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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

Yanni Liu, Ph.D.^a, Mike Angststadt, M.A.S.^a, Stephan F. Taylor, M.D.^a, and Kate D. Fitzgerald, M.D.^a

^aDepartment of Psychiatry, Medical School, University of Michigan, Ann Arbor, 48109

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. 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 preSMA decreased with age, whereas activation in dACC followed a non-linear (i.e., U-shaped) pattern in relation to age. In addition, connectivity of preSMA with anterior insula/frontal operculum (AI/FO) increased with age. These findings suggest differential development of preSMA and dACC sub-regions within the pMFC. Moreover, as children age, decreases in preSMA activation may couple with increases in preSMA-AI/FO connectivity to support gains in processing speed in response to demands for task control.

Keywords

development; posterior medial frontal cortex; task control; functional connectivity; salience network

Address correspondence to Dr. Yanni Liu, University of Michigan, Department of Psychiatry, 4250 Plymouth Rd., Ann Arbor, MI, 48104; telephone: 734-936-9275 ; fax: 734-936-7868; yanniliu@umich.edu.

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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 (Durstun et al., 2006). Task control demands engage the posterior medial frontal cortex (pmFC), encompassing dorsal anterior cingulate cortex (dACC) and pre-supplementary motor cortex (preSMA), 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 (Adelman et al., 2002; Fitzgerald et al., 2010; Rubia et al., 2006, 2007), decreases (Durstun et al., 2002; Tamm et al., 2002) and no change (Casey et al., 1997; Konrad et al., 2005; Marsh et al., 2006; Rodehack et al., 2014). The inconsistent findings may derive from differences in specific neuroimaging paradigms (i.e., the use of cognitive interference versus response inhibition 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.

Factors that may have contributed to discrepancies between studies include small sample sizes, variability 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 (Adelman 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 minutes, consisting of 24 incongruent, 24 congruent trials and 12 fixation trials. Incongruent and congruent stimuli appeared for 500 milliseconds (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 degree, field of view = 22 centimeter (cm), 40 slices, 3.0 millimeter (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 $1.02 \times 1.02 \times 1.20$, TE = 1.84 ms, TR = 9.04 ms, flip angle = 15 degree, 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 used to assess for differences in accuracy and RT for incongruent compared to congruent trial types. Correlations were used to test the effects of age on accuracy and RT for each trial type, across trial types (i.e., overall accuracy, RT) and between trial types (i.e. interference accuracy, RT).

Imaging data pre-processing

Functional data were analyzed in SPM8 (SPM8, Statistical Parametric Mapping, Wellcome Trust Centre, London, United Kingdom). The raw data were slice-time corrected and rigidly realigned to the tenth image acquired. The low-resolution T1 structural image was coregistered with the mean functional image after realignment. Next, the high-resolution SPGR was co-registered to the (now coregistered) low-resolution T1. The coregistered high-resolution SPGR was then segmented using the VBM8 toolbox (VBM, voxel based morphometry; VBM8, <http://dbm.neuro.uni-jena.de/vbm>) and normalized using high dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) normalization (McLaren et al., 2010). The deformations calculated by DARTEL were then applied to the functional images, resulting in functional data being warped into common stereotactic space (Montreal Neurological Institute; MNI). The fMRI data were smoothed with a 5-mm Gaussian kernel.

Motion control

Motion during fMRI scanning is typically more pronounced at younger ages and can confound developmental fMRI research. Thus, several steps were taken to reduce the impact of motion on fMRI data analyses. First, measures of head movement were obtained from the output of the rigid body motion correction algorithm (i.e., realignment). Runs were excluded from further analyses if the range of movement (x, y, z, roll, pitch and yaw) for one or more TRs exceeded 3 mm translational or rotational movement. Participants were required to have at least 3 of 5 runs of usable data, leading to the exclusion of 2 participants (an 8 year old female and a 10 year old female).

To further understand and control for the effects of motion, several additional steps were taken. First, a widely accepted summary of motion, mean framewise displacement (FD) (Power et al., 2012), was calculated for each run and averaged across runs for each participant. As expected, mean FD negatively correlated with age ($r(72) = -0.52$, $p < 0.001$); that is, motion declined at older ages (see Figure S1). Thus, to reduce the impact of

motion on fMRI data, the six motion parameters (x, y, z, roll, pitch, yaw) generated during realignment, as well as their first derivatives, were regressed from time series for each participant at the first level in both task activation and connectivity analyses. To further query motion effects on task activation results, post-hoc linear regression analyses were used to test mean FD – alongside terms for the linear effect of age, non-linear effect of age, and RT – as predictors of BOLD contrast estimates extracted from the developmentally sensitive regions identified in the primary whole brain analysis. Given particular concern that motion may confound age effects in low frequency correlational data (Van Dijk et al., 2012), mean FD was included as a regressor of no interest in connectivity analyses at the second-level (Fair et al., 2012; Satterthwaite et al., 2012).

