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Conflict Processing Across Development: The Progression of Response Inhibition Networks

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Abstract

Cognitive control processes allow individuals to guide their behaviour in the face of distracting or irrelevant stimuli, and typically continue developing into early adulthood. These processes are often tested using response inhibition paradigms such as the size congruency task, which require participants to select between conflicting responses. Previous studies have shown that activity in the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) parallels the protracted development of cognitive control. Recent evidence suggests that children and adolescents may rely on more subcortical regions such as the cerebellum to process conflict. The present study aimed to comprehensively investigate activity in the DLPFC, ACC, and cerebellum during response inhibition across developmental stages, thereby proposing conflict processing neural pathways utilized at various developmental stages. Five children, five adolescent and five adult participants completed a size congruency task while undergoing fMRI scanning. Incongruent trials (25%) elicited conflict processing. Incongruent-congruent contrasts were averaged within groups and compared across groups via visual inspection. While small regions of unilateral DLPFC activity were measured for children and adolescents, adults showed large regions of bilateral DLPFC activity. Children and adolescents showed no ACC activity while adults exhibited bilateral ACC activity. Children showed more widespread cerebellar activity compared to adolescents and adults. In light of these results and recent research findings, we propose a DLPFC-cerebellar conflict processing network in children, with the cerebellum performing conflict resolution by cancelling an ongoing but incorrect motor program. Adults are suggested to utilize a DLPFC-ACC network, where the ACC suppresses a prepotent response before it is initiated. Adolescents show evidence of activity in both networks. Future studies should focus on how conflict processing develops as a network, rather than identifying localized regions of development.

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Conflict processing across development: The progression of response inhibition networks

Executive functioning, also known as cognitive control, is a set of higher level cognitive processes that allow individuals to voluntarily guide their behaviour. Specifically, these processes facilitate behavioural guidance in the face of distracting or irrelevant stimuli. Cognitive control encompasses a range of abilities, including: problem solving, task flexibility, working memory and the planning and execution of goal-directed behaviour.

Disparities in ability to apply cognitive control have been well documented across developmental stages. Behavioural studies have reliably demonstrated a linear trajectory of development from childhood to adulthood^{1,2}. Thus, although other aspects of development (such as motor coordination) may reach full maturation by adolescence, development of cognitive control is protracted and does not typically become fully realized until early adulthood¹. One major facet of cognitive control ability is response inhibition: the ability to stop an ongoing, inappropriate, or dominant response. Improper development of response inhibition has been associated with detrimental health outcomes including development of Tourette's syndrome and obsessive compulsive disorder⁴.

Several tests have been developed to probe response inhibition, including the go/no-go task⁵ and the Stroop task⁶. Some modified versions of these assessments have been created to account for the measured limitations in young children's cognitive control abilities. For example, the day-night Stroop task is a simplified task used to test response inhibition in young children⁷. Response inhibition paradigms often involve conflict monitoring and processing, as they require selection of two competing or conflicting responses⁸. One common response inhibition and conflict monitoring paradigm is the size-congruency task⁹. In this task, participants are required to select the numerically larger number in a pair where one number is physically larger than the other. Conflict processing abilities are most often tested with trials in which the numerically larger digit

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is physically smaller¹⁰. This paradigm has been used successfully to measure cognitive control from a wide variety of age ranges including children as young as six years of age¹¹.

An abundance of neuroimaging studies employing response inhibition paradigms have revealed regions associated with cognitive control and its development. Areas found to be robustly associated with exertion of cognitive control include the dorsolateral pre-frontal cortex (DLPFC) and the anterior cingulate cortex (ACC).

Several studies have implicated the DLPFC in application of cognitive control, specifically in aspects such as perceptual decision making¹², planning of responses¹³ and manipulating information in working memory¹⁴. Further, a lesion study performed on monkeys found that DLPFC was involved in conflict-induced behavioural adjustments during a cognitive control task¹⁵.

Previous research has shown that the ACC is involved in error detection and conflict monitoring. Researchers have shown that the ACC contributes to cognition by detecting conflicts that might occur during information processing, and once a conflict is encountered, the ACC signals the need to engage in top-down attentional processing^{8,16}.

Neuroimaging studies have shown that development of DLPFC and ACC activity parallels the protracted development of cognitive control. For example, a study by Crone et al. in 2006 found that children had no measureable activity in DLPFC while performing a cognitive control task. In the same study, adolescents displayed only low levels DLPFC activity compared to adults¹⁷. Children and adolescents have also been found to have significantly reduced ACC activity in response to cognitive control tasks compared to adult ACC activation levels¹⁸.

