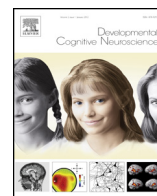




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Neural mechanisms of inhibitory control continue to mature in adolescence



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ABSTRACT

Inhibition is a fundamental executive function necessary for self-management of behaviour. The ability to withhold prepotent responses shows protracted development, extending through childhood and into adulthood. Using magnetoencephalography (MEG) with co-registered MRI, the spatiotemporal neural processes involved in inhibitory control were examined in 15 adolescents and 15 adults during a Go/No-go task. Two tasks were run that contained inverse ratios of Go to No-go trials for the experimental (2:1) and control conditions (1:2). Using vector beamforming, images of neural activation between No-go and Go trials were compared for both age-groups and revealed recruitment of the right inferior frontal gyrus in adults (BA 45; 200–250 ms), but delayed recruitment of the left inferior frontal gyri in adolescents (BA 45; 250–300 ms). Left anticipatory-related activity near the hand motor region (BA 6) was present in both adolescents and adults, but for a longer duration in adults. Adolescents additionally recruited the right middle and superior temporal gyri (BA21, BA22), while adults engaged the right temporal gyrus (BA41) but for a much briefer duration. These findings of delayed recruitment of canonical inhibitory control areas with supplementary and prolonged involvement of temporal areas in adolescents compared to adults indicate an immature inhibitory network even in adolescence.

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1. Introduction

Executive control involves the planning, management and execution of volitional behaviour. An executive function that is vital for behavioural control is inhibition, which

is the ability to restrain or refrain from a response, such as cancelling planned or ongoing actions or withholding impulsive responses. Inhibition is defined here as the ability to withhold a prepotent response. Intact inhibition ensures that behaviours carried out by an individual are consistent with his/her internal goals and motivation, while irrelevant or inappropriate behaviours are suppressed (Miller and Cohen, 2001). Inhibition is particularly important in adolescence, as this period coincides with increased social awareness, peer-group interactions and responsibility, and inhibitory control plays a critical

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role in these evolving social executive functions in adolescents (Crone et al., 2008; Ellis et al., 2004; Pharo et al., 2011; Vetter et al., 2013). Poor inhibitory skill development impacts negatively on adolescent socialisation processes.

Although impulsivity characterises adolescence (Chambers et al., 2003; Wilson and Daly, 1985), the neural processes that underlie the transition towards lower impulsivity levels of adulthood are not well described. Inhibitory control improves not only through the teenage years, but into adulthood as well (Asato et al., 2006; Leon-Carrion et al., 2004; McAuley et al., 2006; Van Leijenhorst et al., 2010). Inhibition is dependent on the frontal lobes, which undergo protracted development through adolescence into adulthood (Sowell et al., 1999, 2004; Paus et al., 1999), and while inhibitory processes have been reasonably well characterised in adults, this is not the case in adolescents.

One of the most common and well-established paradigms used to investigate the withholding component of inhibition is the Go/No-go task. The simplicity of the Go/No-go task, that requires an all-or-none decision about responding to stimuli, allows inhibition to be measured more directly than other tasks (Rubia et al., 2001). Cognitive theory supporting this task suggests that the required, rapid responses to the repetitive, fast-paced Go trials serves to develop a prepotent tendency to respond, such that a response may be initiated before a No-go stimulus appears. The temporal convergence of the conflicting neural activity underlying the Go and No-go processes results in a successful inhibition if sufficiently biased towards the No-go processes (Miller and Cohen, 2001). As the Go/No-go paradigm is simple to understand, yet can be made challenging by increasing the prepotency of the Go response with a rapid stimulus presentation rate, higher ratio of Go relative to No-go responses and short stimulus durations, it is well suited to examine the developmental trajectory of inhibition.

It is recognised that examining the cognitive transformation occurring from 12 to 19 years is critical to understanding the overall maturation of cognitive abilities (Bunge et al., 2002) and a number of neuroimaging studies have used inhibition tasks to study cognitive development over this period. Activity in the dorsolateral prefrontal region has been reported in fMRI studies in both adults and adolescents (Bunge et al., 2002; Tamm et al., 2002; Vaidya et al., 2005; Konishi et al., 1999; Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001; Wager et al., 2005; Watanabe et al., 2002). Although various studies have reported that younger participants displayed both diffuse, hypo- (Rubia et al., 2007) and hyper- (Velanova et al., 2008; Casey et al., 1997; Tamm et al., 2002) activation compared to older participants, they all found activity related to inhibition predominantly in the prefrontal regions. Activity in the inferior frontal gyri (BA 45/46) has been found to vary with age in a number of different inhibition paradigms, typically associated with increased frontal lobe maturation over childhood and adolescence (Adleman et al., 2002; Bunge et al., 2002; Rubia et al., 2006, 2007; Tamm et al., 2002; Vidal et al., 2012). Thus, imaging research, in addition to cognitive theories, implicates the prefrontal cortex as a crucial player in inhibitory control.

The timing of brain processes associated with inhibition has also been investigated using event related potentials (ERPs). A negative deflection in the No-go ERP waveform around 250 ms, localised to the right lateral orbito-frontal cortex, and a positive inflection at about 365 ms, localised to the left homologous cortical area were found in an ERP study on adults by Bokura et al. (2001). These results were interpreted as an earlier right than left frontal activation for inhibition processing in adults and align with a number of subsequent ERP studies (e.g., Albert et al., 2013; Bruin and Wijers, 2002; Lavric et al., 2004; Smith et al., 2007) that report that the N2 and/or the P3 may be related to inhibition. Magnetoencephalography (MEG) provides not only the temporal resolution of ERPs, but also improved spatial resolution (Hari and Salmelin, 2012).

