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Effects of age and gender on neural networks of motor response inhibition: From adolescence to mid-adulthood ☆

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ABSTRACT

Functional inhibitory neural networks mature progressively with age. However, nothing is known about the impact of gender on their development. This study employed functional magnetic resonance imaging (fMRI) to investigate the effects of age, sex, and sex by age interactions on the brain activation of 63 healthy males and females, between 13 and 38 years, performing a Stop task. Increasing age was associated with progressively increased activation in typical response inhibition areas of right inferior and dorsolateral prefrontal and temporo-parietal regions. Females showed significantly enhanced activation in left inferior and superior frontal and striatal regions relative to males, while males showed increased activation relative to females in right inferior and superior parietal areas. Importantly, left frontal and striatal areas that showed increased activation in females, also showed significantly increased functional maturation in females relative to males, while the right inferior parietal activation that was increased in males showed significantly increased functional maturation relative to females. The findings demonstrate for the first time that sex-dimorphic activation patterns of enhanced left fronto-striatal activation in females and enhanced right parietal activation in males during motor inhibition appear to be the result of underlying gender differences in the functional maturation of these brain regions.

Introduction

Inhibitory self-control is an executive function that is crucial for mature adult behaviour. Inhibitory motor control can be measured in the laboratory with Go/No-go and Stop tasks that measure the ability to restrain or withdraw a motor response, respectively. Motor response inhibition as measured in Go/No-go and Stop tasks develops throughout adolescence and into adulthood (Aarnoudse-Moens et al., 2011, 2012; Williams et al., 1999). Sex differences become more pronounced during this period of adolescence, concomitant with the hormonal changes of puberty (Sisk and Zehr, 2005), with females being more efficient than males in tasks of selective attention, verbal fluency and conductive reasoning (Anderson, 2001; Klenberg et al., 2001; Schaie, 1994), and males outperforming females in cognitive functions that rely on visual–spatial processing, especially mental rotation (Astur et al., 1998; Collins and Kimura, 1997; De Luca et al., 2003; Weiss et al., 2003).

There is evidence that ratings of impulsiveness are higher in men than women (Campbell and Muncer, 2009; Labouvie and McGee, 1986) and disorders of impulse control such as ADHD, substance abuse and conduct disorder are more common in males (Eme, 2007; Kessler et al., 2005; Newman et al., 2005). Behavioural impulsiveness has consistently been associated with poor performance in tasks of motor and cognitive inhibition (Spinella, 2004). In line with this, patients with disorders of impulsiveness, such as ADHD, have consistently been found to be impaired in motor response inhibition in Go–no-go and Stop tasks (Rubia, 2011; Rubia et al., 2007a; Willcutt et al., 2005) and to have deficits in the recruitment of underlying inhibitory inferior prefronto-striato-thalamic networks (Cubillo et al., 2012; Hart et al., 2013; Rubia, 2011; Rubia et al., 1999, 2005).

Despite evidence for sex differences in behavioural impulsiveness (Campbell and Muncer, 2009; Labouvie and McGee, 1986), relatively few neuropsychological or imaging studies have investigated gender differences during motor response inhibition performance. With respect to neuropsychological studies, some studies observed no sex differences in Stop or Go/No-go task performance (Garavan et al., 2006; Li et al., 2009; Williams et al., 1999) while other paediatric studies showed that girls had better inhibitory capacity than boys (Aarnoudse-Moens et al., 2011, 2012; Bezdjian et al., 2009).

During childhood and adolescence, and presumably underlying these cognitive changes, the brain continues to mature via processes such as

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synaptic remodelling and competitive elimination, programmed cell death and myelination (de Graaf-Peters and Hadders-Algra, 2006; Huttenlocher and Dabholkar, 1997). Structural imaging studies demonstrate a linear increase with age in white matter, presumably reflecting myelination, that peaks at around age 45, and a non-linear decrease, up to age 40, in grey matter density, presumably reflecting synaptic pruning and myelination (Gogtay et al., 2004; Sowell et al., 2004, 2007). These processes are heterochronous and heterogeneous with higher association areas in frontal, parietal and temporal regions maturing latest and primary sensory areas maturing earliest (Giedd and Rapoport, 2010; Gogtay et al., 2004; Sowell et al., 2004). Gender differences show that males exhibit steeper developmental slopes in grey matter reduction and white matter increase than females (Giedd et al., 1999, 2010; Gogtay et al., 2004), partly explained by earlier maturation peaks in females in frontal, striatal and temporal areas (Giedd et al., 1999; Lenroot and Giedd, 2010). Gender differences in cognitive abilities may at least in part be explained by these sex differences in brain structure and its development (Gur et al., 1999; Sowell et al., 2007).

Developmental imaging studies show that the functional substrates of motor response inhibition change between childhood and adulthood. During motor response inhibition in Go/No-go tasks, adults show enhanced activation in lateral and medial frontal and parietal regions relative to children (Bunge et al., 2002), and there is furthermore evidence for linear progressive enhancement of functional activation with age in lateral and medial frontal regions between childhood and late adulthood (Rubia, 2011; Rubia et al., 2006). Similarly, during withdrawal of already planned motor responses in the Stop task, progressive increase of activation as well as progressively increased inter-regional connectivity was observed between childhood and late adulthood in a typical motor response inhibition network of inferior frontal, striato-thalamic and cerebellar brain regions (Rubia et al., 2007b). This was furthermore correlated with faster motor inhibition speed, as measured with the stop signal reaction time (SSRT) (Rubia et al., 2007b). In all developmental fMRI studies, the findings remained when performance was covaried or performance matched subgroups were compared, suggesting that changes were truly age and not just performance-related (for review see Rubia, 2013).

Relatively few fMRI studies have studied sex differences in cognitive functions. The most consistent findings have been that of increased prefrontal activation in females and increased parietal activation in males during tasks of working memory, mental rotation, attention, cognitive switching and interference inhibition (Bell et al., 2006; Christakou et al., 2009b; Garavan et al., 2006; Goldstein et al., 2005; Rubia et al., 2010b; Thomsen et al., 2000; Weiss et al., 2003). To our knowledge, only 4 fMRI studies have tested for sex differences in motor response inhibition. Males and females did not differ in their inhibitory performance in Stop (Li et al., 2006, 2009) and Go/NoGo tasks (Garavan et al., 2006; Liu et al., 2012), which is not in line with some paediatric neuropsychological studies showing performance superiority in females (Aarnoudse-Moens et al., 2012; Bezdjian et al., 2009). The differences in performance findings between neuropsychological and fMRI studies may be due to the fact that the typically small-numbered fMRI studies are statistically underpowered to show behavioural effects or differences in gender, while the relatively larger paediatric neuropsychological studies show performance differences for gender. Gender was, however, associated with differences in brain activation, although findings were not consistent across studies. Using the Go/No-go task, one study found that females had significantly increased activation in several task-relevant cortical and subcortical areas such as the bilateral middle frontal and inferior parietal lobes, right superior, middle and inferior temporal gyri, thalamus, lentiform nucleus and cerebellum, with males showing no increased activations (Garavan et al., 2006). Another study found increased activation in females in left middle temporal gyrus and increased activation in males in anterior cingulate (Liu et al., 2012). During successful versus failed stop trials in the Stop task, however, males compared to females showed increased activation in left superior frontal gyrus, anterior and posterior cingulate, pre-SMA and cerebellum (Li et al., 2006, 2009). Some of these gender differences in ACC and pre-SMA, however, were due to increased activation in females than males during error processing rather than successful inhibition (Li et al., 2009). Furthermore, more efficient response inhibition was associated with greater activation in the tail of the caudate in females relative to males and with increased activation in the anterior cingulate cortex in males relative to females (Li et al., 2006), suggesting differences in strategies or differences in neural recruitment to achieve similar task performance.