Recently, researchers have focused on expanding their understanding of the roles of other regions in conflict-involving paradigms, especially the cerebellum. In 2007, Schweizer et al. completed a study in which they investigated conflict resolution abilities of individuals with

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cerebellar lesions. Their results indicated that the cerebellum plays a role in conflict resolution and has an important role in coordinating with other active cortical areas during such tasks¹⁹. Another study by Rubia et al. investigated inhibitory control between late-childhood/adolescents and adults. The results of their investigation suggested that, as expected, when performing an inhibitory control task, adults exhibited activation in the prefrontal cortex and ACC. Children and adolescents, on the other hand, displayed activation in fronto-striatal-thalamic and fronto-cerebellar neural pathways rather than in the prefrontal areas¹⁸. This line of evidence appears to suggest that children and adolescents may rely on more subcortical regions such as the cerebellum to monitor and process conflict during cognitive control tasks.

The goal of the present study is to comprehensively investigate activity in the DLPFC, ACC, and cerebellum during response inhibition across developmental stages; inasmuch, we aim to propose neural pathways used by individuals at various developmental stages to deal with conflict processing. To achieve this objective, the present study will investigate response inhibition in a group of children, adolescents and adults using a size congruency task. The DLPFC and ACC have been shown to be involved in response inhibition and conflict processing and are known to have protracted development. Therefore, we predict that adults will show robust activity in the DLPFC and ACC. Adolescents are expected to show moderate levels of activation in DLPFC and ACC, and children are expected to have little to no activity in DLPFC and ACC. Studies have also shown a role for the cerebellum in conflict processing, but more so in children and adolescents than adults. Therefore, we hypothesize that children will display robust cerebellar activity. Adolescents are expected to show moderate cerebellar activity, while adults are expected to show low levels of activity in the cerebellum.

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Method

Participants

Participants included five children (aged 9 to 12 years), five adolescents (aged 13 to 17 years) and five adults (aged 18+). Participants younger than 18 years of age ($n = 10$) were recruited from the institution's Child Development Participant Pool and underwent a practice scanning session in a mock scanner (0 Tesla) prior to testing. The mock session was used to alleviate fear and uncertainty regarding scanning procedures and to help participants practice stillness during testing. Participants under age 18 gave verbal assent to participate, and a legal parent or guardian gave written consent for participation. Participants 18 years of age and older ($n = 5$) were recruited from the institution's undergraduate and graduate student populations and provided written consent prior to participation. All participants had normal or corrected-to-normal vision and were right handed. All procedures were approved by the local Research Ethics Board and were in accordance with the 1964 Declaration of Helsinki.

Data Acquisition

Data were collected using a 3 T Siemens Tim Trio MRI system fitted with a Siemens 32-channel head coil (Erlangen, Germany). One structural (anatomical) T1-weighted scan was collected. The anatomical scan was comprised of 192 slices of 1 mm thickness, with a 1 mm^3 spatial resolution. Two functional runs consisting of 234 whole-brain volumes were collected from each participant. Functional volumes consisted of 32-slices with a thickness of 3 mm, yielding a 3 mm^3 voxel resolution. T2*-weighted functional volumes were collected in an ascending interleaved order using an echo-planar imaging sequence (TR = 2000 ms; TE = 30 ms; flip angle = 78°). There were no gaps between slices.

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Task

Participants were administered a size-congruency task⁹. On each trial, two Arabic digits were presented on a computer screen back-projected into the MRI scanner (E-Prime software, Psychology Software Tools, Inc). Participants viewed the stimuli through a mirror attached to the head coil. The two digits differed in both physical size (one digit presented in 60-point font, the other in 30-point font) and numerical magnitude (digits ranged from 1 to 9). The digits were simultaneously presented for 1950 ms, in white on a black background (see Fig. 1). One digit was presented to the left of screen centre while the other digit was presented to the right. Trials in which the numerically larger number was also physically larger were considered compatible trials. Incompatible trials were those in which the numerically larger digit was physically smaller. Participants were asked to select the numerically larger digit using a button box held in their right hand. To select the digit on the left side of the screen, participants pressed a button with their right index finger and to select the digit on the right side of the screen, participants pressed a button with their right middle finger.