The advantage of MEG, over the more commonly seen fMRI studies of inhibition, is its millisecond temporal resolution, comparable to ERPs, concurrently with its spatial localisation approaching that of fMRI (Hari and Salmelin, 2012). Although the sensitivity to radial and deep sources is a concern with MEG, there are many studies now showing excellent localisation for such sources with advanced analysis techniques (Hung et al., 2012, 2013; Hamada et al., 2004; Cornwell et al., 2008; Moses et al., 2009); see papers by Sekihara et al. (2005), Quraan and Cheyne (2010) and Quraan et al. (2011) for discussion of methodological considerations in MEG and means of addressing them. Given the importance of rapid brain processes for successful inhibition, as well as the continued changes in processing speed over adolescence, the temporal sensitivity of MEG is critical and a significant advantage over fMRI.

Although a few studies have utilised MEG to investigate aspects of inhibition (e.g., Joliot et al., 2009; Nakata et al., 2005, 2013) and have found consistent evidence of frontal inhibition-related activity, these reports used somatosensory or interference tasks, not the more classic visual Go/No-go tasks, and did not investigate development. Our earlier study, Vidal et al. (2012) examined inhibition-related frontal activation only and found similar results to the literature for the adults, whereas the adolescent group exhibited bilateral frontal activation that was temporally delayed. However, one concern was that the contrasted inhibition and control conditions had different Go/No-go ratios (67%/33% and 93%/7%, respectively), and this maybe have created a stronger 'oddball' effect for the latter; thus, confounding the findings with a larger overlapping P3 response. In the current study, we use the same ratios for both inhibition and control conditions; this increases our ability to investigate the true inhibitory response. Unlike many fMRI studies that contrasted No-go trials to Go trials, introducing the confound of a motor-related brain activity only in the Go trials, our comparison contrasted only the No-go trials in the control and inhibition runs, thus avoiding the motor activity confound.

We employed the reciprocal-ratios Go/No-go paradigm to better compare experimental and control conditions, as both runs would have some speeded motor responses to inhibit, but the strength of the established inhibitory response was manipulated between runs. We measured

brain activity across consecutive time windows and compared the measures between adolescent and adult groups to further our understanding of inhibitory control maturation. We hypothesised that inhibitory control would be poorer in adolescents (seen as higher false alarm scores); as well, adolescents would show greater overall activation compared to adults due to poorer inhibitory control, thus requiring more activation for task performance.

2. Methods

2.1. Participants

Thirty participants were recruited through posters placed in public locations in the hospital and at local schools and by word of mouth. Prior to acceptance into the study, all participants were screened with a questionnaire for a history of neurological or developmental disorders, psychotropic medication, preterm birth and standard contraindications to MEG and MRI and were not recruited if they reported any of these. The groups that were studied included 15 typically developing adolescents aged 13–17 years and 15 healthy adults aged 20–35 years (see Table 1 for details). Participant IQs were obtained from the two-subtest WASI (Wechsler, 1999); a lower IQ cut-off was set at 80 although none of the subjects approached this cut-off. The imaging study was approved by the institutional REB at the Hospital for Sick Children, where the imaging was conducted. Informed consent was obtained from all adolescents and adult participants.

2.2. Behavioural measures

2.2.1. Reaction time

RT was measured from the onset of the stimulus until the button press by the participant. RTs were only measured for Go trials, as responses to No-go trials were false alarms and not included in the RT measure. RTs under 100 ms were not included, as they were most likely anticipatory responses or a delayed response to the previous stimulus.

2.2.2. False alarm rate

The false alarm (FA) rate is the ratio of incorrect No-go trials (to which participants responded) to the total number of No-go trials, and is a measure of impulsivity. Higher FA percentage values are indicative of higher impulsivity.

2.2.3. Hit rate

Hit rate is the number of Go trials with correct responses divided by the total number of Go trials. Go/No-go hit rate ratio is thought to indicate attention levels, with higher hit rates, or accuracy, implying increased attention (Eimer, 1993).

2.3. Experimental paradigm

We employed a simple Go/No-go task, where Go stimuli were solid black shapes and No-go stimuli were shapes with a superimposed grey 'X' on them. Stimuli appeared in

the centre of the screen with a white background and had a visual angle of 5°. A black fixation-cross was presented during interstimulus intervals, to encourage subjects to maintain eye-fixation at the centre of the screen. Participants were instructed to respond to the Go stimuli as rapidly as possible and withhold their response to the No-go stimuli. We ran two conditions, a control condition, which consisted of 67% No-go and 33% Go trials, and an inhibition condition which contained 33% No-go trials, allowing the other 67% Go trials to build up a prepotent tendency to respond (see Fig. 1). To equate the behavioural performance on our task (specifically the accuracy) across our groups, we used adaptive inter-stimulus intervals (ISIs) that were dependent on performance. Starting at 500 ms ISI for the first trials, the ISI was adjusted every five stimuli where three errors or more on No-go trials would cause the ISI to increase by 100 ms, while fewer than three errors decreased the ISI by 100 ms, with the minimum ISI set to 300 ms. The stimulus duration was 200 ms.

2.4. Neuroimaging procedures

MEG data were acquired on a 151-channel CTF system with axial gradiometers (MISL, Coquitlam, BC) at the Hospital for Sick Children. Participants were trained on the Go/No-go task on a PC computer outside the MEG room; a condition with 50% Go and 50% No-go was used as the training example. Participants were instructed to respond as quickly and as accurately as possible upon seeing the Go stimulus by pressing a button with their right index finger. After training, fiducial coils were attached at the nasion and left and right preauricular points to track head movement. Prior to placing these coils, we marked the skin at the three centre points of the coils to guide later placement of radio-opaque markers used in the magnetic resonance imaging (MRI) scanner, for the purpose of co-registration. The participants lay in a supine position, with their head inside the MEG dewar, and padding was added to minimise head movement.