In conclusion, fMRI findings of gender differences during tasks of inhibition have been inconsistent, possibly due to relatively small subject numbers, and need further study. The findings however, point towards sex differences in the recruitment of brain areas for task performance, possibly reflecting sex differences in performance strategies.

It is likely that sex differences in brain activation are related to differences in underlying brain development. However, to our knowledge, only four developmental imaging studies have investigated sex by age interactions on brain activation during cognitive tasks and none of them tested motor response inhibition. Thus, no age by gender interaction effect was found in children, adolescents and adults during a reward reversal task (Crone et al., 2006). However, during interference inhibition, age by sex interaction effects in adolescents and adults showed exclusively female contributions for the age-related increases in lenticular nucleus activation (Marsh et al., 2006). Age by sex interaction effects were also observed in adolescents and adults during cognitive control and attention tasks with exclusive female-specific age correlations in inferior and medial prefrontal brain regions during interference inhibition, cognitive switching and selective attention, and exclusive male age-correlations in superior parietal regions during switching, in temporal regions during interference inhibition and in temporo-parietal areas during selective attention (Christakou et al., 2009b; Rubia et al., 2010b). Overall, these findings suggest that gender differences in frontal and parietal recruitment during tasks of cognitive control and attention may be related to gender differences in the underlying neuro-functional maturation of these brain regions.

To our knowledge, however, no fMRI study to date has investigated age by gender effects in tasks of motor response inhibition. Given evidence for sex differences in behavioural impulsiveness (Campbell and Muncer, 2009; Labouvie and McGee, 1986), and evidence that male-predominant impulsive developmental disorders such as ADHD and conduct disorder are impaired in motor response inhibition (Hobson et al., 2011; Rubia, 2011), the study of sex by age interactions on neural networks of impulse control as measured in a motor inhibition task is particularly relevant and may shed light on the underlying neural basis of gender differences in impulsive control.

In this fMRI study, we hence aimed to investigate the effects of age, sex, and sex by age interaction on neuro-functional activation in a relatively large sample of sixty-three male and female adolescents and adults during a challenging tracking Stop task (Rubia et al., 2003, 2007b).

Given evidence for linear age-correlated activation increase in inferior and medial prefrontal and striatal brain regions during previous developmental imaging studies of the Go/No-go and Stop tasks (Rubia et al., 2006, 2007b), we expected that these brain areas would be progressively more recruited with increasing age between childhood and adulthood. Given previous evidence for increased frontal activation in females and increased parietal activation in males during higher level cognitive control and attention tasks (Bell et al., 2006; Christakou et al., 2009b; Garavan et al., 2006; Goldstein et al., 2005; Rubia et al., 2010b; Thomsen et al., 2000; Weiss et al., 2003), and evidence for increased activation in females in frontal and striatal areas and in males in anterior cingulate during Go/No-go and Stop tasks (Garavan et al., 2006; Li et al., 2006, 2009; Liu et al., 2012) we expected that females would show increased activation in lateral fronto-striatal brain regions while males would show increased activation in anterior cingulate and parietal cortices. Furthermore, in line with our previous age by gender interaction

findings during higher cognitive control and attention tasks including a related task of interference inhibition (Christakou et al., 2009b; Rubia et al., 2010b) we hypothesised that fronto-striatal and parietal brain regions that differed in activation between males and females would be related to underlying sex differences in the neurofunctional maturation of these brain regions.

Methods and materials

Participants

Sixty six right-handed healthy adolescents (N = 31; 20 males, 11 females; age range: 13–19 years) and adults (N = 35; 21 males, 14 females; age range: 21–45 years), in total 41 males and 25 females, ranging in age from 13 to 45 years (mean age in years (SD) = 22 years, 3 months (7 months)) were recruited through advertisement. The proportion of males to females was balanced in the adolescent and adult groups (Chi-square test (df = 1), p = .7).

Exclusion criteria were current or past substance abuse, head injury, learning disability, or mental, endocrine or neurological disorders. All participants scored above the 10th percentile (IQ estimate over 80) on the Raven's Standard Progressive Matrices test (Raven, 1960) of performance intelligence quotient (IQ) (Converted Mean Performance IQ estimate (SD) = 106 (12); Male IQ estimate = 108 (12); female IQ estimate = 104 (11)). There were no gender differences in IQ (df = 1,65, F = 2.3, p = n.s.).

The 41 males (mean age (SD) = 21 years, 8 months (7 months, 2 months)) and 25 females (mean age (SD) = 23 years, 2 months (7 years, 9 months)) did not differ significantly in age (F = .7; df = 1,61; p = n.s.).

The study was approved by the local Ethics Committee and all participants gave informed consent and received £30 for their participation.

Stop task

Task administration

A video projector was used to present the task, which participants viewed via a prism attached to the head coil. Behavioural response data were recorded through a key pad onto a time-locked automated PC system. All participants were trained once on the task prior to scanning. A randomised presentation, rapid, event related fMRI design was used with jittered inter-trial intervals as well as random events with randomised inter-target intervals to optimise statistical efficiency (Dale, 1999).

The tracking stop task requires withholding of a motor response to a go stimulus when it is followed unexpectedly and unpredictably by a stop signal (Logan et al., 1997). In our visual fMRI adaptation of this task (Rubia et al., 2003, 2007b), arrows (of 1 s duration) pointing either to the left or right side appeared at the middle of the screen with a mean inter-stimulus-interval (ISI) of 1.8 s, jittered between 1.6 s and 2 s. Subjects were instructed to respond to the arrow direction by making a button response with their left or right thumb. On the unpredictable, infrequent stop trials (20% of trials), the arrows pointing left or right were followed (about 250 ms later) by arrows pointing upwards (of 300 ms duration), and subjects had to inhibit their motor responses. The time interval of 250 ms between go-signal and stop-signal onsets changes according to each subject's performance and is calculated based on the subject's overall probability of inhibition on all previous trials, which is re-calculated after each stop trial. If the overall probability of inhibition on previous trials was over 50%, then the stop signal delay would increase in steps of 50 ms—thus making it harder to inhibit. If the overall probability of inhibition of all previous trials reaches below 50% after any given stop trial, the stop signal delay would decrease in steps of 50 ms, making it easier to inhibit. The tracking algorithm ensures that the task is equally challenging and difficult for each individual, providing 50% successful and 50% unsuccessful inhibition trials. Forty stop trials were pseudo-randomly interspersed with 156 go trials (78 left and 78 right pointing arrows) and were at least 3 repetition times apart for adequate separation of the hemodynamic response (see Fig. 1).

The main inhibitory measure is the stop signal reaction time (SSRT), calculated by subtracting the mean stop signal delay (the average time between go and stop signals, at which the subject managed to inhibit to 50% of trials) from the mean reaction time (MRT) to go trials (Logan et al., 1997). The main dependent variables of the go process of the task are the MRT to go trials and the intra-subject standard deviation to go trials (SD).

In the event-related fMRI analysis, brain activation to the 50% successful stop trials is contrasted with that to go trials (for details of the task see Rubia et al., 2003, 2005, 2007b, 2008, 2010a).

Performance data analysis

The effect of sex on the dependent variables was analysed using multivariate analysis of variance (MANOVA) with sex as the independent factor. Linear effects of age on behavioural performance variables were investigated using two tailed Pearson correlation analyses.