Task activation analysis

Task-based functional data were analyzed using a standard random effects analysis within the framework of the modified General Linear Model (Worsley et al., 1997) in SPM8. At the first level, incongruent correct (IC), congruent correct (CC), incongruent error (IE) and congruent error trials were modeled against fixation trials as implicit baseline. Omission trials were modeled as covariates of no interest. In addition, the six motion regressors generated from the realignment step, as well as their first derivatives, were included in the regression models to remove nuisance effects. Activation maps were derived for linear contrasts of IC compared to CC for interference processing (IC versus CC) and the linear combination of IC and CC for task processing (IC plus CC, against implicit baseline) for each participant. Error contrasts, including participants with at least five incongruent errors (Kern et al., 2004), were also constructed (IE versus IC), since error processing may represent a unique element of task control (Ordaz et al., 2013; Rushworth et al., 2004) with a distinct trajectory of development (relative to correct processing of cognitive demands) in task control regions such as pmFC (Fitzgerald et al., 2010; Ordaz et al., 2013). Contrasts were entered into second-level random effects analyses to produce activation maps (Friston et al., 1999).

In the second-level whole-brain voxel-wise analysis, two sets of models were constructed to test (1) the effect of age (linear and non-linear) on interference, overall task, and error processing (age included as regressor of interest); and (2) the effect of age (linear and non-linear) on these contrasts, controlling for performance (interference RT, overall RT, and error rates, respectively, as regressors of no interest). Linear age was mean-centered and quadratic age was orthogonalized with respect to linear age. This second set of analyses allowed for the isolation of specific effects of age from those of performance, since performance improves with age (Casey, 2005) and may impact brain response to task control demands (Fitzgerald et al., 2010). Results examining age effects were masked with the main effect of task (Figure 3, Table 2) to limit corrections for multiple comparisons to regions engaged by task, thus reducing the risk of type 2 error. If not stated otherwise, contrasts were displayed at a peak threshold of $p < 0.005$, uncorrected and significance was defined at the cluster-level as $p = 0.05$, correcting for false discovery rate (FDR) across the whole brain.

Intrinsic functional connectivity analysis

Analysis of functional connectivity examined coupling between pMFC regions of interests (ROIs) and other voxels in the brain throughout the entire task. Specifically, preSMA and dACC ROIs, were defined by the whole brain analyses testing linear and non-linear effects of age on activation to overall task processing (see Results, Figure 3). The preprocessed fMRI data were detrended with covariates for six motion regressors and their first derivatives, all task events and their first derivatives, cerebrospinal fluid (CSF) and white matter signals regressed out¹; smoothed with 5-mm Gaussian kernel; and bandpass-filtered (0.01–0.10 Hz). Global signal was not regressed in the low-frequency data because it might induce spurious negative correlations and non-uniform changes in connectivity patterns, which are problematic to interpret (Saad et al., 2012). Residual time series of the seed regions for each participant were used as covariates to examine positive and negative correlations between residual seed region activity and residual activity of all gray matter voxels in the brain. These correlations are described as intrinsic because this method identifies interregional coupling that is independent of and linearly superimposed upon event-related activity (Fox et al., 2006). Single participant connectivity maps were then entered into a second-level regression analysis in SPM8; as with second-level analyses of task-based activations, two sets of models were constructed to test (1) effects of age on seed region connectivity with all gray matter voxels in the brain (i.e., whole brain connectivity); (2) effects of age on seed region connectivity, controlling for reaction times. Only overall RT, not interference RT, was included as a regressor since incongruent and congruent conditions had been regressed from the time series for the connectivity analysis. In both models, motion, calculated as mean framewise displacement (FD), was included as a covariate of no interest. Of note, there were no significant effects of the non-linear age term on connectivity for either seed region ($p < 0.005$ uncorrected at height level, $p < 0.05$ corrected for FDR at cluster level), so results are reported only for analyses testing the linear effects of age on seed region connectivity.