The data were collected at a sampling rate of 600 Hz for both the inhibition and the control conditions and recorded with bandpass of 0–150 Hz. Data were acquired with CTF-based-software 3rd order spatial gradients to enhance noise removal. The condition order was counterbalanced across participants. We collected about 110 correct No-go trials in each condition; allowing for some rejection of trials due to artefact. An average of 10 trials were rejected for both groups, leaving 100 trials for each condition. The MEG study required 10–15 min.

Following the MEG scan, the fiducial coils were replaced with radio-opaque markers and an MRI was completed on a 3 T MAGNETOM Tim Trio (Siemens AG, Erlangen, Germany) scanner in an adjacent suite to the MEG, using a 12-channel head coil. A set of 192 high-resolution T1-weighted sagittal images were acquired using a 3D MPRAGE sequence (TR/TE = 2300/2.96 ms; FA = 9°; PAT, GRAPPA = 2; FOV = 28.8 × 19.2 cm, 1 mm isotropic voxels). This allowed co-registration of MEG data with each individual's MRI.

Table 1
Sex, age, IQ of participants.

	<i>n</i>	Sex ratio	Mean age \pm SD (years)	Mean IQ \pm SD
Adolescents (13–17 yrs)	15	12 M:3 F	15.6 \pm 1.3	112.4 \pm 10.3
Adults (20–35 yrs)	15	11 M:4 F	25.3 \pm 4.5	117.8 \pm 5.9 ^a

^a There was no significant difference in IQ between groups.

2.5. MEG analyses

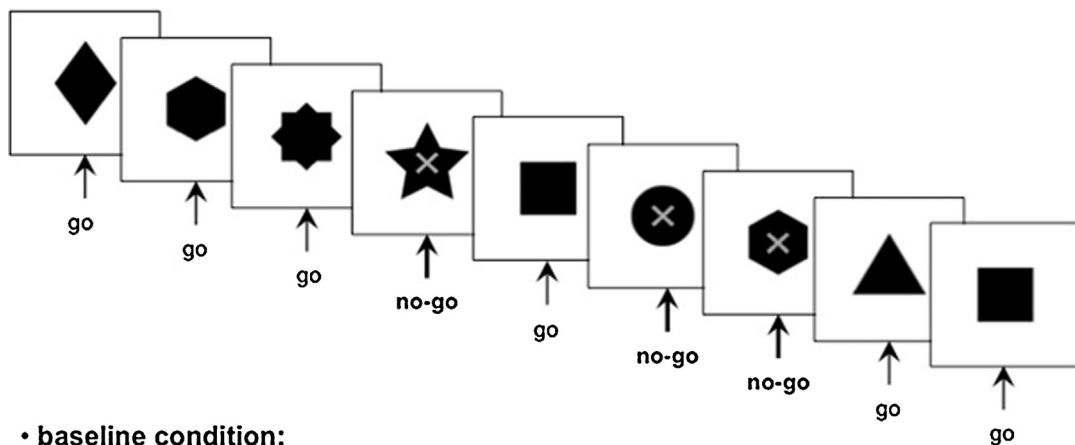
2.5.1. Pre-processing

Each dataset was parsed into single trials. The trials were epoched into 600 ms windows: 100 ms pre and 500 ms post-stimulus onset. Using a MATLAB script, *only* correct No-go trials were selected for further analyses. These No-go trials were inspected for artefacts such as blinks and heartbeats, and removed on a trial-by-trial basis. The remaining No-go trials (approximately 100 trials for each participant) were then averaged. Grand averages were created across participants, by condition and age group.

2.5.2. Global field power plots

We calculated the global field power (GFP), which is the root mean squared power across all sensors, for our grand-averaged datasets for each condition and age, to visualise temporal changes in the overall amplitude of the magnetic field. Following our a priori hypothesis of frontal lobe involvement in inhibition, and to better visualise the differences between age groups, we also generated frontal GFP plots, based on the sensors overlaying the frontal lobes ($n=32$) plus vertex sensors ($n=3$) (see Fig. 2). Based on peak latencies seen in these GFP plots, as well as our ERP-based hypothesis of activity after 200 ms, we focused on the 200–400 ms time range.

• inhibition condition:



• baseline condition:

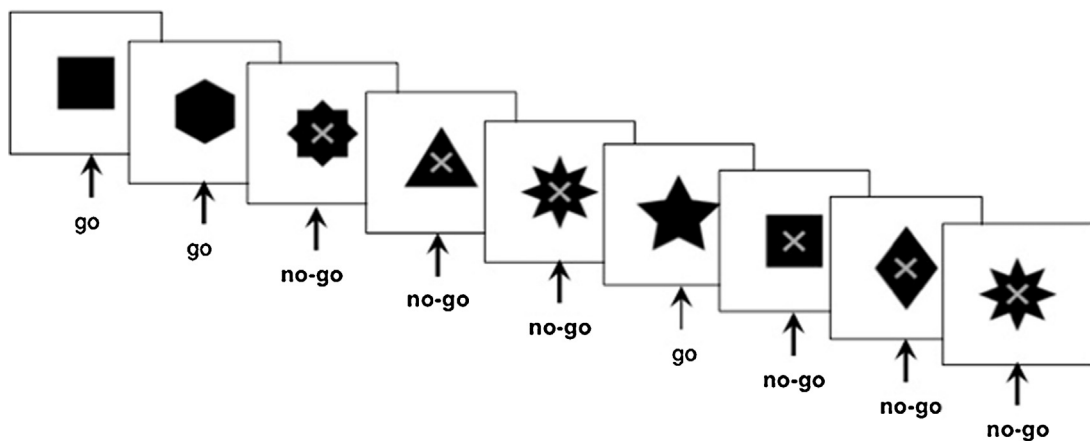


Fig. 1. Illustration of Go/No-go paradigm with the inhibition condition above (consisting of 33% No-go trials) and the control condition below (consisting of 67% No-go trials). Go stimuli, seen as solid black shapes, and No-go stimuli, seen as black shapes with an X superimposed on them, are labelled.