Functional magnetic resonance imaging (fMRI)

Image acquisition

Gradient echo-planar magnetic resonance (MR) imaging data were acquired on a GE Signa 1.5 Tesla Horizon LX System (General Electric, Milwaukee, WI, USA) at the Institute of Psychiatry, London. Reliable image quality was obtained by using a semi-automated quality control procedure (Simmons et al., 2009, 2011). A quadrature birdcage head coil was used for radiofrequency transmission and reception. In each of 16 non-contiguous planes parallel to the anterior–posterior commissure, 196 T2*-weighted MR images depicting blood oxygen level dependent (BOLD) contrast covering the whole brain were acquired with echo time (TE) = 40 ms, TR = 1.8 s, flip angle = 90°, in plane voxel size = 3.1 mm, slice thickness = 7 mm and slice skip = 0.7 mm.

At the same time, a high-resolution inversion recovery echo-planar image of the whole brain was acquired in the inter-commissural plane with TE = 40 ms, TI = 180 ms, TR = 16 s, in-plane voxel-size = 1.5 mm, slice thickness = 3 mm, slice-skip = 0.3 mm.

fMRI data analysis

XBAM (Brammer et al., 1997), the method of fMRI analysis used, makes no assumptions of normality, which are often violated in fMRI data, but instead uses median statistics to control outlier effects and permutation rather than normal theory based inference. Furthermore the most common test statistic is computed by first standardising for individual difference in residual noise, before embarking on second

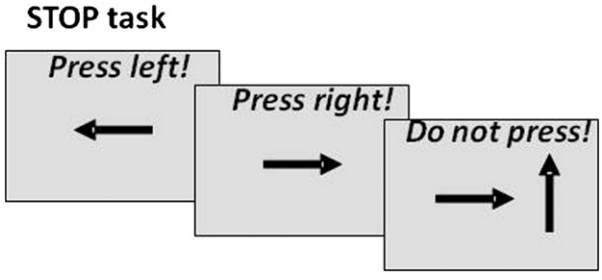

Fig. 1. Schematic presentation of the tracking Stop task. Subjects have to respond to go arrows that point either right or left with a right/left button response. In 20% of trials, the go-signals are followed (about 250 ms later) by stop signals and subjects had to inhibit their motor responses. A tracking algorithm changes the time interval between go-signals and stop-signals according to each subject's performance on previous trials (average percentage of inhibition over previous stop trials, recalculated after each stop trial), resulting in 50% successful and 50% unsuccessful inhibition trials.

level, multi-subject testing using robust permutation-based methods. This allows a mixed effects approach to analysis. A detailed analysis of the validity and impact of normal theory based inference in fMRI in large number of subjects (81) by Thirion et al. (2007) found substantial deviations from normality in a significant number (22%) of intracerebral voxels using the most common measure of response size (unstandardised beta) used in fMRI analysis. Based on this, they recommend a mixed effects rather than simple random effects analysis, permutation-based inference and cluster or parcel level rather than voxel level inference, all of which are implemented in XBAM.

Individual analysis

Firstly, fMRI data were realigned in order to minimise movement artefacts (Bullmore et al., 2001) and smoothed using a Gaussian filter (full-width half maximum, 7.2 mm). Time-series analysis of individual subject activation was performed using XBAM, with a wavelet-based re-sampling method (described in Bullmore et al., 2001). Briefly, we first convolved the experimental condition (i.e. the 20 successful stop trials) with two Gamma Variate model functions (delays of 4 and 8 s). Standard go stimuli were not convolved with the Poisson functions, but they formed a saturated baseline condition used in the modelling of the experimental condition. We then calculated the weighted sum of these two convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (the SSQ-ratio (sum of squares quotient-ratio)) was then computed at each voxel consisting of the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing the significance of any given SSQ-ratio was established using the wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the re-sampled data. This process was repeated 20 times at each voxel and the permuted data combined over the whole brain (i.e. all voxels) (global determination of statistical threshold). A global (brain-wide) threshold for activation at $p < 0.05$ was then identified from the permuted data and used for thresholding. Voxels that passed this threshold then went on to second (cluster) level analysis. The statistic we use for identifying group activations (SSQ-ratio) is essentially equivalent to the activation level (beta) divided by its variance and the group mean of such a statistic (mean of activations inversely weighted by variance) has been shown by Thirion et al. (2007) to have very good reproducibility in identifying activated voxels. The same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data. The null distribution can then be used to threshold the activation maps at any desired Type I error rate. The resulting activation map hence reflects activation associated with successful stop trials relative to standard go trials that formed the implicit baseline.

Group analysis

The individual maps were normalised into standard Talairach space, beginning with rigid body transformation of the fMRI data to an inversion recovery image of the same subject and followed by affine transformation onto a Talairach template (Talairach and Tournoux, 1988). A group brain activation map (GBAM) for the task was then produced by calculating the median observed SSQ-ratio over all subjects at each voxel in standard space and testing them against the null distribution of median SSQ-ratios computed from the identically transformed wavelet re-sampled data (Brammer et al., 1997). A voxel-wide statistical threshold was first set to $p < 0.05$ to give maximum sensitivity and to avoid type II errors. Surviving voxels were assembled into 3D clusters using a contiguity criterion. The mass of each cluster was calculated by summing the statistical values of all the voxels making up a cluster. The same clustering procedure was performed in the permuted data. The masses of the random clusters occurring in the permuted data were pooled to create a null distribution of cluster masses. Using this null distribution, a cluster-level threshold was computed such that the final expected number of Type I error clusters was <1 per whole brain. The necessary combination of voxel and cluster level thresholds was not assumed from theory but rather was determined by direct permutation for each data set, giving excellent Type I error control (Bullmore et al., 1999). Cluster mass rather than a cluster extent threshold was used, to minimise discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999). For this group activation analysis, less than one false activated cluster was expected at a p value of <0.05 at the voxel level and $p < 0.01$ at the cluster-level.

Whole-brain correlations between brain activation and age across all subjects

In analyses across groups (gender group differences, correlations with age), there is less information on global stability of the statistics that we have studied and we have thus adopted the more conservative strategy of determining the threshold for a significant response at each voxel using a larger number of permutations (1000) and not combining the permuted data across values to obtain a global threshold (as with the group and individual analyses) but, instead, to threshold locally (local determination of statistical threshold). The voxels passing this threshold are again subjected to second level cluster analysis. This is a more computationally intensive procedure than the global approach but makes fewer assumptions about stability of thresholds across voxels.

Therefore, to test for a linear correlation between whole-brain activation and age, the Pearson product-moment correlation coefficient was first computed at each voxel in standard space between age data and signal change over all subjects. The correlation coefficients were recalculated after randomly permuting the ages but not the fMRI data. Gender was covaried in the analysis.

Repeating the second step many times (1000 times per voxel for local determination of statistical threshold), gives the distribution of correlation coefficients under the null hypothesis that there is no association between specific ages and specific BOLD effects. This null distribution can then be used to assess the probability of any particular correlation coefficient under the null hypothesis. The critical value of the correlation coefficient at any desired Type 1 error level in the original (non-permuted) data could be determined by reference to this distribution. The analyses were then extended to the 3D cluster level using the procedure described above. In this analysis, less than one error cluster was observed at a p-value of <0.05 at the voxel level and <0.001 at the cluster level.

To test whether that brain activation changes with age are truly age related and not confounded by performance variance across development between adolescence and adulthood, the analysis was repeated covarying for the performance variable that correlated with age across the sample, i.e. probability of inhibition.

ANCOVA for sex differences in brain activation

ANCOVA was conducted for between-group differences in gender using age as covariate using a randomisation-based test for voxel- and cluster-wise activation differences (Bullmore et al., 1999). Less than one false positive 3D cluster in the final map was expected at $p < 0.05$ at the voxel level and $p < 0.01$ at the cluster level.