Stimuli were administered in seven blocks, each containing 16 trials. For each block, 75% (12 of 16) of stimuli were compatible, while 25% (4 of 16) were incompatible. The ordering of trials was fixed for all participants and all start trials presented incompatible stimuli. Three start trials were added at the beginning of the session to establish expectations about the frequency of compatible stimuli. These trials were not included in subsequent analyses. Digits were not repeated in adjacent trials, to avoid potential repetition effects. Individual trials were randomly jittered by means of an inter-trial interval ranging from 1500 ms to 4500 ms ($M = 3000$ ms). During all inter-trial and inter-block intervals, participants remained fixated on a centrally presented white cross. Participants each completed two separate, 7.8-minute runs.

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Data Preprocessing

All data processing and analysis were carried out using Statistical Parametric Mapping, version 8 (SPM 8), run within MATLAB 2010. Motion was confined to 3.0 mm and 3.0 degrees within each run. Consequently, one child run (participant PK42) was excluded from further analyses. Motion correction was subsequently applied within subjects, correcting each functional volume to the first volume of the first run. T2*-weighted functional volumes were warped to Montreal Neurological Institute (MNI) stereotactic space following alignment with the T1-weighted anatomical scans (within subjects). An 8mm full-width at half maximum Gaussian smoothing kernel was applied to all functional volumes.

Single Subject Analysis

Three MATLAB scripts were run to perform first level, single subject analysis. The first script collected behavioural data for use in subsequent scripts by extracting onset time of the incongruent and congruent stimuli. Onset times for one child participant (PK16) were compromised during data conversion; data from this participant were excluded from further analyses. The second script was used to create the design matrix, which calculated the beta coefficients for all data predictors. Several variables were used to predict observed variability within a single voxel over time. The predictors utilized were congruent stimuli, incongruent stimuli, and the six realignment parameters utilized during preprocessing (x plane, y plane and z plane transformations as well as roll, pitch and yaw rotations). This test was performed successively for all voxels. The final script computed the incongruent-congruent contrast for all voxels, using beta coefficients extracted from the second script. The beta coefficients for these two predictors were used to compute a t-statistic for each voxel. These t-tests were used to indicate which brain regions were activated in response to incongruent stimuli. Activity measured during the congruent trials served as a control condition.

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Group Analysis

Incongruent-congruent contrasts for each voxel were compared across participants of each age group. Data were compared separately across the five adult, five adolescent and three child participants. As age was not used as a regressor in this analysis, all following comparisons made regarding differences in brain activation between groups are based on visual inspection alone. An alpha level of 0.05 was used for all group analyses. No further statistical thresholds or corrections were employed due to inherently low statistical power.

Results

All reported MNI coordinates for activated brain regions represent peak voxel activity in the cluster of interest and are presented as (x coordinate, y coordinate, z coordinate).

Dorsolateral Prefrontal Cortex (DLPFC)

Significant activation was found in the right DLPFC for children [(42, 28, 48), $T = 52.87$, $p < .001$; see Fig. 2A], adolescents [(44, 20, 54), $T = 26.89$, $p < .001$; see Fig. 3A], and adults [(34, 26, 42), $T = 15.54$, $p < .001$; see Fig. 4A]. Significant activation was also found in the left DLPFC, but only for adults [(-36, 10, 40), $T = 6.62$, $p = .001$; see Fig. 4B]. Visual analysis showed clusters of right hemisphere DLPFC activity were of approximately equal size for children and adolescents but much larger for adults.

Intraparietal Sulcus (IPS)

Significant activation was found in the left IPS for children [(-32, -66, 36), $T = 61.05$, $p < .001$; see Fig. 2B], adolescents [(-32, -80, 50), $T = 23.33$, $p < .001$; see Fig. 3B], and adults [(-48, -56, 52), $T = 6.21$, $p = .002$; see Fig. 3C]. Significant activation was also found in the right IPS for children [(38, -78, 46), $T = 29.37$, $p = .001$; see Fig. 2C], adolescents [(38, -54, 36), $T = 10.40$, $p < .001$; see Fig. 3C], and adults [(42, -66, 36), $T = 6.77$, $p = .001$; see Fig. 4D]. Visual analysis

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revealed that bilaterally, clusters of IPS activity were of approximately equal size for adolescents and adults, but much smaller for children.