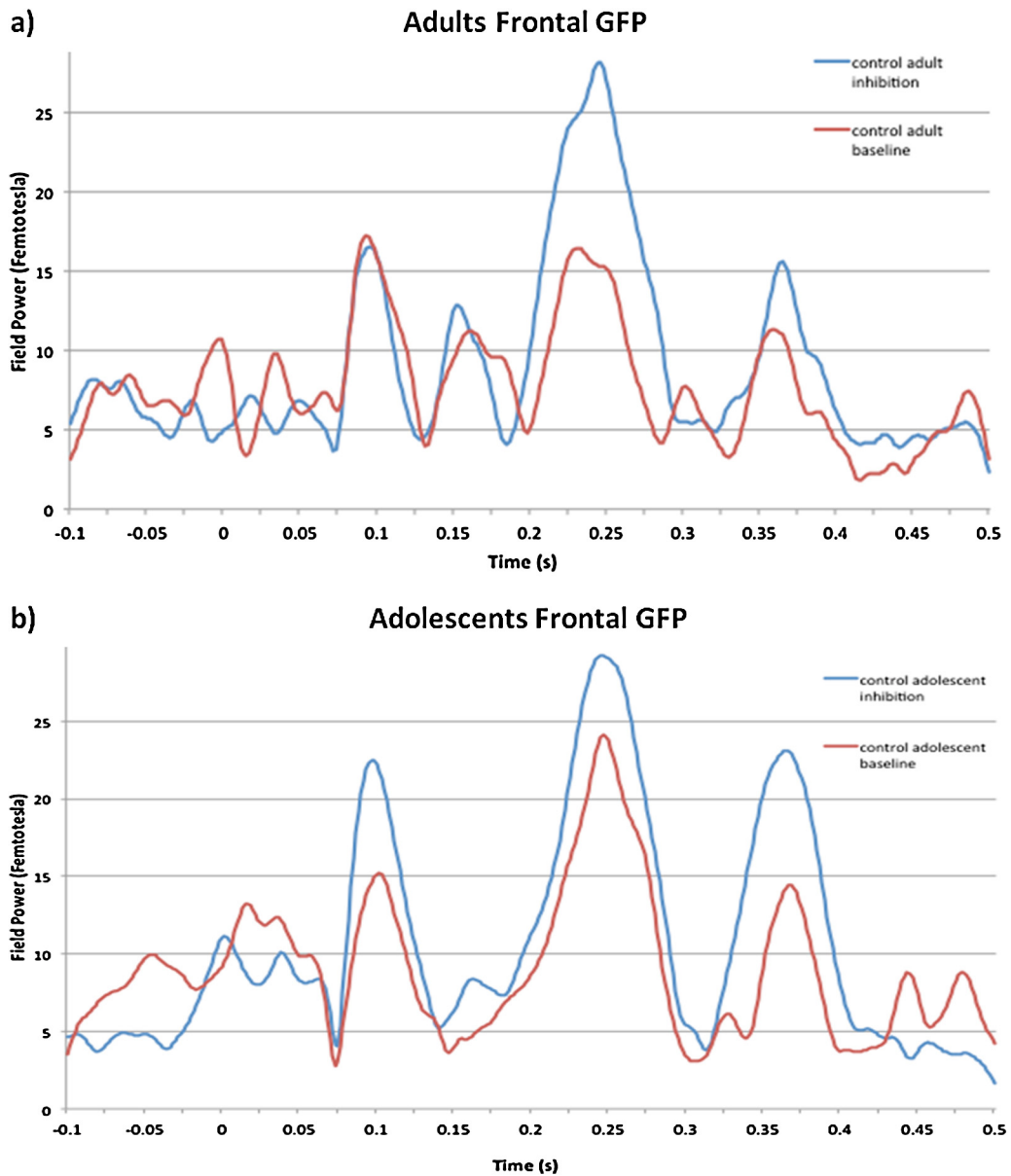


Fig. 2. Grand-average global field power (GFP) plots from frontal electrodes for inhibition (solid black line) and control (dotted grey line) conditions in (a) adults and (b) adolescents.

2.5.3. Vector beamforming

While GFPs were used to visualise activity in the frontal lobes, all subsequent analyses were conducted over the whole head. For source localisation, we used a vector beamformer (SPF) developed in-house (Quraan and Cheyne, 2010), as vector beamforming can identify activity in deep frontal sources as well as mesial temporal and limbic structures (Quraan et al., 2011; Hung et al., 2012, 2013). Multisphere headmodels were created based on initial fiducial positions that had been registered to the T1 anatomical image (Lalancette et al., 2011). Data were band-pass filtered from 0.5 to 30 Hz and beamformer images computed using mean power integrated over 50 ms non-overlapping time intervals, starting from 200 to 400 ms, for

each condition and cohort. Images had a spatial resolution of 5 mm and were normalised to a template using SPM2. The 3-D images for the control condition (67% No-go) were subtracted from the images in the inhibition condition (33% No-go) to partially remove the visual activity that occurs in visual tasks, as well as improve the source localisation of more subtle brain activity as seen in the frontal lobes (Mills et al., 2012; Quraan et al., 2011).