First, the difference between the mean SSQ-ratio values in each group was calculated at each voxel. The mean ratio was then recalculated 1000 times at each voxel following random permutation of group membership and the difference in SSQ-ratios was calculated after each permutation. The same set of random numbers was employed for the permutation at each voxel to preserve spatial correlations in each permuted map. The probability of the original SSQ-ratio difference under the null hypothesis of no effect of group membership is the number of times we observed an SSQ-ratio difference as large as or larger than the original difference during the permutation process, divided by the total number of permutations. If this value exceeded our threshold for voxel-level activation, the

voxel was deemed to show a significant difference. The analysis was then extended to the 3D cluster level as described above.

We wanted to investigate whether findings were purely gender-related and not secondary to performance differences between genders. Therefore we test whether findings survived when performance differences between males and females were covaried. For this purpose data were re-analysed using ANCOVA with those performance variables as covariates that differed between males and females, i.e. MRT and SSRT.

Age by sex interaction effects: sex differences in whole-brain correlations between brain activation and age

In order to test whether gender had differential effects on the linear age correlations across the whole brain, sex differences were examined in the correlation coefficients of brain activation with age. For each group independently, the average Pearson product moment correlation coefficient between subject age and fMRI response was computed, and the difference in correlation between the two groups calculated. To determine the significance of this difference, the appropriate null distribution was generated by randomly permuting subjects and their ages between the groups (without replacement), thus scrambling any group differences. For each of the permutations the difference in correlation between the scrambled groups was calculated and the resulting values were combined over all voxels to produce a whole-brain null distribution of differences in correlation. Testing was then extended to cluster level, with the cluster probability under the null hypothesis chosen to set the level of expected Type I error clusters to less than one. Less than one error cluster was observed with a p-value of <0.05 at the voxel level and <0.001 at the cluster level. Areas where either sex showed exclusive significant progressive or regressive changes are reported.

For all experimental contrasts, information can be obtained about the size, and also the direction of the activation from the general linear model fit to the time series of activation. The sign of the BOLD response can either be positive or negative with respect to the regressor (the implicit baseline in this case). We were careful to consider the possibility of negative BOLD signal change by examining the sign of the signal change relative to the regressor, particularly in brain regions known from prior research to be areas that "deactivate" relative to various baseline conditions. For all analyses only BOLD responses were considered where the average SSQ ratio in response to the activation condition was positive.

For all analyses the Brain Extraction Tool (BET) from the FSL (FMRIB Software Library) software package (Smith, 2002) was used to create a grey matter mask of the Talairach template used for normalisation. This mask was then subsequently used to restrict the analysis to those voxels lying within the grey matter mask.

Conjunction analysis between the ANCOVA comparison of gender differences in activation and the age by sex interaction analysis

We wanted to specifically test the hypothesis that brain activations that differed between genders were also brain activation clusters that differed in their underlying functional brain maturation between males and females. For this purpose we conducted a conjunction analysis between activation clusters that differed in the ANCOVA sex difference analysis and activation clusters that differed between the sexes in their functional brain maturation with age. In order to test whether brain activation clusters that differed between the sexes overlapped with brain activation clusters that showed differential functional maturation between gender, we conducted a conjunction analysis between areas that differed between males and females in brain activation (i.e. ANCOVA of gender differences in activation) and areas that showed significantly different age correlations between males and females (i.e. ANOVA sex by age interaction effects). The resulting activation clusters from this conjunction analysis therefore reflect brain regions that differ in their activation between gender and which at the same time also differ between gender in their age correlations, i.e., in their age-associated functional maturation.

Results

Behavioural performance

The probability of inhibition (PI) was about 50% in all subjects (i.e. mean PI (SD) all participants: 52% (6%); males: 52% (5%); females: 53% (7%)) with no significant sex differences ($F(df) = 0.6$ (1,64); p = n.s.).

Pearson correlation analyses between age and performance, however, showed that across all subjects only the probability of inhibition was significantly positively correlated with age ($r = .3$, $p < 0.01$). MANOVA showed significant sex differences in performance variables ($F(df) = 2.8$ (3,62); $p < 0.046$), which was due to females being significantly faster in both the main dependent inhibitory measure of the task, i.e. the SSRT, as well as in the executive go process of the task, i.e. MRT to go trials (see Table 1).

Given prior evidence, where paediatric studies showed that girls had better inhibitory capacity than boys (Aarnoudse-Moens et al., 2011, 2012; Bezdjian et al., 2009) while adult studies showed no gender effects (Garavan et al., 2006; Liu et al., 2012), we tested the hypothesis that sex differences in SSRT were driven by sex differences in the paediatric but not the adult age group. For this purpose we therefore tested for sex differences in SSRT within adolescence (i.e., 13–19 years) and within adulthood (i.e., 21–45 years), separately. As expected, in adulthood the sex differences in SSRT were no longer significant, but they were significantly different for gender in the adolescent sample ($F(df)$ (1,31) = 6, $p < 0.02$).

fMRI results

Motion

No significant differences in x, y, z maximum displacement were observed between either adolescents and adults ($F(df) = 1.2$ (3,60); $p = .3$) nor was there a significant correlation between maximum x, y, z displacement and age ($r > .2$, p = n.s.). Also, no differences were observed in these measures between males and females ($F(df) = 1.3$ (3,60); $p = .3$).

Brain activation across all subjects

Across all subjects, brain activation was observed in a large cluster in the right inferior prefrontal cortex, in the right superior frontal lobe, as well as in extensive clusters in the left and right temporo-parietal regions comprising superior, middle, and inferior temporal and inferior parietal regions (see Table 2, Fig. 2A).

Whole-brain correlation between brain activation and age across all subjects

Across all subjects, and when covaried for gender, there was a significant positive correlation between age and brain activation in a large cluster comprising key areas of inhibition (Chambers et al., 2009), including the right and left inferior and medial prefrontal cortices, right anterior cingulate, right premotor and superior temporal areas, bilateral caudate and thalamus, right inferior and superior parietal cortex, the lateral cerebellar hemispheres and the cerebellar vermis (see Fig. 2B, Table 3).

Negative age-associations were observed in the left and right orbitofrontal and ventromedial frontal cortices, right superior frontal lobes and SMA, posterior insula reaching into ventral striatum, left and right superior, middle and inferior temporal regions including the parahippocampal area, posterior cingulate and precuneus and predominantly medial cerebellum (see Fig. 2B, Table 3).

Given that probability of inhibition correlated significantly positively with age, the analysis was repeated covarying for probability of inhibition to ensure that age correlated brain activation was not due to performance variability with age. The findings remained essentially

Table 1
Performance variables for the Stop task.

Variable	All Mean (SD)	Females Mean (SD)	Males Mean (SD)	Sex diff. F (p) df = 1,64	Age correlation All r (p)	Age correlation Females r (p)	Age correlation Males r (p)
PI (%)	52 (6)	52 (5)	53 (7)	0.30 (n.s.)	0.30 (.01)	0.40 (.05)	0.30 (.06)
SSRT (ms)	247 (214)	173 (211)	291(205)	5.06 (0.03)	0.12 (n.s.)	0.11 (n.s.)	0.18 (n.s.)
MRT Go (ms)	759 (208)	673 (231)	812 (176)	7.62 (0.008)	0.02 (n.s.)	−0.12 (n.s.)	0.21 (n.s.)
SD to Go (ms)	199 (67)	183 (51)	209 (73)	2.40 (n.s.)	−0.13 (n.s.)	−0.22 (n.s.)	−0.07 (n.s.)

Performance variables, univariate ANOVA analyses results for sex differences and Pearson correlations between performance variables and age for all subjects and for males and females separately. PI: probability of inhibition to stop trials in percentage. SSRT: stop signal reaction time; MRT go: mean reaction time to go trials; SD: intra-individual standard deviation of the MRT to go trials; = MRT Go–stop signal delay.

unchanged, with only a few clusters being slightly smaller or larger in extent after the covariate analysis.