Cerebellum

Significant activation was found in the left lateral superior cerebellum for children [(-38, -86, -24), $T = 55.06$, $p < .001$; see Fig. 2D], adolescents [(-28, -44, -22), $T = 3.00$, $p = .020$; see Fig. 3D], and adults [(-32, -48, -28), $T = 15.63$, $p < .001$; see Fig. 4F]. Significant activation was also found in the right lateral superior cerebellum for children [(34, -52, -24), $T = 32.45$, $p < .001$; see Fig. 2E], and in the medial cerebellum for adults [(2, -58, -26), $T = 26.64$, $p < .001$; see Fig. 4E]. Visual analysis showed clusters of left cerebellar activity were of approximately equal size for children and adults but much smaller for adolescents. It can also be seen that there are more clusters of cerebellar activity for children than adults, and these clusters are more widespread across the cerebellum.

Anterior Cingulate Cortex (ACC)

Significant activation was found in the right [(6, 22, 16), $T = 6.00$, $p = .002$; see Fig. 4G] and left [(-4, 20, 20), $T = 5.84$, $p = .002$; see Fig. 4H] ACC for adults only. Both children and adolescents displayed no ACC activity during incongruent versus congruent trials.

Discussion

The current study investigated brain activity associated with the exertion of cognitive control across development. Specifically, patterns of activation associated with conflict monitoring and response inhibition were examined in late childhood, adolescence and adulthood through application of a size congruency paradigm. Based on previous findings, it was hypothesized patterns of activity for each developmental stage: we hypothesized adults to show robust DLPFC and ACC activity, and low cerebellar activity; adolescents to exhibit moderate levels of DLPFC,

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ACC and cerebellar activity; and children to show little DLPFC and ACC activity, but high levels of cerebellar activity.

Although not hypothesized, our results showed activity bilaterally across all groups in the IPS. Previous research has implicated the IPS in aspects of numerical processing such as perception and manipulation of quantity²⁰ and accurate magnitude comparisons²¹. Moreover, while only the left IPS was originally thought to be involved in numerical calculations²⁰, neuroimaging studies have shown that both right and left IPS are involved in number processing²². In a size-congruency task, congruent stimuli essentially only require processing of the physical size of the digit. Therefore, congruent trials require more visual discrimination than numerical discrimination and do not induce IPS numerical processing activity. On incongruent trials, however, numerical magnitude processing must be carried out to override the dominant response towards the physically larger stimulus, which therefore elicits IPS activity⁹. The current study also found differences in IPS activity cluster sizes, with children having much smaller regions of activity compared to adolescents and adults. These findings support those of other functional neuroimaging studies, which have found that IPS activity in response to numerical magnitude computation tasks increases across development²³.

While it was hypothesized that activity in DLPFC would be minimal for children, moderate for adolescents and high for adults, results of the current study displayed significant levels of DLPFC activity for all participant groups. Only adults, however, showed bilateral DLPFC activity, and the cluster of DLPFC activity was much larger for adults than for the children and adolescents. In terms of ACC activity, the results of the current study supported the hypothesis, with children and adolescents showing no ACC activity and adults exhibiting bilateral ACC activity in response to incongruent stimuli. The DLPFC and ACC are theorized to be a two-part cognition system involved in the regulation of cognitive control¹³. Previous research has shown that the DLPFC is

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involved in certain aspects of cognitive control tasks, such as manipulating information with regard to a rule held in working memory¹⁴. The ACC has been shown to be involved with slightly different aspects, such as dealing with conflicting information¹⁶. Accordingly, MacDonald et al. (2000) have suggested that in cognitive control tasks, the DLPFC actually implements control while the ACC monitors performance, and signals the DLPFC when further adjustments to control are required¹³. Multiple theories have been put forth to explain the developmental differences in activity levels within this cognitive control system. Firstly, children are known to simply perform more poorly than adolescents and adults on cognitive control tasks²⁴. Thus, it has been hypothesized that this difference in activation represents a behavioural or performance difference between children and older individuals. Another theory posits that children and adolescents use a different strategy than adults for handling incongruent stimuli in tasks such as the size-congruency paradigm²⁵. It is proposed that as individuals age, they develop a prospective mode of control used to maintain attention-guiding rules across a task, which involves use of the DLPFC to maintain the task goal and the ACC to monitor and deal with incongruent stimuli when they appear²⁶.