Results

Behavioral

72 participants were included in the behavioral data analysis. Participants responded more slowly and less accurately to incongruent trials than to congruent trials (response times: IC, 1070 ± 218 ms, CC: 756 ± 160 ms, paired t-test, $t(71) = 25.31$, $p < 0.001$; accuracy: incongruent, 0.90 ± 0.06 , congruent, 0.98 ± 0.03 , paired t-test, $t(71) = 10.20$, $p < 0.001$). However, age effects were similar across trial types, with increasing age associated with faster response times (response times: IC, $r(72) = -0.67$, $p < 0.001$; CC, $r(72) = -0.62$, $p < 0.001$; overall, $r(72) = -0.66$, $p < 0.001$, see Figure 1). In addition, increasing age was associated with greater accuracy (incongruent, $r(72) = 0.23$, $p = 0.05$; congruent, $r(72) = 0.30$, $p = 0.01$; overall, $r(72) = 0.29$, $p = 0.01$, see Figure 1). By contrast, correlation between age and interference RT was not significant ($r(69) = -0.14$, $p = 0.26$) after

¹CSF and white matter signals were regressed from the data to reduce residual noise effects. To create white matter and CSF regressors, segmented images from the DARTEL processing were thresholded to create ROI masks.

controlling for overall RT, and there was no correlation of age with interference accuracy ($r(72) = 0.12$, $p = 0.32$).

Task activation

Analyses of interference processing (IC versus CC) and overall task processing (IC plus CC, against implicit baseline) included 72 participants each. Both analyses showed extensive activation of pMFC and bilateral AI/FO, left pre- and post-central gyri, bilateral parietal cortex, bilateral occipital cortex, and thalamus at a stringent statistical threshold ($p < .05$, corrected for family wise error rate, FWE; Figure 2, Table S1). The error processing analysis included 53 participants (19 participants excluded due to <5 errors) and showed activation of bilateral anterior insula ($p_{FWE} < .05$), as well as pMFC at $p < .001$, uncorrected (Figure S2; Table S2).

Linear and non-linear effects of age were tested as predictors of activation during interference (IC versus CC), overall task (IC plus CC, against implicit baseline) and error (IE versus IC) processing in whole-brain voxel-wise analyses. For the interference and error analyses, there were no significant linear or non-linear effects of age on activation in any brain region. However, for overall task processing, there was a significant linear effect of age (negative) on activation in the preSMA (Brodmann area 6) and a significant non-linear effect of age (i.e., positive quadratic) on activation in the dACC (Brodmann area 24/32) (see Figure 3a, Table 2). Specifically, preSMA activation during task processing decreased with age (Figure 3b), whereas dACC activation decreased with age from late childhood (8 years) through middle adolescence (~14 years), but then increased with age from middle- through late adolescence (~19 years) (Figure 3c). In addition, there was a significant negative linear effect of age on caudate / putamen activation and a positive linear effect of age on left post-central gyrus activation (Table 2).

After covarying overall RT from the whole-brain voxel-level analysis of task processing, the linear and non-linear effects of age on preSMA and dACC activations remained significant and, in fact, became even more pronounced in terms of size (i.e., greater number of voxels/cluster) and peak magnitude (i.e., higher Z-scores). In part, the preSMA cluster size defined by linear effects of age became larger, after covarying RT, due to coalescence with the caudate/putamen area that had been previously observed as a separable cluster. In contrast, the linear effects of age on left post-central gyrus, observed when *not* considering performance, was no longer significant after controlling for overall RT (see Table 2).

Effects of age on preSMA and dACC activations were tested for goodness of fit in follow-up analyses within SPM. Beta values were extracted from all voxels in each ROI and averaged to generate regression equations (preSMA: $y = 0.84 - 0.11 \cdot \text{age} + 0.02 \cdot \text{age}^2$; dACC: $y = 0.71 - 0.01 \cdot \text{age} + 0.04 \cdot \text{age}^2$). Partial R-squared values were calculated as $R^2 = t^2 / (t^2 + df)$ (where t is the average SPM t-score corresponding to the age effect averaged over all voxels in each ROI; <http://afni.nimh.nih.gov/sscc/gangc/tr.html>). For the preSMA region, goodness of fit was greater for linear age (partial $R^2 = 0.14$, $p = 0.002$) than for quadratic (partial $R^2 = 0.02$, $p = 0.37$). By contrast, for the dACC region goodness of fit was greater for quadratic age (partial $R^2 = 0.12$, $p < 0.001$) than for linear (partial $R^2 = 0.04$, $p = 0.08$). Consistent with recent developmental neuroimaging research (Ordaz et al., 2013), higher order non-linear

fits (e.g., cubic) were not considered in whole brain analyses and, thus, were not considered in the post-hoc analyses testing goodness of fit for the relationship of age.