To test for the association between positive age-associated brain activation changes and inhibitory performance variables, we extracted the BOLD activation in each cluster and correlated these with SSRT and probability of inhibition. The probability of inhibition correlated significantly positively with the positive age-correlated activation clusters in right IFG ($r = .3, p < 0.04$) and in left superior temporal/inferior frontal junction ($r = .3, p < 0.005$). No significant correlations were observed with SSRT.

In order to test whether increases in brain activation with age were potentially disproportionately driven by the younger participants or by males or females, we used the Fisher r–Z transformation to compare the correlation coefficients of the adolescent and adult subgroups of our sample and of the male and female subgroups of our sample for every cluster identified in the whole-brain correlation analysis with age. There were no significant differences in the correlation coefficients between BOLD response and age in any of the clusters between adolescents and adults or between males and females.

Sex differences in brain activation

ANCOVA of sex differences in activation, covaried for age, showed that males had significantly increased activation relative to females in rostro-medial frontal cortex including anterior cingulate, reaching into SMA, in the right inferior parietal lobe and in the right posterior cingulate/precuneus. Females showed significantly increased activation relative to males in the left ventrolateral and superior prefrontal cortices, reaching into the superior temporal lobe, and in the left inferior frontal lobe and anterior and posterior insula reaching into putamen (see Table 4, Fig. 2C). All findings remained when performance variables that differed between gender, i.e. SSRT and MRT, were covaried, with the exception that the frontal activation cluster that was increased in males was somewhat smaller and no longer reached into the SMA and the left frontal cluster that was increased in females no longer reached into the superior temporal lobe in females. This suggests that the main brain activation difference findings were truly gender-related and not confounded by the performance differences between males and females.

We tested whether brain activation that differed between the sexes was correlated with performance measures. The activation in the posterior cingulate (that was increased in males relative to females) was at a trend-level significantly negatively correlated in males with SSRT ($r = -0.3, p < 0.07$), while in females, MRT to go trials (which was decreased in females relative to males) was at a trend-level negatively correlated with the activation in left IFC/insula/putamen which was enhanced in activation in females ($r = -0.4, p < 0.08$).

Age by sex interactions: sex differences in whole-brain correlation between brain activation and age

The sex by age interaction analysis tested for brain activations that were significantly differentially correlated with age in males and females. All activation clusters resulting from this analysis were therefore positively age-correlated either in males relative to female or in females relative to males. Brain areas that were positively age-correlated in females relative to males were in predominantly left hemispheric brain areas, including the left but also the right ventrolateral and superior prefrontal cortices, left premotor cortex, midbrain, left thalamus, bilateral parahippocampal gyri, left superior and inferior temporal lobes, right precuneus, middle cerebellum/vermis and medial occipital cortex. Brain areas that were exclusively positively age-correlated in males relative to females were in more predominantly right hemispheric areas of rostromedial and dorsolateral prefrontal cortices, SMA, right putamen, globus pallidus and thalamus, predominantly right insula, predominantly right superior temporal and inferior parietal cortices, left precentral cortex, bilateral postcentral gyri and bilateral anterior cerebellum (see Fig. 2D, Table 5).

Conjunction analysis

To test whether brain activations that differed between genders were also brain activation clusters that differed in their underlying functional brain maturation between males and females, we conducted a conjunction analysis between activation clusters that differed in the ANCOVA sex difference analysis and activation clusters that differed between the sexes in their functional brain maturation with age. The conjunction analysis revealed 5 brain activation clusters. Three clusters were thus significantly enhanced in activation in females and at the same time were also exclusively age-correlated in females relative to males in 1) the left ventrolateral prefrontal cortex (BA 47; Talairach coordinates: −38;36;−12; 14 voxels) 2) the left superior prefrontal cortex (BA 10; Talairach coordinates: −30;51;5; 10 voxels; 3) a small cluster in the left putamen (Talairach coordinates: −30;0;−1; 3 voxels). Two activation clusters, one in the right inferior parietal/postcentral gyrus (BA 40/1/2; Talairach coordinates: 42;−29;52; 58 voxels), and one in the left superior frontal lobe (BA 6; Talairach coordinates:

Table 2
Brain activation for all participants during successful motor response inhibition.

Brain regions of activation	Brodmann area	Peak Talairach coordinates (x;y;z)	Number of voxels	p-Value of cluster
R inferior frontal gyrus	47/45/46/10	43;33;−7	108	0.008
R middle/superior frontal	8/6	43;11;42	135	0.0016
R superior/middle/inferior temporal/inferior parietal	42/22/39/37/40	50;−59;−2	726	0.001
L superior/middle/inferior temporal/inferior parietal/occipital/	22/39/37/40/19	−47;−60;15	542	0.001