2.5.4. Permutation testing

To test for significant within-group activity, permutation tests were run on subtracted beamformer images (>6000 permutations). We used a single-threshold maximal statistic permutation test adapted for MEG (Singh et al.,

2003; Chau et al., 2004). This type of approach has been demonstrated to provide strong control for experiment-wise, or family-wise, Type I errors (Nichols and Holmes, 2002). This generated activation maps at $p < 0.01$, which we corrected for multiple comparisons using a Sidak Correction (Blair and Karniski, 1993). Permutation tests were conducted by shuffling the group membership of the two samples, while maintaining the direction and cardinality, and calculating the mean differences between the two samples (or possible sets of group membership). The calculated mean difference for each of many ($n > 6000$) permutations was plotted to create a distribution, allowing for the comparison of the mean difference from the original sample to the distribution of values to obtain the p -value. Anatomical names and BA areas were then verified in Talairach Client (Lancaster et al., 1997, 2000). To allow a direct comparison between age groups, the MEG pseudo-Z values at significantly activated areas were submitted to a 2 (age group) \times 2 (condition) mixed design repeated measures ANOVA.

3. Results

3.1. Behavioural results

Three univariate 2 \times 2 mixed designs repeated measures ANOVAs were run on behavioural data using STATISTICA, Version 8, with age group as an independent variable, and condition type as the repeated factor for reaction time (RT), false alarm (FA) rate and hit rate (see Table 2).

3.1.1. Reaction time

A main effect of condition type was found on RTs [$F(1,24) = 27.3$, $p < 0.001$], with longer RTs for the control condition ($M = 336 \pm 40$ ms) than the inhibition condition ($M = 312 \pm 34$ ms); no main effect of age group was found on RTs [$F(1,24) = 2.7$, $p = 0.115$]. The shorter RTs for the Go trials in the inhibition condition are consistent with participants in both groups having established speeded prepotent responding. The interaction effect was not significant.

3.1.2. False alarm rate

There was no main effect of age group [$F(1,24) = 2.68$, $p = 0.115$] for FA. However, a main effect of condition type was found for FA rate, where the inhibition condition ($M = 14.6 \pm 9.4\%$) had a greater FA rate than the control condition ($M = 3.6 \pm 4.4\%$), irrespective of age group [$F(1,24) = 108.92$, $p < 0.001$]. The higher rate of FA in the inhibition condition is consistent with the Go/No-go manipulation and the increased inhibition required for this task. The interaction effect was not significant.

3.1.3. Hit rate

No main effect of age group [$F(1,24) = 1.69$, $p = 0.205$] or condition type [$F(1,24) = 0.09$, $p = 0.77$] was found for hit rate. The interaction effect was not significant.

The absence of main effects for age for all of our behavioural measures indicates comparable performance between the adolescent and adult groups.

3.2. MEG results

3.2.1. Identification of frontal brain activity latencies

Grand-averaged frontal GFP plots for the inhibition and control condition for the adult and adolescent cohorts are displayed in Fig. 2. The two peaks of interest occurred at 200–300 ms and 350–400 ms.

3.2.2. Localisation of neural activity

The within-group activations ($p < 0.01$) for the inhibition minus control condition for both groups are shown in Fig. 3. The anatomical names and Talairach locations of the within-group activations are listed in Table 3.

Significant within-group inhibition activation for the adults began in the right inferior frontal gyrus (BA 45) from 200 to 250 ms post-stimulus. The left precentral area (BA 6) was recruited simultaneously and remained active until 400 ms. The right temporal region (BA 41) was also recruited from 350 to 400 ms.

Significant within-group inhibition-related activity for the adolescents began 200–250 ms post-stimulus onset in the left middle frontal/precentral gyrus (BA 6), followed by activity in the left inferior frontal gyrus (BA45), left middle frontal (BA6) and right inferior frontal (BA9) from 250 to 300 ms. From 300 to 350 ms the right middle temporal gyrus was recruited, then from 350 to 400 ms, the right precentral gyrus (BA4), right superior temporal gyrus (BA22) and right inferior parietal lobe (BA40) were more active with inhibition. After correction for multiple comparisons at $p < 0.01$, the right inferior frontal (BA9) and right inferior parietal lobe (BA40) activations no longer passed threshold.

The ANOVA identified significant main effects between groups and between conditions. At 200–250 ms, only a condition effect was seen with greater activation in the right inferior frontal gyrus and left precentral areas for the inhibition trials [RIFG: $F(1,28) = 10.11$, $p < 0.003$; Lprecentral: $F(1,28) = 14.64$, $p < 0.0007$]. Between 250 and 300 ms, the right inferior frontal gyrus showed significantly greater magnitude for the adults than adolescents [$F(1,28) = 5.98$, $p < 0.021$], and the inhibition condition showed increased activity in the left inferior frontal and left middle frontal gyri [LIFG: $F(1,28) = 4.87$, $p < 0.036$; LMFG: $F(1,28) = 12.28$, $p < 0.0017$], with sustained greater activity in the left precentral area [$F(1,28) = 5.67$, $p < 0.024$]. This latter effect continued until 350 ms [$F(1,28) = 17.14$, $p < 0.0003$], with recruitment of right middle temporal gyrus with inhibition from 300 to 350 ms [$F(1,28) = 15.07$, $p < 0.0006$]. The only significant group by condition interactions were found from 350 to 400 ms; the right temporal area was greater in adults in the inhibition condition [RTG: $F(1,28) = 8.09$, $p < 0.009$], whereas the left middle frontal and right precentral areas [LMFG: $F(1,28) = 6.04$, $p < 0.021$; Rprecentral: $F(1,28) = 4.13$, $p < 0.05$] showed greater activation for the adolescents than the adults during inhibition.