In addition, post-hoc analyses evaluated whether effects of age on preSMA and dACC activation to overall task processing were independent of head motion. Contrast estimates extracted from preSMA and dACC ROIs, defined by linear and non-linear effects of age in the whole brain analysis respectively, served as dependent variables in linear regression models that tested age effects (linear and non-linear), RT and mean FD as predictors. Linear and non-linear effects of age remained significant in pre-SMA ($\beta = -0.49$, $p < 0.001$) and dACC ($\beta = 0.45$, $p < 0.001$), respectively, whereas mean FD (i.e., motion) was not a significant predictor of activation in either region (preSMA, $\beta = -0.02$, $p = 0.90$; dACC, $\beta = -0.19$, $p = 0.13$).

Intrinsic functional connectivity

72 participants were included in the connectivity analysis. Whole brain connectivity maps for preSMA and dACC seed regions, as defined by linear and non-linear effects of age on activation to overall task processing, were examined. As expected, positive connectivity was observed for both pMFC seeds with lateral prefrontal (left mid-frontal and pre-central; right post-central), bilateral anterior insular, and left parietal cortex (see Figure 4, Table S3), consistent with previous research implicating these regions as key nodes in networks for task control (Dosenbach et al., 2006; Seeley et al., 2007; Sridharan et al., 2008). By contrast, negative connectivity was observed with posterior cingulate cortex, superior medial frontal cortex, right middle temporal lobe, and bilateral angular gyrus (Figure S3, Table S3), areas typically associated with default mode processes, rather than task control (Dosenbach et al., 2006; Seeley et al., 2007; Sridharan et al., 2008).

Next, the effects of age on connectivity maps were examined. For the preSMA seed region, age-related increases in positive connectivity of preSMA with bilateral AI/FO were demonstrated (Table 3, Figure 5), consistent with prior research showing resting state connectivity within salience network increases with age (Fair et al, 2007). Age-related decreases in positive connectivity of preSMA were noted with right pre-central and post-central gyrus (Table 3, Figure 5). Other linear effects of age (increases and decreases) on positive connectivity of preSMA, as well as dACC, failed to reach significance after covarying RT (see Table 3 and Table 4). There were no significant effects of the non-linear (i.e., quadratic) age term on positive connectivity and no effects of either linear or non-linear age terms on negative connectivity for the preSMA or dACC seed regions.

Discussion

To characterize the development of pMFC activation and connectivity to task control demands, the current study tested effects of age on brain activation and connectivity during the Multisource Interference Task (MSIT), an established probe of pMFC-based interference processing function (Bush and Shin, 2006) in a large sample of 8 – 19 year old youth. With increasing age, performance became faster and more accurate, across both high-interference (incongruent) and low-interference (congruent) conditions, consistent with age-related improvement in capacity for overall task control. As predicted, activations of pMFC, as well

as AI/FO, pre- and post-central gyri and parietal cortex were elicited during both interference (i.e., incongruent relative to congruent trials) and overall task processing (i.e., across incongruent and congruent conditions). However, in whole brain analyses testing linear and non-linear effects of age on activations for these contrasts, significant findings were observed only for overall task processing. Specifically, in response to overall task processing, there was a negative linear effect of age in the preSMA and a positive quadratic effect of age in the dACC. Age-defined preSMA and dACC sub-regions were then used as seed regions in whole brain connectivity analyses. Interestingly, the preSMA region defined by age related *decreases* in activation showed age-related *increases* in connectivity with AI/FO. Given age-related improvement in overall task performance, these developmental changes in pMFC function and connectivity may contribute to the maturation of capacity for task control.