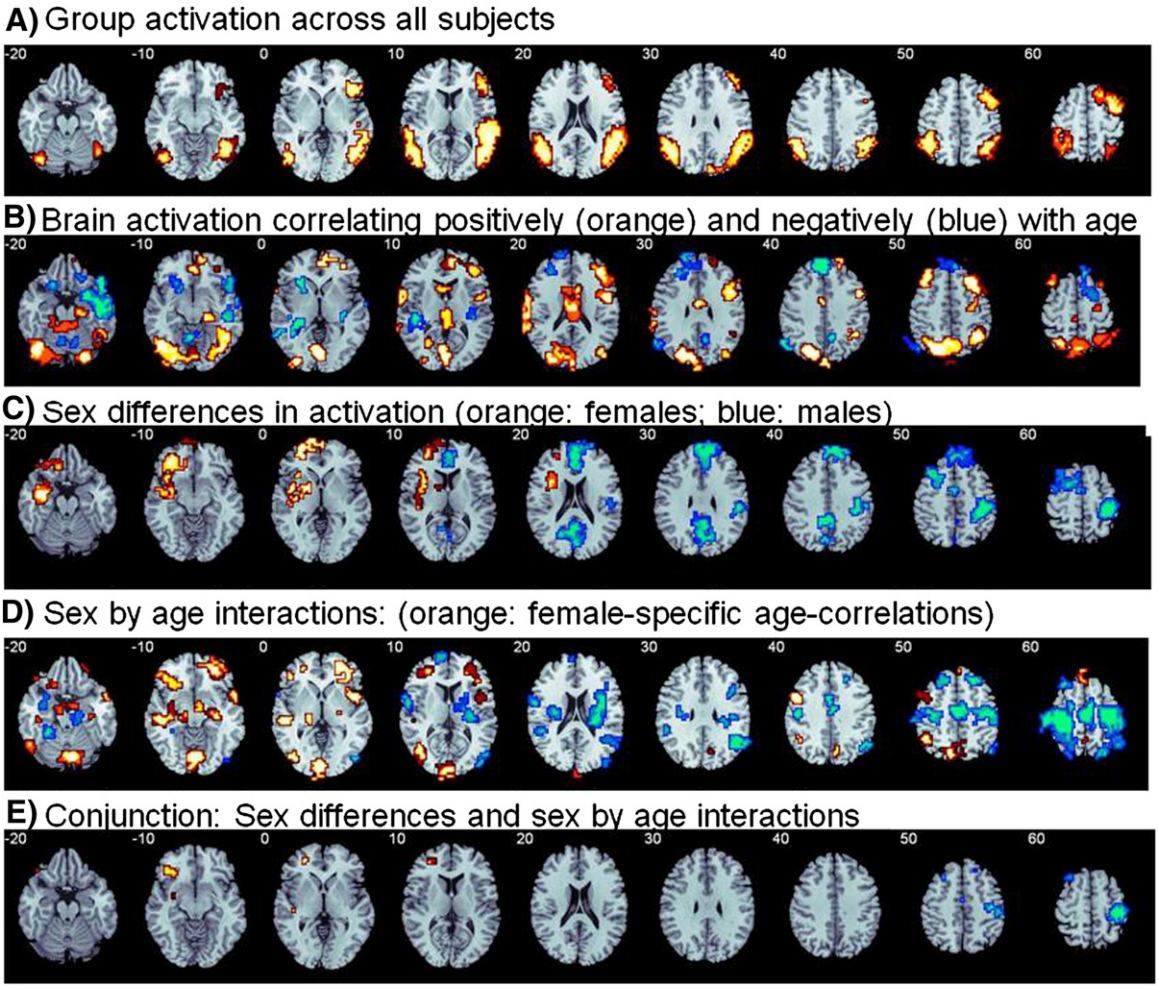

Fig. 2. A. Group brain activation during successful stop trials relative to go trials across all subjects ($p < 0.05$ for voxel- and $p < 0.01$ for cluster-wise analysis). B. Whole-brain correlation of activation with age covaried for gender: clusters exhibiting linear positive (orange) or negative (blue) correlation with age across all subjects (at $p < 0.05$ for voxel and $p < 0.001$ for cluster levels). C. ANCOVA of gender differences covaried for age in brain activation ($p < 0.05$ for voxel- and $p < 0.01$ for cluster-wise analysis). Females > Males is represented in orange, while Males > Females is represented in blue. D. Sex by age interaction analysis: Brain areas that were significantly differentially age-correlated in males and females. Orange activation clusters show activations that were significantly positively age-correlated in females but not males, while blue clusters describe activations that were significantly positively age-correlated in males but not females. E. Conjunction analysis between the ANCOVA analysis of gender differences in activation and the sex by age interaction analysis that tested for areas that differed between gender in their age correlations (at $p < 0.05$ for voxel- and $p < 0.001$ for cluster-wise analysis). The analysis shows brain regions were females had greater activation and at the same time had stronger positive age-correlations than males (orange) and areas where males had greater activation and at the same time had greater positive age-correlations relative to females (blue). For all analyses, statistical thresholds were selected to elicit less than one error cluster. For all images, 3D clusters of activation are presented superimposed on horizontal slices. Slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

−31;24;56; 9 voxels) were enhanced in males relative to females and at the same time were significantly positively age-correlated in males but not females (see Fig. 2E).

Discussion

This study investigated the effects of age, sex, and age by sex interaction on brain activation during motor response inhibition in a tracking Stop signal task. As expected, all subjects activated key motor response inhibition areas of the right IFC, right DLPFC, bilateral temporo-parietal regions and the cerebellum. The likelihood to inhibit increased progressively with age. Analysis of age-associated brain function changes, covaried for gender, showed that performance maturation was paralleled by progressively increased activation in the key motor inhibition area of the right IFC and bilateral DLPFC and medial frontal regions, caudate and thalamus, as well as the parieto-temporal and lateral cerebellar regions. Age-associated activation changes in all areas survived after covarying with inhibitory capacity, suggesting that the age effects were truly age-related and not an artefact of age-associated performance differences. Negative age correlations were observed in the lateral orbitofrontal and rostromedial frontal cortices, middle and inferior temporal lobes, posterior cingulate, posterior insula and vermis of the cerebellum. Several of these regions form part of the default mode network (DMN) and may reflect an immature lack of deactivation of the DMN during task performance in younger subjects. The gender comparison showed that females were faster in inhibiting their motor responses, as expressed in faster SSRT, and were also faster in the executive go-process of the task. ANCOVA gender comparison, covaried for age, showed that females showed enhanced activation relative to males in the left ventrolateral and superior prefrontal cortices, insula and putamen, while males showed relatively stronger activation in the right rostromedial frontal cortex, right inferior parietal lobes and posterior cingulate. Importantly, a conjunction analysis between areas that differed in activation between gender and that showed sex-dimorphic linear age correlations revealed that the left ventrolateral and superior frontal activation that was increased in females was also significantly more age-correlated in females relative to males, while the right inferior parietal activation that was increased in activation in males was also

Table 3
Linear correlations between brain activation and age.

Brain regions of activation	Brodmann area	Peak Talairach coordinates (x;y;z)	Number of voxels	p-Value of cluster
Positive correlations between brain activation and age				
R inferior/middle/superior frontal gyri	8/9/45/46	33;26;42	234	0.000001
R ventromedial frontal/anterior cingulate	11/10/32	11;59;−2	73	0.000001
R superior frontal	9/46	22;56;26	15	0.0003
R premotor cortex	6	29;−11;42	14	0.0001
L middle frontal gyrus	8	−36;30;48	51	0.000001
R + L thalamus/caudate		4;−19;4	133	0.000001
L inferior frontal/premotor/superior temporal	44/6/22	−61;0;9	105	0.000001
R inferior/superior parietal lobe	40/7	43;−52;42	83	0.000001
L precuneus	7	−4;−26;59	25	0.000001
R occipital cortex	19	40;−74;15	26	0.000001
L middle occipital/precuneus/posterior cingulate	17/18/19/31	−25;−81;15	703	0.000001
L + R cerebellum (vermis)		18;−26;−40	221	0.000001
R lateral cerebellum		29;−78;−24	119	0.000001
Negative correlations between brain activation and age				
L orbitofrontal/superior temporal/insula/putamen	11/47	−22;26;−35	89	0.000001
L orbitofrontal gyrus	11/47	21;37;−35	49	0.000001
L rostromedial frontal cortex	9/8	0;48;31	111	0.000001
R superior frontal lobe	8	11;44;53	12	0.0005
R superior frontal lobe/SMA	6	22;7;58	62	0.000001
R posterior insula/ventral striatum		36;−22;−2	16	0.00002
L middle temporal/inferior parietal lobe	39/40	−58;−59;26	35	0.000001
L middle temporal gyrus	21/22	−40;−30;−2	55	0.000001
R superior/middle/inferior temporal/fusiform/parahippocampal gyri	38/20/21/28/36	54;26;−24	236	0.000001
R posterior cingulate/precuneus	31	11;−56;26	16	0.0001
L cerebellum, anterior lobe		−4;−52;−18	40	0.000001
R cerebellum, posterior lobe		14;−59;−35	29	0.000001

significantly more positively age-correlated in males relative to females. The findings show for the first time that sex differences in inhibition-related brain activation, of increased left prefrontal activation in females and increased right inferior parietal activation in males, are due to underlying differences in the functional maturation of these regions. This demonstrates that sex-dimorphic activation patterns during cognitive control are not static but determined by sex-dimorphic differences in the functional maturation of inhibitory networks between adolescence and adulthood in the two sexes.

Age effects

As expected, all subjects activated the key motor inhibition area of the right IFC, as well as the right DLPFC, bilateral temporo-parietal regions and cerebellum. These regions also showed significantly increased activation with age across all subjects, when covaried for gender, including a large cluster comprising the right inferior and middle prefrontal cortex, as well as the left inferior frontal and superior temporal and inferior parietal regions, right premotor cortex, caudate and thalamus, and cerebellum.