4. Discussion

We examined the spatiotemporal MEG activity and age-related (group) differences underlying inhibition during No-go trials in the Go/No-go task. Consistent with the inhibition literature we found right dominant inferior frontal

Table 2
Behavioural measures (mean \pm SD) for the adult and adolescent groups.

	Condition	RT* (ms)	Hits (%)	FA* (%)
Adults	Inhibition	317 \pm 36	97.5 \pm 2.8	12.2 \pm 6.7
	Control	341 \pm 47	97.3 \pm 2.6	3.0 \pm 4.1
Adolescents	Inhibition	307 \pm 34	95.1 \pm 2.8	18.7 \pm 7.3
	Control	332 \pm 34	95.5 \pm 2.5	4.2 \pm 4.1

There were no significant performance differences in RTs, Hits or FA between groups.

* $p < 0.001$. The inhibition condition had faster RTs and a higher false alarm (FA) rate than the control condition for both groups.

activity in adults, whereas adolescents showed left dominant, bilateral activity in the inferior frontal regions. As well, there was a delay of the inferior frontal activity in adolescents (250–300 ms) compared to adults (200–250 ms) suggesting an immaturity in adolescent neural inhibition patterns. Adding to the literature, we found supplemental cortical recruitment was implicated in the adolescent group; we suggest that this allowed them to maintain adequate inhibitory performance. We discuss the behavioural

findings and then the neuroimaging results by brain region below.

4.1. Task assessment: based on performance measures

The effectiveness of our Go/No-go paradigm was demonstrated by our behavioural findings; the rapid response to Go trials during the inhibition condition encouraged a bias towards responding, thus faster

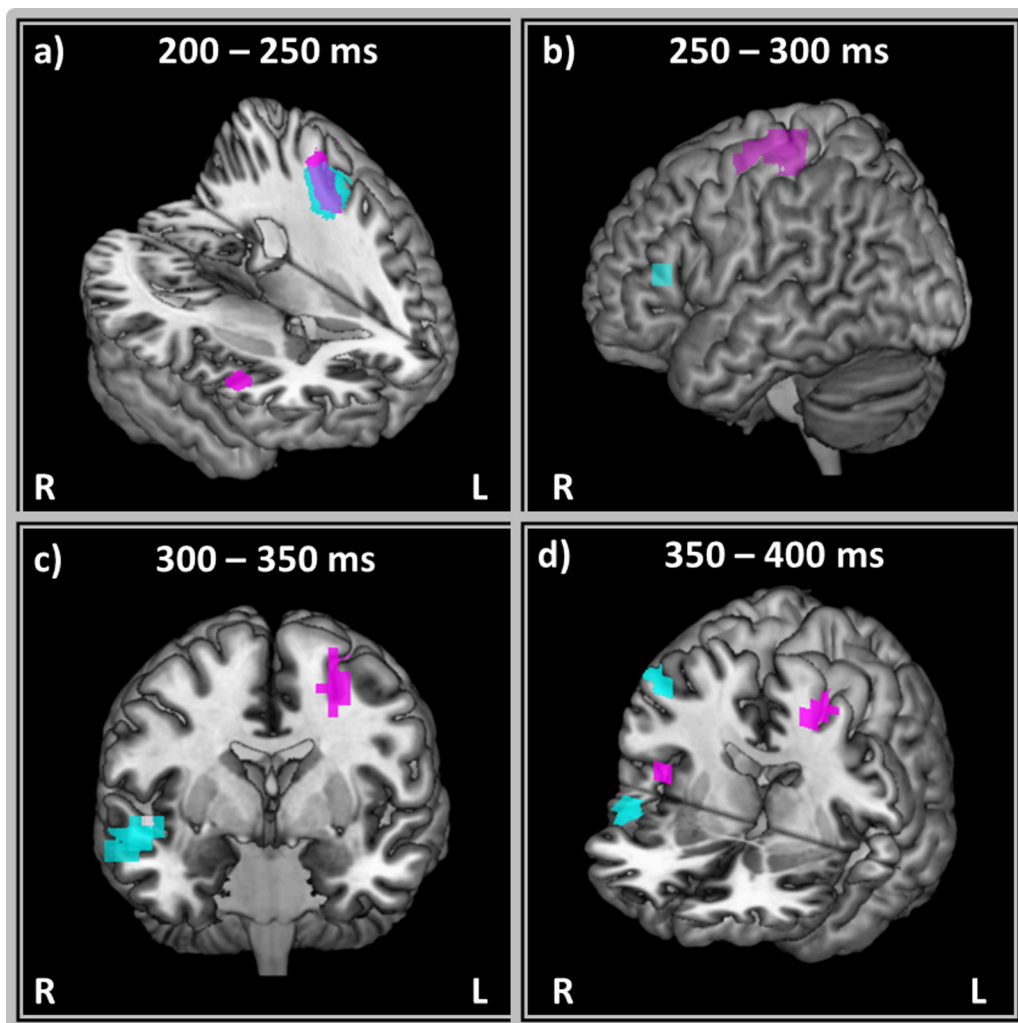


Fig. 3. Within-group activations overlaid on brain images showing brain areas where there was significantly greater activation for the inhibition than control condition ($p < 0.01$, corrected) for adults (in magenta) and adolescents (in blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3Areas of activation ($p < 0.01$) during time windows of interest in adults and adolescents.