Another explanation for developmental differences in activation of the DLPFC-ACC cognitive control system could involve differences in cerebellar activity across development. To date, cerebellar activity measured during cognitive control tasks has largely been left uninterpreted. Only relatively recently has the role of the cerebellum in cognitive control been investigated. Two previous studies by Rubia et al. (2007) and Schweizer et al. (2007) have implicated the cerebellum in conflict processing and resolution, specifically in younger individuals who do not show fully developed ACC activation in response to incongruent stimuli. The findings of the present study indicated more concentrated cerebellar activity in adolescents and adults, and more widespread cerebellar activity in children. The cerebellum is widely known to play a role in fine-tuning and adjusting motor responses²⁷. In light of these results, we propose that the

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cerebellum is able to perform conflict resolution by cancelling an ongoing but incorrect motor program. In contrast, we suggest that the ACC is able to mediate conflict by suppressing prepotent responses before an incorrect motor program can be put into action. When adults encounter an incongruent trial, the ACC and connected prefrontal regions are able to suppress the prepotent response of reacting to the physically larger stimulus, and select the proper motor program for responding to the numerically larger stimulus. When children encounter an incongruent trial, the lack of ACC-prefrontal development results in the initial selection of an incorrect motor program. If the motor program were carried out, it would lead the child to incorrectly respond to the physically larger, but numerically smaller, number. The cerebellum, through connections to the frontal lobe¹⁸, is able to cancel the incorrect motor program and allow for the generation of a new, correct motor response. Over time, as the ACC becomes more developed, there is less reliance on the cerebellum for conflict resolution as the ACC becomes more fully developed and is able to perform this function more effectively. In summary, we propose that adults utilize a DLPFC-ACC network during conflict processing tasks, whereby the DLPFC selects the correct response and the ACC inhibits the prepotent but incorrect response. In contrast, children use a DLPFC-cerebellar network during such tasks, where the DLPFC initially selects the incorrect prepotent response, without the necessary ACC activity to inhibit that response. In turn, the cerebellum cancels the incorrect response selected by the DLPFC, allowing it to properly respond in the face of conflict. Adolescents likely exhibit activity in both networks, relying more on the efficient DLPFC-ACC network as they develop.

One limitation of the current study was that behavioural data such as error rates and response times were not investigated. In future studies examining behavioural data, it would be expected that the children would have longer response times, even if their error rates were comparable to adults and adolescents. If our theory is correct, this would occur because the

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cerebellum is only able to cancel incorrect motor programs after they have been initiated, while the ACC is able to stop incorrect motor programs from being put into action. After cancellation of an incorrect response, a new motor program must be generated and executed, which would take more time than simply executing a correct response. Thus, the children (with no ACC activity and widespread cerebellar activity) would be expected to show longer response times than the adults (with significant ACC activity and smaller clusters of cerebellar activity).

Another limitation of the current study is that the effects of previous trials were not investigated. Previous research has identified that for adults and adolescents, cortical responses to incompatible trials differed when preceded by an incompatible versus compatible trial. Children's responses, however, did not vary based on preceding trial type²⁶. This suggests that children may adopt a different mode of control than adults and adolescents to handle incompatible stimuli²⁸. Very few studies have investigated this effect and of those that have, subcortical activation has remained largely uninterpreted. The current study has outlined the importance of interpreting activity in subcortical areas. Future researchers may consider including previous trial identity in analysis of developmental changes in cognitive control, in order to evaluate the combined effects of cortical and subcortical regions on development of a different modes of control. Finally, future studies should consider including larger populations to improve statistical power.

The results of the current study, with regard to findings for the DLPFC and ACC, have reinforced the theory of protracted prefrontal cortex development from children to adolescents to adults. Understanding proper development of cognitive control allows for better understanding of developmental deficits, as seen in disorders such as obsessive compulsive disorder and Tourette's syndrome⁴. The results for cerebellar activity also have wide implications for the field of psychiatry. Despite originally being believed to only play a role in motor functions, studies have now shown several non-motor roles for the cerebellum^{29,30}. Recent evidence has implicated

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cerebellar pathology in various developmental and neurological conditions including attention deficit hyperactivity disorder³¹, Tourette's syndrome³² and autism³³. Increased knowledge of the role of the cerebellum in executive functioning and cognitive control, in general, will likely aid in further understanding of the neuropathology of these disorders and may even reveal new therapeutic targets. Finally, the results of the present study suggest a discrepancy in neural pathways underlying response inhibition across developmental stages. While acknowledging that all results presented are based on visual assessment, these findings warrant further investigation into how conflict processing develops as a network, rather than as localized regions of development. Many previous studies have focused on localization of neural regions involved in exerting cognitive control^{8,13}. However, as the field of neuroscience leans more towards understanding cognitive processing through network activity³⁴, future studies should consider focusing on studying the pathways underlying conflict processing. The results of a similar study conducted on a larger sample may aid in understanding how cognitive control pathways develop, eventually helping researchers treat various disorders associated with improper cognitive control.