The right IFC in particular has been documented as the key region for motor response inhibition in fMRI (Aron and Poldrack, 2006; Rubia et al., 2001, 2003, 2007b), lesion (Aron et al., 2003) and transcranial magnetic stimulation (TMS) studies (Chambers et al., 2006, 2007; Juan and Muggleton, 2012) (for review see Chambers et al., 2009). This was also observed in a recent conjunction analysis of fMRI studies of inhibition tasks that showed that the right IFC activation for Stop and Go/No-go tasks was one of the most consistent findings across studies, together with DLPFC, insula and inferior parietal activation (Boehler et al., 2010). There was a correlation between the right IFC activation and probability of inhibition, both of which were positively correlated with age. However, the findings survived when we covaried for the probability of inhibition, suggesting that they are true age effects and not secondary to developmental performance improvements with age. While the right IFC, caudate and thalamus have been directly correlated with inhibitory control in several studies (Aron and Poldrack, 2006; Aron et al., 2003; Chambers et al., 2006; Rubia et al., 2007b), there is evidence to suggest that the insula and parietal regions may reflect increased visual–spatial attention load for the processing of stop signals rather than inhibition-specific processes (Boehler et al., 2010; Chambers et al., 2009; Rubia et al., 2007b; Zhang and Li, 2012). The findings of a linear increase in activation with age in these prefrontal, striato-thalamic, parietal and lateral cerebellar hemispheres extend our previous findings of significant age-associated activation increase in these areas in a purely male sample in the Stop task (Rubia et al., 2007b) and are in line with developmental imaging findings of age-associated increased activation in these areas for the related Go/No-go task (Bunge et al., 2002; Rubia et al., 2006).

Significant negative age-correlations were observed in the left and right ventrolateral orbitofrontal cortex, reaching into the insula and putamen in the left hemisphere, in the posterior right insula and ventral striatum, in the SMA and rostromedial frontal cortex, left temporal

Table 4
Sex differences in brain activation.

Brain regions of activation	Brodmann area	Peak Talairach coordinates (x;y;z)	Number of voxels	p-Value of cluster
Increased activation in males relative to females				
Anterior cingulate/rostromedial frontal/SMA	24/32/10/9/8/6	4;59;15	291	0.0008
R inferior parietal lobule	40	40;−22;48	291	0.0007
L/R posterior cingulate/precuneus/cuneus	31/23/7/19	7;−44;26	200	0.002
Increased activation in females relative to males				
L ventrolateral prefrontal cortex	11/47/10	−25;51;−2	146	0.008
L inferior frontal/anterior/posterior insula/putamen/superior temporal	45/13/38	−32;−4;−23	184	0.004

Table 5
Sex by age interaction analysis: brain activations that were exclusively positively age correlated in females and in males.

Brain regions of activation	Brodmann area	Peak Talairach coordinates (x;y;z)	Number of voxels	p-Value of cluster
Positive correlations between brain activation and age in males but not females				
L medial/superior frontal	8	−15;33;42	39	0.000001
R middle/superior frontal	8	22;32;42	28	0.000001
L superior frontal	10	−11;70;4	15	0.001
R medial globus pallidus/putamen	–	14;0;−2	17	0.000031
R putamen/thalamus/posterior insula	–	29;−18;9	130	0.000001
L posterior insula	–	−25;−15;15	29	0.000001
R middle/superior temporal/supramarginal	39/22/40	43;−48;20	86	0.000001
L superior/medial temporal	38/21	−32;4;−29	12	0.000025
L precentral/superior temporal	6/4	−57;4;9	34	0.000001
L precentral/postcentral/inferior/superior parietal	4/3/1/2/5/40/7	−22;−22;59	940	0.000001
L superior temporal lobe	22	−50;−33;20	18	0.000001
R inferior occipital	18	48;−77;−1	27	0.000001
L cerebellum (anterior lobe)	–	−25;−33;−24	20	0.000066
L cerebellum(anterior lobe)		−18;−22;−46	11	0.000746
R cerebellum(anterior lobe)		14;−19;−46	11	0.000001
Positive correlations between brain activation and age in females but not males				
R middle/superior/inferior frontal	11/10/45/47/46	29;48;−13	118	0.000001
R superior frontal	8	4;48;48	19	0.000077
L ventrolateral/middle frontal/insula/putamen	47/45/10	−25;48;−2	68	0.000001
R ventrolateral/superior temporal/insula	47/38/21	51;11;−7	52	0.000001
L middle frontal/premotor	9/6	−51;15;37	27	0.000001
L hippocampus/globus pallidus/putamen	38	−14;−15;−13	26	0.000001
R amygdala/hippocampus/thalamus/posterior globus pallidus	–	25;−11;−13	23	0.000001
L inferior/middle temporal	20/21/22	−47;−22;−13	66	0.000001
L precuneus	7	−7;−70;37	42	0.000001
L inferior parietal lobule	40	−40;−44;37	26	0.000001
L paracentral	5/7	−4;−44;64	33	0.000001
L inferior/middle occipital	19/18	−36;−70;−2	44	0.000001
R cerebellar uncus	28/34	11;0;−24	17	0.000001
R cerebellum (posterior lobe)	–	7;−74;−24	252	0.000001
L cerebellum (posterior lobe)	–	−51;−56;−35	28	0.000001
L Brainstem	–	29;−8;−51	16	0.000001
R Brainstem	–	0;4;−51	44	0.000001

regions and parahippocampal gyrus, posterior cingulate/precuneus and medial parts of the cerebellum. The findings of increased recruitment with younger age in earlier developing posterior temporal as well as subcortical limbic areas such as parahippocampal gyrus, insula and posterior cingulate (Gogtay et al., 2004; Sowell et al., 2004), are in line with similar observations of negative age-correlations in these regions in the context of other tasks of cognitive control and attention (Andrews-Hanna et al., 2011; Bunge et al., 2002; Christakou et al., 2009b; Konrad et al., 2005; Marsh et al., 2006; Rubia et al., 2006). The increased activation in younger subjects in these earlier maturing brain areas may reflect enhanced reliance on "bottom–up" primary sensory and limbic processes (Corbetta & Shulman, 2002) as opposed to the recruitment of the more task-relevant but still structurally (Gogtay et al., 2004; Sowell et al., 1999, 2004), and functionally maturing "top–down" fronto-striato-thalamic inhibitory networks (Andrews-Hanna et al., 2011; Bunge et al., 2002; Christakou et al., 2009b; Konrad et al., 2005; Marsh et al., 2006; Rubia et al., 2000, 2006, 2007b; Smith et al., 2011a, 2011b; for review see Rubia, 2013), mediating a more immature, and less supervised cognition.

Interestingly, in particular the rostromedial frontal cortex and posterior cingulate/precuneus, as well as the inferior temporal lobe, form part of the DMN (Weissman et al., 2006). The DMN consists of intercorrelated co-activation of the medial frontal lobe, anterior and posterior cingulate and inferior temporal and parietal areas during the resting state, that are parametrically attenuated during effortful cognitive load, presumably reflecting increases in attentional and computational resources that impinge upon task-unrelated thoughts and processes (Weissman et al., 2006). Developmental imaging studies have shown that children and adolescents have significantly weaker DMN than adults and are significantly worse in switching off their DMN networks during effortful cognitive tasks, which results in larger attention lapses and worse performance (Fair et al., 2007, 2008; Marsh et al., 2006; Supekar et al., 2010; Thomason et al., 2008). In this study, the enhanced activation in younger subjects of areas that form part of the DMN such as the rostromedial frontal cortex, posterior cingulate and inferior temporal lobe could therefore reflect a reduced deactivation of the DMN during motor response inhibition.

Within prefrontal regions, the age-correlated activation patterns showed that development appears to be associated with a shift from the recruitment of earlier developing left ventrolateral prefrontal regions and the SMA, both of which have been associated with inhibitory control (Chambers et al., 2009; Chao et al., 2009; Duann et al., 2009; Mostofsky and Simmonds, 2008; Zhang and Li, 2012) to the stronger recruitment of later developing right inferior and dorsolateral prefrontal regions, which form also part of the inhibitory control network (Chambers et al., 2009; Rubia et al., 2003, 2007b). This is in line with evidence for progressive specialisation of task-relevant activation with development and cognitive maturation, as shown in a shift from more ventral to more dorsal frontal activation patterns during other inhibition and cognitive control tasks (Andrews-Hanna et al., 2011; Bunge et al., 2002; Christakou et al., 2009a; Durston et al., 2006; Konrad et al., 2005; Marsh et al., 2006; Rubia et al., 2006; Smith et al., 2011a, 2011b; for review see Rubia, 2013). This pattern of increased recruitment with age of the dorsal over ventral brain regions was also observed in the basal ganglia, where more ventral striatal areas were significantly more recruited at younger ages while the key subcortical inhibitory regions of the caudate head (and thalamus) (Aron and Poldrack, 2006; Chambers et al., 2009; Rubia et al., 2007b) were progressively more activated with increasing age.