Time window		Anatomical area	BA	Talairach coordinates			Absolute effect size (pseudo-Z)
<i>Adults</i>							
200–250 ms	L	Precentral/middle frontal gyrus*	6	–30	–10	55	0.25
	R	Inferior frontal gyrus*	45	55	25	10	0.23
250–300 ms	L	Precentral gyrus*	4	–35	–25	60	0.29
300–350 ms	L	Precentral gyrus*	6	–25	–10	50	0.30
350–400 ms	L	Middle frontal/precentral gyrus*	6	–25	–5	55	0.27
	R	Transverse temporal gyrus*	41	50	–25	10	0.24
<i>Adolescents</i>							
200–250 ms	L	Middle frontal/precentral gyrus*	6	–25	–5	55	0.28
250–300 ms	L	Inferior frontal gyrus*	45	–55	25	15	0.16
	L	Middle frontal gyrus	6	–25	15	60	0.15
	R	Inferior frontal gyrus	9	60	10	25	0.14
300–350 ms	R	Middle temporal gyrus*	21	50	0	–10	0.22
350–400 ms	R	Precentral gyrus*	4	50	–10	50	0.18
	R	Superior temporal gyrus*	22	50	5	–5	0.18
	R	Inferior parietal lobule	40	40	–50	45	0.15

* $p < 0.01$, corrected.

reaction times were seen compared to the control condition. Also higher false alarm rates for the inhibition condition illustrate that a prepotent response tendency occurred to a greater extent for the inhibition than the control condition. As hit rate acts to index attention (Eimer, 1993), the lack of between-condition differences in hit rate for both adults and adolescents indicated that both groups of participants were able to maintain comparable attention levels for both the inhibition and control conditions. Thus, we were assured that our control was an effective match for our inhibition condition, and we did not have a performance confound between age groups.

4.2. Imaging of inhibition: right inferior frontal activity

4.2.1. Adults: right inferior frontal gyrus activation consistent with literature

Early (200–250 ms) right inferior frontal gyrus activation during inhibition was seen in our adult sample, being significantly greater for the inhibition than control trials. This region has been associated with the top-down processing related to goal monitoring, such as inhibiting an action (Miller and Cohen, 2001) and in the suppression of intrusive thoughts (Anderson et al., 2004) in tasks requiring attentional control and top-down processing. Aron et al. (2003) demonstrated the importance of the right inferior frontal gyrus for inhibition by showing deficits in individuals with right inferior frontal gyrus lesions, using the Stop-signal task.

Our findings are consistent with those from event-related fMRI studies (Garavan et al., 1999; Kiehl et al., 2000; Konishi et al., 1998, 1999; Liddle et al., 2001; Rubia et al., 2003), in which right lateralised prefrontal activation was found during inhibition tasks, although some studies (Garavan et al., 1999; Kiehl et al., 2000; Liddle et al., 2001) also found left lateralised prefrontal activity. It is possible that left frontal activity was present in our adults, but did not pass our stringent significant levels, or it occurred outside the time windows; given the poor temporal resolution of fMRI, this activation may have been at a much longer latency in those studies.

4.2.2. Adolescents: bilateral inferior frontal activity and lateralisation differences between adolescence and adulthood

From 250 to 300 ms, adolescents recruited both the left inferior and to a lesser extent right frontal gyri, consistent with this aspect of an earlier study (Vidal et al., 2012). This was seen as a significant group difference in the right inferior frontal gyrus (adults > adolescents) and a condition effect in the left inferior frontal gyrus. Activity in both the left and right inferior frontal gyri has also been reported in several fMRI studies (Bunge et al., 2002; Konishi et al., 1999; Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001; Wager et al., 2005; Watanabe et al., 2002), and the left inferior frontal gyrus activity in fMRI studies has been associated with inhibition in adults (Rubia et al., 2001; Tamm et al., 2002) as well as children (Bunge et al., 2002; Tamm et al., 2002; Vaidya et al., 2005). Two conflicting theories on this activity exist: one states that increased left inferior frontal gyrus activation is correlated with poor inhibition (Bunge et al., 2002), while Tamm et al. (2002) postulated that increasing left inferior frontal gyrus activation occurs with development, as they found a positive correlation with age in participants aged 8–20 years using a Go/No-go task. However, the Tamm et al. study did not compare adolescents with adults, whereas Bunge et al. (2002) found that both adults and children activated the left ventrolateral PFC, while only the adults activated the right, consistent with our finding of bilateral inferior frontal activation in adolescents and only right inferior frontal activation in adults.

The substantial neuroanatomical changes that continue into late adolescence and early adulthood (Changeux and Danchin, 1976; Paus et al., 1999) would foster faster and more efficient networks, but may leave the adolescent inhibitory network in a transitional state where frontal lobe regions, such as the right inferior frontal gyrus, are not developed sufficiently to be recruited effectively. Of note, is that we saw the right inferior frontal activity at a more liberal threshold in adolescents, suggesting that there is a transition period in late adolescence or very early adulthood, when the right inferior activity gains dominance and

the left diminishes. In an event-related Stop-signal task [Rubia et al. \(2007\)](#) showed correlations between age and activation of the right inferior prefrontal cortex in adolescents and adults aged 10–42 years. However, as this was an fMRI study, there was no temporal information and the activation reported could have occurred far later in time than we found.