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Figures

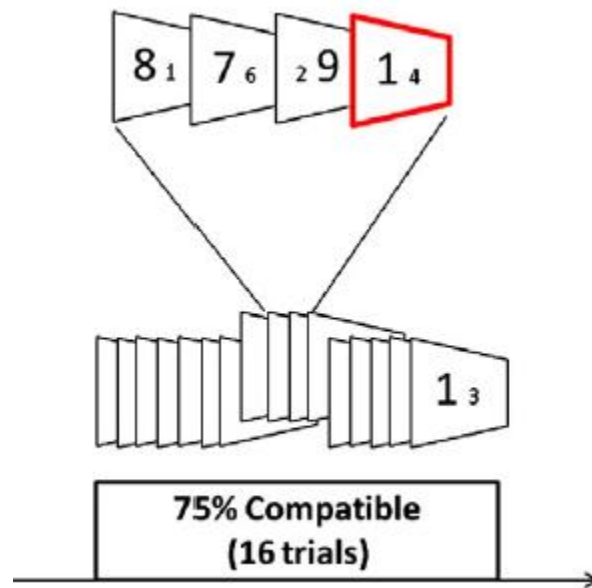


Figure 1. Size-Congruency Task³⁵ (Wilk & Morton, 2012). Figure replicated with authors' permission. Two Arabic digits were presented side by side, differing in numerical and physical magnitudes. Participants were asked to select the numerically larger digit. Twenty five percent of trials were incompatible, in which the numerically larger digit was physically smaller.

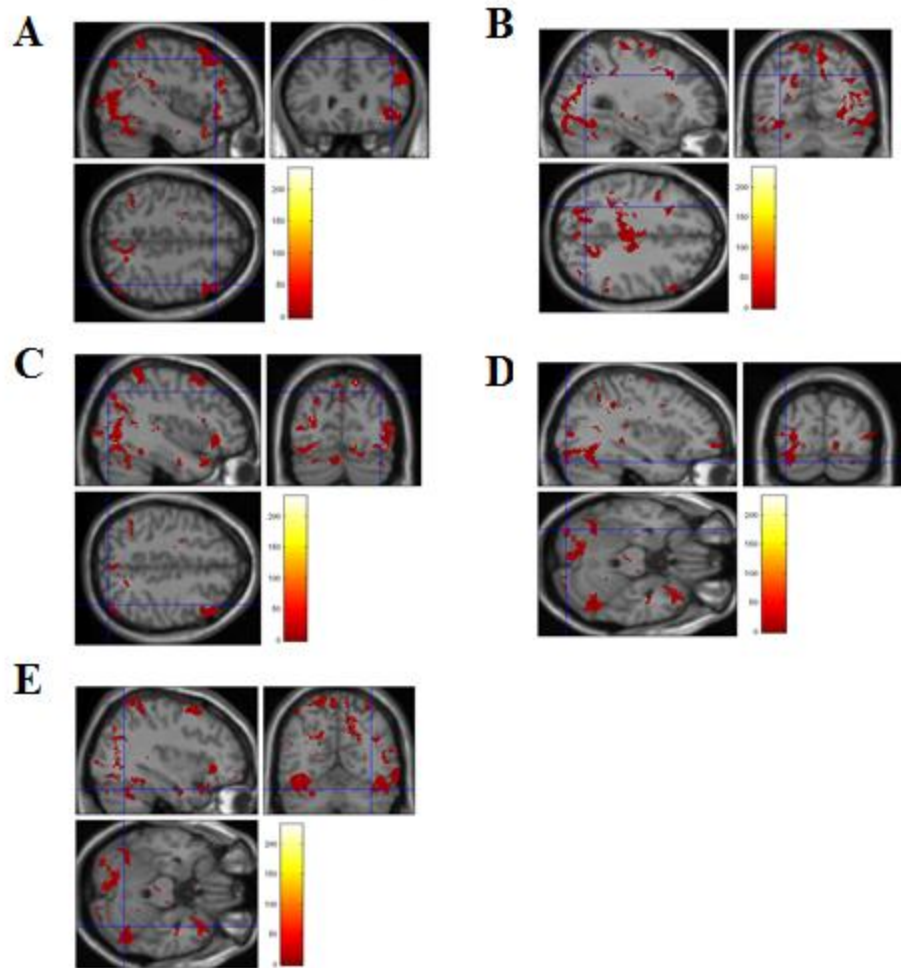


Figure 2. Activation in Children. Activation in response to incongruent stimuli for participants aged 9-12 years ($n = 3$). Child participants exhibited activation in (A) the right dorsolateral prefrontal cortex, (B) the left inferior parietal sulcus, (C) the right inferior parietal sulcus, (D) the left lateral and medial superior cerebellum, and (E) the right lateral superior cerebellum.

