the Multisource Interference Task (MSIT), designed to elicit pMFC activation (Bush and Shin, 2006). The MSIT requires participants to identify the unique number among three digits, "1", "2", and "3", by pressing a button with the index, middle, and ring fingers of the right hand. Participants were shown a string of three numbers (e.g., "331") and asked to press the button corresponding to the unique number (i.e., index finger to select "1" for "331"). On the high-interference, incongruent trials, the position of the target is incongruent with its associated response (i.e., for "331", "1" is in the 3rd position, but requires a button press with the first, or index, finger). On congruent trials, the position of the target is congruent with its associated response (i.e., for "100," the target is in the first position and the correct answer is a button press with the index finger). Participants performed five runs of the MSIT consecutively. Each run lasted 3 min, consisting of 24 incongruent, 24 congruent trials, and 12 fixation trials. Incongruent and congruent stimuli appeared for 500 ms, followed by a 2500 ms inter-stimulus interval to comprise a trial. Fixation trials consisted of a white crosshair presented on a black background and were 3000 ms each. The three trial types were presented in pseudorandom order, with ordering unique for each of the five runs. The task was run using Eprime software on a desktop computer, with stimuli projected onto a head-coil mounted mirror. Prior to scanning, participants were trained on the task in a magnetic resonance simulator to ensure task understanding and reduce potential anxiety about the scanning environment.

Data acquisition

Using a 3.0 T General Electric (GE) Signa scanner with single channel birdcage head coil, a reverse spiral T2* sequence was collected (gradient echo, echo time (TE) = 30 ms, repetition time (TR) = 2000 ms, flip angle = 90 degrees, field of view = 22 cm, 40 slices, 3.0 mm/slice, matrix 64 × 64) (Stenger et al., 2002), as participants performed the MSIT. Additionally, a low-resolution axial T1 was collected in the same prescription as the functional images to aid in later co-registration. Finally, a high-resolution T1-weighted Spoiled Gradient Recalled (SPGR) echo image was acquired for anatomic normalization (whole-brain coverage, resolution 1.02 × 1.02 × 1.20, TE = 1.84 ms, TR = 9.04 ms, flip angle = 15 degrees, field of view = 26.1 cm, matrix 256 × 256). Head movement was minimized through instructions to the participant and packing with foam padding.

Behavioral data analysis

Behavioral measures included accuracy and reaction times (RT) for incongruent and congruent trials. For RT, only correct trials were considered. Average accuracy and RT were computed for incongruent and congruent trial types. Overall accuracy and RT were computed by averaging across incongruent and congruent trial types. Interference accuracy and RT were computed by subtracting the relevant behavioral measure for incongruent minus congruent trials. Paired *t*-tests were

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