Linear effects of age on pMFC activation

The finding of age-related decrease in preSMA activation to a cognitively demanding task concurs with some prior reports (Durstun et al., 2002; Tamm et al., 2002), but conflicts with others (Adleman et al., 2002; Bunge et al., 2002; Fitzgerald et al., 2010; Konrad et al., 2005; Rubia et al., 2006). Seemingly conflicting reports of increasing (Adleman et al., 2002; Fitzgerald et al., 2010; Rubia et al., 2006, 2007), decreasing (Durstun et al., 2002; Tamm et al., 2002) or unchanging (Casey et al., 1997; Konrad et al., 2005; Marsh et al., 2006; Rodehack et al., 2014) pMFC response to task demands across prior studies may result from the use of different fMRI probes. For example, probes of cognitive interference compared to response inhibition engage overlapping (Chambers et al., 2009; Simmonds et al., 2008; Wager et al., 2005), yet distinct (Bari and Robbins, 2013; Van Velzen et al., 2014) elements of task control and it is possible that distinguishable neural networks with unique maturational trajectories may underlie the development of these task control sub-process.

On the other hand, the current study showed age-related changes in pMFC activation to *overall* task processing (i.e., across incongruent and congruent trial types), but not interference or error processing, suggesting that consideration of task-general, rather than task-specific, control processes may be especially relevant for understanding functional development of the pMFC. This notion is consistent with research in adults showing pMFC activation across a wide variety of cognitive tasks, including cognitive interference, response inhibition, errors, and other types of performance feedback (Dosenbach et al., 2006; Ridderinkhof et al., 2004; Wager et al., 2005) and accumulating evidence showing that the pMFC, in conjunction with AI/FO, serve as critical nodes within a network that serves to detect increased need for task control (Dosenbach et al., 2006; Menon, 2011; Seeley et al., 2007; Sridharan et al., 2008). This “cingulo-opercular” or “salience” network is widely held to signal for engagement of a “frontal-parietal” or “central executive” network that, in turn, mediates the implementation of higher order cognitive processes (e.g., top-down attention, working memory) to improve ongoing performance (Dosenbach et al., 2006; Menon, 2011; Seeley et al., 2007; Sridharan et al., 2008). Theoretically, age-related change in pMFC and AI/FO engagement across both difficult and less difficult trial types *within* a given task (e.g., incongruent and congruent conditions) may be most relevant for understanding how development of these regions contributes to the maturation of general capacity for task

control. However, to test this possibility, additional research testing different types of tasks (e.g., interference, response inhibition) in the same participants will be needed. At present, it remains unclear whether a task-general framework, as compared to one that considers more granular task control “subprocesses”, serves as a more useful model for understanding developing capacity for the flexible adjustment of behavior.

Indeed, the absence of age-related change in pMFC activation to interference processing (IC versus CC) in the present study was unexpected and merits consideration. This negative finding can be partially explained by the age-related decreases in preSMA activation for *both* incongruent and congruent trial types. That is, there was no difference in the effect of age on incongruent compared to congruent trials. As with preSMA activation, age effects on performance were similar across incongruent and congruent trial types: with age, participants became faster and more accurate for both conditions, with no significant difference between them. Considering that the MSIT is an interference-inducing task specifically designed to engage pMFC (Bush and Shin, 2006), this behavioral finding is consistent with the possibility that task-general (i.e., overall task processing), rather than task-specific (i.e., interference processing) demands may be important for understanding the development of pMFC-based task control function.

Notably, whole brain analyses revealed no significant effects of age on activation to error processing in any brain region. This null finding conflicts with prior work finding age-related increases in dACC response to errors (Fitzgerald et al., 2010; Ordaz et al., 2013; Rubia et al., 2007), and may stem from lower error rates observed in the current study. In fact, insufficient error rates (< 5 incongruent errors of commission) led to the exclusion of 19 participants from analyses, possibly reducing power to detect effects of age on activation in the pMFC or elsewhere in the brain.

Non-linear effects of age on pMFC activation

In addition to the negative linear effects of age on preSMA activation, whole brain analyses revealed a positive quadratic effect of age to overall task processing in an adjacent pMFC sub-region, the dACC. This positive quadratic pattern was characterized by decreasing dACC activation from childhood (8 years) through mid-adolescence (~14 years), followed by increasing activation through late adolescence (19 years). Previous studies have also reported non-linear developmental changes in brain function, including during inhibitory control of emotional reactivity (Hare et al., 2008; McRae et al., 2012; Uhlaas et al., 2009), reward processing (Galvan et al., 2006) and social cognition (Blakemore, 2012). The current study represents the first evidence of non-linear development of brain function in response to a cognitive task.