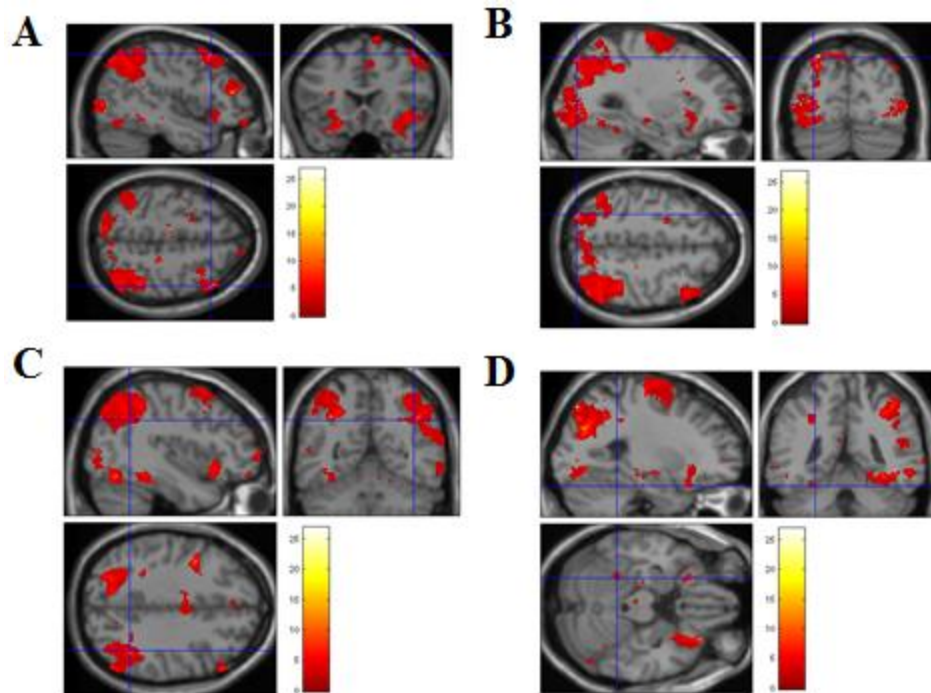


Figure 3. Activation in Adolescents. Activation in response to incongruent stimuli for participants aged 13-17 years ($n = 5$). Adolescent participants exhibited activation in (A) the right dorsolateral prefrontal cortex, (B) the left inferior parietal sulcus, (C) the right inferior parietal sulcus, and (D) the left lateral superior cerebellum.