MEG allows the determination of temporal as well as spatial processing and both of these aspects of brain function change with age. Not only did we see frontal activity starting later in adolescents than adults (250 ms vs. 200 ms), there was also a shifting lateralisation within these time windows. Our finding of significantly greater right inferior frontal activity in adults than adolescents also aligns with ERP studies, where an inferior fronto-temporal positivity has been found to peak around 260 ms, during No-go trials ([Kiefer et al., 1998](#)). However, inhibition-related activity was found to be bilateral in the Kiefer et al. study, in which No-go trials were contrasted with the Go trials of an auditory task. The above study used a low probability target, which may be biased by an oddball effect that is localised to midline ([Donchin and Coles, 1988](#)). In the current study using conditions with inverse ratios of Go to No-go trials, we expect that our results show a true inhibition effect without the oddball confound; MEG also has the advantage of greater spatial resolution than ERPs.

The decrease in latency over this approximately 10-year period could be due to a number of factors. The myelination, particularly of the frontal lobes, is continuing and would impact processing speed. Also, activity seen in adolescents in several other brain regions during task performance (discussed below), suggests that a larger network was invoked for inhibitory control in this group. The coordination within a larger neural network could require more time. Thus, with the continued structural changes (e.g., myelination and pruning) in adolescence, the neural processing would become more efficient, both in terms of speed and neural extent, which would very plausibly lead to this latency shift between groups.

4.3. Left lateralised activity in motor-planning areas

Adults and adolescents exhibited left lateralised activity in the pre-central regions (BA 6). As the response was made with the right hand, contralateral supplementary motor area or premotor cortex activity, despite only analysing trials with no motor response, was likely due to anticipatory or preparatory activity. This left BA 6 activity that has been found in fMRI studies ([Chikazoe, 2010](#)), was observed between 200 and 400 ms, which is consistent with ERP literature, where a peak in frontal activity between 300 and 600 ms is termed the “No-go P3” ([Falkenstein et al., 1999](#); [Kiefer et al., 1998](#)). [Kiefer et al. \(1998\)](#) found that sources in the left precentral area (comparable to our BA 6 finding) peaked around 500 ms. As well, a recent ERP study ([Albert et al., 2013](#)) localised the inhibition-related P3 to bilateral pre-supplementary motor cortices with a peak latency occurring well after the response. However, we showed significantly greater recruitment during inhibition trials of the precentral area beginning in the first time window (200–250 ms) and continuing until 400 ms.

Although the BA 6 anticipatory activation ended earlier in the adolescent than adult group (300 ms vs. 400 ms) in the individual group analyses, suggesting that the adolescents were quicker in relinquishing the preparation to respond following a No-go stimulus, there was not a group difference, suggesting that this effect was subtle, and both groups maintained some activity in this left precentral regions from 200 to 400 ms. It is possible that our simpler task design yielded earlier latencies than those observed by [Kiefer et al. \(1998\)](#) and [Albert et al. \(2013\)](#). Another possibility is that our use of a more balanced Go/No-go ratio (67/33%) did not evoke a strong inhibition-related P3, and we are able to see these other earlier, lateral cortical responses related to motor planning and anticipation.

4.4. Imaging of inhibition: areas outside the frontal lobes

The adolescent inhibitory neural network continued to recruit the left middle frontal region significantly more than the adults during inhibition trials from 350 to 400 ms; they also engaged right temporal areas from 300 to 400 ms. Right temporal regions have been found to be activated in inhibition studies using No-go trials ([Liddle et al., 2001](#); [Vidal et al., 2012](#)), and we found that this was greater in adults between 350 and 400 ms. In a Go/No-go study contrasting typically developing adolescents (aged 14–16 years) to age-matched adolescents with ADHD, [Tamm et al. \(2002\)](#) found that typical adolescents recruited a large region in the right hemisphere that included the right superior temporal sulcus, consistent with our findings in the adolescents of more extensive right temporal activity from 300 ms.

The right precentral gyrus ($p < 0.01$, corrected) and right the parietal lobule ($p < 0.01$, uncorrected) were also activated from 350 to 400 ms in the adolescent sample. The right precentral activation was significantly greater in the adolescents than adults for the inhibition trials, demonstrating the bilateral precentral activity in this younger age group. Inhibition-related right parietal activity has been observed in many fMRI studies ([Braver et al., 2001](#); [Garavan et al., 1999](#); [Konishi et al., 1999](#)) and is associated with sustaining attention ([Fassbender et al., 2004](#)). Processing No-go stimuli requires the mental exertion of attention in order to monitor for No-go cues ([Hampshire et al., 2010](#)). [Durstun et al. \(2002\)](#) found right parietal activation was greater for the inhibition condition than the control condition in both children and adults. This activity in the current study thus likely reflects increased attention-related resources being recruited by the adolescents to perform at adult levels. We are also able to show the timing of this frequently reported activity, and note that it was only seen in the adolescent group at this latency. The reports of right parietal activity from fMRI studies in adults may therefore be reflecting a longer latency response.

5. Conclusions

Differences between our adult and adolescent groups demonstrate changes in timing and spatial localisation of inhibitory processing. Adults recruited the right inferior frontal gyrus in addition to left motor-planning areas, in

contrast to adolescents who recruited bilateral, but left dominant, inferior frontal gyri at a later time window as well as bilateral motor-associated regions. Furthermore, adolescents recruited the temporal lobe earlier than adults, and the inferior parietal lobe, possibly to supplement their immature frontal lobe functions (Sowell et al., 1999). These findings underscore the immaturity of the inhibitory network in adolescents and the importance of whole-head neuroimaging studies of temporal and spatial changes to understand the maturation in brain processing into adulthood.

Conflict of interest

The authors declare no conflicts of interest.

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