Determining the functional significance of non-linear development of dACC activation (reduced in middle adolescence, compared to younger and older ages) relative to linear decreases in preSMA activation, will require further study, but may be informed by prior work describing these pMFC sub-regions as functionally distinct (Etkin et al., 2011; Margulies et al., 2007; Power et al., 2011; Ridderinkhof et al., 2004). Specifically, dACC and preSMA are associated with distinguishable patterns of connectivity to other cortical areas in human neuroimaging and animal research (Etkin et al., 2011; Margulies et al.,

2007). Based on these patterns and accumulating functional neuroimaging evidence, the dACC has been suggested to mediate integration of cognitive and emotional processes via connectivity with emotion processing regions such as amygdala, whereas preSMA may be preferentially involved in the implementation of “top-down” cognitive control through connectivity with lateral frontal cortex (Etkin et al., 2011; Ridderinkhof et al., 2004; Shackman et al., 2011). Prior developmental imaging work distinguishes linear maturation of neural substrate for cognitive control from nonlinear development of neural networks underlying cognition-emotion integration (Blakemore and Robbins, 2012; Casey et al., 2013). The MSIT paradigm used in the present study did not specifically elicit emotional responding; however, even cognitive demanding tasks require affective motivation to enable high-level performance (Okon-Singer et al., 2015) and, given its critical role in the salience network, the dACC could mediate this aspect of task control.

Surprisingly, the null effect of age on pMFC interference processing and negative linear effect of age on preSMA activation to overall task processing in the current study have some discrepancy with our prior work (Fitzgerald et al., 2010) using a similar task, but showing age-related increases in pMFC activation to interference. Several differences between the current and prior study may have impacted the results. First, the prior study did not examine overall task-processing — the contrast in which age effects were significant in the present work. Second, the prior study did not control for motion at the first level; given that motion decreases with age, it is possible that age-related change in activation for incongruent relative to congruent trial types may have been confounded by decreases in motion with age and/or change in motion on some task conditions, which further interacted with age. Third, participants from the two studies performed differently: in the previous study, participants made more mistakes and responded slightly faster; in the current study, participants made fewer mistakes and responded more slowly. This difference in speed-accuracy emphasis may have been due to a pre-scan practice session in which participants in the present study were required to achieve at least 70% accuracy on both incongruent and congruent trial types, which could have influenced the patterns of brain activation that were observed. Finally, the sample size in the previous paper was substantially smaller ($n = 23$ compared to $n = 72$ youth) and, thus, results from the current paper may be more reliable.

Intrinsic connectivity of pMFC and its change with age

The current study is the first to show the development of preSMA-AI/FO connectivity during a cognitive task. Consistent with prior resting-state literature (Fair et al., 2007; Uddin et al., 2011), preSMA connectivity with AI/FO increased with age, from childhood through late adolescence. Both the pMFC (including preSMA) and AI/FO are critical components of the salience network which detects task control demands to engage frontal-parietal mechanisms for attentional and inhibitory control (Menon, 2011; Seeley et al., 2007; Sridharan et al., 2008). Critically, in our sample of youth, age-related increase in preSMA-AI/FO connectivity occurred alongside age-related decrease in preSMA activation to overall task processing. Given age-related improvement in performance among our participants, these reciprocal shifts in connectivity and task-based activation may index the maturation of neural mechanisms that support developmental gains in speed and accuracy in response to task control demands.

Moreover, the coupling of age-related increases in connectivity with decreases in activation suggests increased efficiency of the salience network in mediating task control demands. With age, the salience network may become more integrated, enabling lesser activation of the preSMA (i.e., increased efficiency). That is, in response to task control demands, younger children may rely on greater engagement of the preSMA, while older children may be able to achieve the same level of performance with less activation due to a more integrated preSMA-AI/FO defined salience network.

In addition to age-related increase in preSMA-AI/FO connectivity, age-related decreases of preSMA with pre- and post-central gyri were noted to occur, independent of behavior performance. These results are consistent with previous reports showing that mutual influences between networks decrease with age, while within-network connectivity increases with age (Fair et al., 2007; Stevens et al., 2009).

Limitations

The current study is among the largest ($n = 72$ for the primary analyses) to examine developmental changes in task control function and the first to consider age-related changes in the connectivity of the salience network during task control demands. Nonetheless, there are important limitations of the study that bear consideration. For example, the current study included participants ranging in age from 8 to 19 years old, but the development of task control function begins earlier and continues later into life course (Best and Miller, 2010). Future work should include younger and older participants to further examine linear and non-linear trajectories of activation and functional connectivity in response to task control demands. In addition, a limitation of the study is its cross-sectional design; future longitudinal study will be needed to map the development of pMFC function and connectivity within individuals, over time. Ideally, such work will consider a variety of cognitive tasks to tease apart the relative characteristics of brain activation and connectivity during task-general processes (i.e., across more and less difficult task components and across different tasks) relative to specific task processes (i.e., cognitive interference compared to response inhibition) to more fully characterize the contribution of individual brain regions (e.g. pMFC) and more broadly distributed networks (e.g., pMFC-AI/FO salience network) to the development of capacity for task control.