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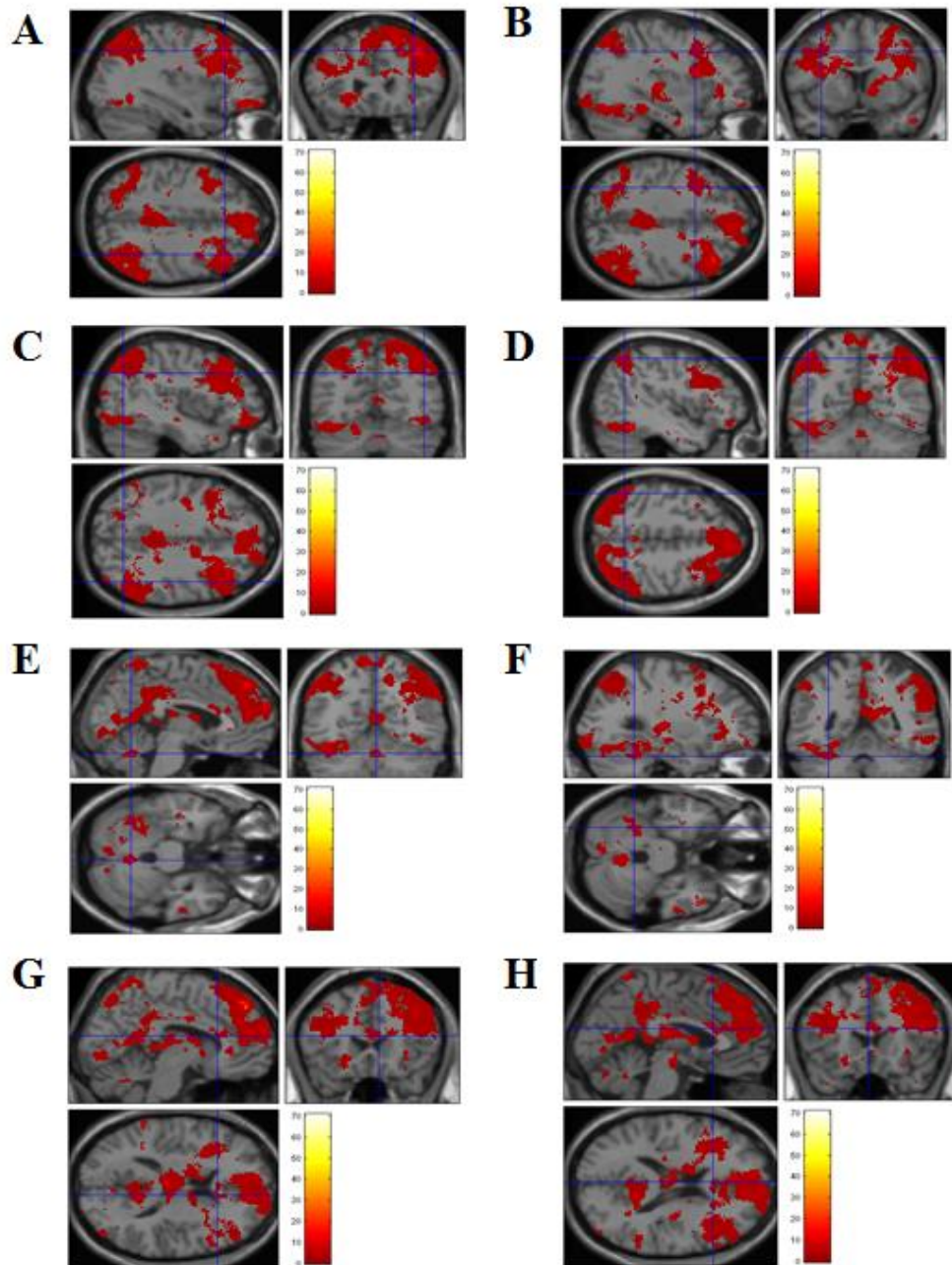


Figure 4. Activation in Adults. Activation in response to incongruent stimuli for participants aged 18 years or older ($n = 5$). Adult participants exhibited activation in (A) the right dorsolateral prefrontal cortex, (B) the left dorsolateral prefrontal cortex, (C) the right inferior parietal sulcus, and (D) the left inferior parietal sulcus, (E) the medial cerebellum, (F) the left lateral superior cerebellum, (G) the right anterior cingulate cortex, and (H) the left anterior cingulate cortex.

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Tables

Region	Hemisphere	Peak Coordinates			<i>T</i>	<i>P_{uncorr}</i>
		MNI X	MNI Y	MNI Z		
DLPFC	R	42	28	48	52.87	< .001
IPS	L	-32	-66	36	61.05	< .001
IPS	R	38	-78	46	20.37	.001
Cerebellum	L	-38	-86	-24	55.06	< .001
Cerebellum	R	34	-52	-24	32.45	< .001

Table 1. Peak Activation – Children.

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Region	Hemisphere	Peak Coordinates			<i>T</i>	<i>P_{uncorr}</i>
		MNI X	MNI Y	MNI Z		
DLPFC	R	44	20	54	26.89	< .001
IPS	L	-32	-80	50	23.33	< .001
IPS	R	38	-54	36	10.40	< .001
Cerebellum	L	-28	-44	-22	3.00	.020

Table 2. Peak Activation – Adolescents.

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Region	Hemisphere	Peak Coordinates			<i>T</i>	<i>P_{uncorr}</i>
		MNI X	MNI Y	MNI Z		
DLPFC	R	34	26	42	15.54	< .001
DLPFC	L	-36	10	40	6.62	.001
IPS	R	42	-66	36	6.77	.001
IPS	L	-48	-56	52	6.21	.002
Cerebellum	M*	2	-58	-26	26.64	< .001
Cerebellum	L	-32	-48	-28	15.63	< .001
ACC	R	6	22	16	6.00	.002
ACC	L	-4	20	20	5.84	.002

**M* refers to medial

Table 3. Peak Activation – Adults.