Conclusions

This study examined the effects of age on brain activation and connectivity during a cognitively demanding interference task. Whole brain analyses revealed differential effects of age on activation in two pMFC sub-regions, the preSMA and dACC, across both high and low interference conditions. These effects were observed for overall task processing (i.e., task general demands), but not for interference or error processing (i.e., task specific demands). Age-related decreases in activation were observed in preSMA, whereas non-linear effects of age were demonstrated in dACC. In addition, age-related increases in preSMA connectivity with AI/FO were observed. Age-related improvements in performance (faster reactions times, greater accuracy across high- and low- interference trial types) were

also observed, suggesting that these age-related changes in activation and connectivity may support the maturation of capacity for task control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- This study examined linear and non-linear effects of age on whole brain activation during task control demands, revealing distinct patterns of development in sub-regions of the posterior medial frontal cortex (pmFC), the pre-supplementary motor area (preSMA) and dorsal anterior cingulate cortex (dACC).
- In the preSMA, activation decreased with age. In the dACC, activation followed a U-shaped trajectory in relation to age, decreasing from childhood (8 years) through mid-adolescence (~14 years), but then increasing from mid- to late adolescence (19 years).
- Effects of age on whole brain connectivity of these pmFC sub-regions were also tested, revealing age-related increases in preSMA connectivity with anterior insula/frontal operculum (AI/FO).

a) Overall Reaction Times

b) Overall Accuracy

Fig.1.

Linear effect of age on a) overall reaction times, and b) overall accuracy in MSIT.

Fig.2.

Brain activation for a) interference processing (IC versus CC) and b) overall task processing (IC plus CC against implicit baseline). Data are presented at height threshold of $p < 0.05$ (corrected for familywise error). The color bar shows t scores, reflecting the relative strength of brain activation in interference and overall task processing. A, anterior; P, posterior; L, left; R, right; IC, incongruent trials; CC, congruent trials; x, y, z, MNI coordinates.

Fig. 3.

Linear and non-linear effects of age were regressed on whole brain activation for overall task processing (IC plus CC against implicit baseline), revealing a) a negative linear effect of age in the preSMA (red) and non-linear effect (positive quadratic) of age in the dACC (yellow). The overlap of these age effects is displayed in green. Whole brain analyses are displayed at a height threshold of $p < 0.005$ uncorrected; cluster volumes for linear and non-linear effects (preSMA and dACC, respectively) were significant at a threshold of $p < 0.05$, correcting for false discovery rate across the whole brain. Contrast estimates from age-defined preSMA and dACC regions, as revealed in the whole brain analyses, were extracted and plotted against age to visualize the b) negative linear effect of age in the preSMA and c) the positive quadratic effect of age in the dACC. A, anterior; P, posterior; L, left; R, right; x, y, MNI coordinates.

Fig. 4.

(a) Intrinsic positive connectivity of preSMA and (b) dACC across whole brain. Data are presented at a peak threshold of $p < 0.05$ (corrected for familywise error). Seed regions for preSMA and dACC were defined by negative linear and positive quadratic effects of age on brain activation during overall task processing. The color bar shows t scores, reflecting the relative strength of positive connectivity with each voxel in the brain. A, anterior; P, posterior; L, left; R, right; x, y, z, MNI coordinates.

Fig. 5.

Pre-supplementary motor area (preSMA) positive connectivity with bilateral anterior insula/ frontal opercular increased with age, whereas preSMA connectivity with right pre- and post-central gyrus decreased with age. The color bar shows t-scores, reflecting the relative strength of age effects on preSMA connectivity with specified brain regions when covarying overall RT; red indicates increasing connectivity with age, while blue indicates decreasing connectivity with age. Age effects are independent of behavioral performance. A, anterior; P, posterior; L, left; R, right; x, y, MNI coordinates.

Table 1

Demographics (age, gender and SES) and number of trials by condition for participants included in the primary analysis.

	Age Range (years)					
	8–9.99	10–11.99	12–13.99	14–15.99	16–17.99	18–19.99
Male (n)	5	9	5	7	6	8
Female (n)	4	7	5	7	5	4
SES (mean(std))	2.6(0.7)	2.1(0.5)	2.2(0.3)	2.2(0.4)	2.4(0.5)	2.1(0.3)
#IC (std)	101.6(12)	111.1(3.5)	108.6(9.0)	104.6(8.8)	109.7(7.0)	113.2(5.0)
#CC (std)	114.4(8)	117.9(7.3)	119.2(0.8)	117.5(2.4)	119.5(1.0)	118.8(1.4)

SES, social economic status, measured by Hollingshead (1975). Std, standard deviation. #CC (congruent correct) and # IC (incongruent correct) refer to the number of each trial type included in analyses.

Brain regions showing effects of age on task-related activation, without (on the left) and with (on the right) overall RT covariate.

Table 2

Effect of Age	Without Performance			With performance		
	Cluster ^a	Coordinates ^b	Z-scores	Cluster ^a	Coordinates ^b	Z-scores
<u>Linear, negative</u>						
PreSMA (6)	140	-6, 14, 46	4.24	1707	-6, 17, 49	4.39
Caudate/putamen	587	-15, 11, 10	3.91		27, 8, 10	3.77
<u>Linear, positive</u>						
Left post-central gyrus (40)	147	-45, -37, 49	3.94			
<u>Quadratic, positive</u>						
dACC (24)	253	6, 8, 31	3.95	418	6, 8, 31	4.19

Height threshold: $p < 0.005$ uncorrected.

^aCluster threshold: $pFDR < 0.05$, whole brain search.

^bRepresentative peak coordinates, x, y, z. PreSMA, pre-supplementary motor area; dACC, dorsal anterior cingulate cortex; FDR, false discovery rate.

Table 3

Positive connectivity of preSMA: linear effects of age, with and without performance covariate (overall RT).

Region (Brodmann Area)	Without Overall RT Covariate			With Overall RT Covariate		
	Cluster ^a	Coordinates ^b	Z scores	Cluster ^a	Coordinates ^b	Z scores
<u>Positive effect of age</u>						
Right AI/FO (47)	209	48, 38, -8	4.66	209	48, 41, -8	4.39
Left AI/FO (47)	81	-42, 56, -5	3.99	258	-48, 23, -5	4.90
	82	-48, 26, -5	3.56			
Perigenual ACC/superior medial frontal (8/10)	206	-6, 35, 34	3.74			
Right middle temporal (21)	97	60, -22, -11	3.80			
<u>Negative effect of age</u>						
Right post-central (2)	458	48, -25, 58	5.04	326	48, -25, 55	4.88
Right pre-central (6)		39, -13, 67	4.06		39, -16, 67	3.65
Left post-central (2)	499	-36, -31, 67	4.62			
Left pre-central (6)		-33, -13, 64	3.94			
Right lingual gyrus (18)	115	24, -79, -2	3.81			
Left superior occipital (19)	81	-18, -85, 22	3.70			

NOTE: the pre-supplementary motor area (preSMA) was defined by linear effects of age on task-based activation in whole brain analyses. Height threshold: $p < 0.005$ uncorrected.

^aCluster threshold: $pFDR < 0.05$, whole brain search.

^bRepresentative peak coordinates, x, y, z. AI/FO, anterior insula/frontal opercular; FDR, false discovery rate.

Table 4

Positive connectivity of dACC: Linear effects of age, with and without performance covariate (overall RT).

Region (Brodmann Area)	Without Overall RT Covariate			With Overall RT Covariate		
	Cluster ^a	Coordinates ^b	Z scores	Cluster ^a	Coordinates ^b	Z scores
<u>Positive effect of age</u>						
rACC (32)	108	6, 29, 25	3.26			
Precuneus (7)	119	6, -49, 52	3.28			
Right Inferior frontal Orbital (47)	107	21, 17, -20	4.41			
<u>Negative effect of age</u>						
Left middle occipital (19)	163	-39, -76, 34	3.81			
Right hippocampus	109	30, -16, -14	3.46			

NOTE: the dorsal anterior cingulate (dACC) was defined by non-linear (i.e., positive quadratic) effects of age on task-based activation in whole brain analyses. rACC refers to rostral anterior cingulate cortex. Height threshold: $p < 0.005$ uncorrected.

^aCluster threshold: pFDR < 0.05, whole brain search.

^bRepresentative peak coordinates, x, y, z. RT, response times.