Most of the positively age-correlated brain regions, and in particular the bilateral IFC, have been associated with inhibitory control in fMRI (Aron and Poldrack, 2006; Rubia et al., 2001, 2003, 2007b), lesion (Aron et al., 2003) and transcranial magnetic stimulation (TMS) studies (Chambers et al., 2006, 2007; Juan and Muggleton, 2012; for review see

Chambers et al., 2009). However, it cannot be excluded that the bilateral IFC as well as the inferior and superior parietal regions were associated with the broader role in target detection or oddball attention processes that may expedite response inhibition (Chao et al., 2009; Duann et al., 2009; Hampshire et al., 2010; Hu and Li, 2012; Zhang and Li, 2012). The contrast of Stop–Failed Stop trials which control for the attentional oddball effect of the low frequency of stop trials, has been argued to be over-conservative as inhibition areas are also activated when the stopping process is too slow to succeed and activation related to monitoring success versus failure is not controlled for (Boehler et al., 2010). The Stop–Go contrast used in this study, however, has as a limitation that it does not control for the attentional oddball effect of the low frequency stimulation of Stop (20%) over the high frequent Go trials (80%). Therefore it is possible, that brain regions that increased in activation with age, in particular the right and left IFC and right inferior/superior parietal regions were associated with attentional oddball processing. The bilateral IFC and inferior parietal regions are part of the ventral attention system and are known to mediate attention allocation to behaviourally relevant salient stimuli (Corbetta et al., 2008; Shulman et al., 2009). Although fMRI studies that have controlled for the attentional oddball process have found the right IFC to be specifically activated during Stop–Failed Stop trials (Duann et al., 2009; Li et al., 2006; Rubia et al., 2003, 2007b), several fMRI studies using different stop task manipulations have shown that the bilateral ventral IFC attention system together with the pre-SMA and inferior parietal lobes is also activated during attention processing or attentional preparatory processes to the behaviourally relevant rare Stop trials (Chao et al., 2009; Duann et al., 2009; Hampshire et al., 2010; Hu and Li, 2012; Zhang and Li, 2012). In fact, in our developmental imaging study using a simple oddball target detection task, in an overlapping cohort of 66 adolescents and adult males and females, we also observed increased activation with age in the right inferior frontal and parietal regions between adolescence and adulthood, albeit far less pronounced than in this study (Rubia et al., 2010b). It is therefore possible that the functional maturation of the bilateral IFC and parietal regions is not exclusively associated with the development of inhibitory processes but may also reflect the functional maturation of top–down orienting attentional processes that interact with, expedite and underlie good inhibitory task performance (Duann et al., 2009; Hampshire et al., 2010; Zhang and Li, 2012).

Gender and age by gender effects

The gender comparison showed that females were faster in their inhibitory capacity as expressed in faster SSRT, and were also faster in the executive go-process of the task. The findings of superior performance of females compared to males are in line with paediatric studies showing better inhibitory control in girls than boys (Aarnoudse-Moens et al., 2012; Bezdjian et al., 2009), but not with negative findings in purely adult samples (Garavan et al., 2006; Li et al., 2009; Liu et al., 2012; Williams et al., 1999). To test the hypothesis that gender differences may be stronger in development and normalise in mid-adulthood, we tested for SSRT differences separately in our adult and adolescent subsamples. This analysis in fact revealed that SSRT only differed between the genders in adolescence, but not in adulthood, hence explaining previous inconsistencies of sex-dimorphic inhibitory performance patterns between paediatric and adult studies. Our age-specific sex difference findings for performance together with the previous paediatric literature therefore could suggest that sex differences in inhibitory capacity are confined to developmental periods and disappear in adulthood.

ANCOVA brain activation comparison between genders, controlling for age, demonstrated that females relative to males showed enhanced activation in the left ventrolateral and ventromedial prefrontal cortex, reaching into the superior temporal lobe, insula and putamen, while males showed relatively stronger activation in the right anterior cingulate/rostromedial frontal cortex, inferior parietal lobe and posterior cingulate/precuneus. The activation differences survived correction for performance differences, suggesting that they were not a mere artefact of gender-specific performance variance. Furthermore, some of the sex differences in activation were associated at a trend-level with the gender dimorphic performance patterns. Thus, the stopping process of the task, i.e. the SSRT, which was slower in males than females was associated at a trend-level significance with the enhanced posterior cingulate activation in males, suggesting that those males with enhanced PCC activation had a faster SSRT. The PCC has commonly been found to be activated in Stop tasks (Chao et al., 2009; Rubia, 2007; Rubia et al., 2003), but suggested to be associated with the attentional perceptual processes necessary for correct inhibition of stop trials. The PCC is a key area for visual–spatial saliency detection to rare stimuli (Mesulam et al., 2001), including Stop signals (Boehler et al., 2010) and has been associated with the attentional processes necessary for correct stop task performance (Chao et al., 2009). The enhanced left IFC/insula/putamen activation in females, on the other hand, was associated at a trend-level with MRT, which was faster in females than males, suggesting that the left IFC may have been associated with the executive process of the task. While the left IFC, and not only the right-hemispheric IFC, has also been associated with inhibition in fMRI and lesion studies (Hampshire et al., 2010; Rubia, 2007; Swick et al., 2008), with some functional connectivity studies even arguing for a stronger role for the left than right IFC in mediating inhibition, together with the pre-SMA (Duann et al., 2009; Zhang et al., 2012), the left IFC has also been argued to mediate attentional target detection processing and to kick-start the inhibitory process via its attention processing role which then initiates the inhibitory process via its connection to the pre-SMA (Chao et al., 2009). The left IFC activation enhancement in females could therefore reflect either enhanced top–down inhibitory or attention control.

In conclusion, the findings hence suggest that there are sex-dimorphic activation patterns in key areas of attention processing and inhibitory control that are associated with the sex-dimorphic performance patterns.

The findings of enhanced anterior cingulate activation in males relative to females are in line with previous sex difference activation findings during the Go/No-go and Stop tasks (Li et al., 2006, 2009; Liu et al., 2012), while the findings of enhanced activation in females in the left ventrolateral and superior prefrontal cortex, insula and putamen extends previous findings of enhanced activation in these regions in females relative to males in a Go/No-go task (Garavan et al., 2006).

The enhanced activation of the frontal and striatal regions in females and the inferior parietal, precuneus and posterior cingulate areas in males extends consistent findings of similar sex-dimorphic fronto-striatal activations in females versus parietal activation patterns in males in the context of other cognitive tasks, such as the related function of interference inhibition (Christakou et al., 2009b), working memory (Bell et al., 2006; Goldstein et al., 2005), mental rotation (Hugdahl et al., 2006; Thomsen et al., 2000; Weiss et al., 2003) and visuo-spatial (Clements-Stephens et al., 2009; Gur et al., 2007) and oddball attention tasks (Rubia et al., 2010b). It has been argued that females use a more top–down cognitive control strategy, while males rely more on parietal lobe based visual–spatial bottom–up processing (Christakou et al., 2009b; Rubia et al., 2010b). While the right ventrolateral/inferior prefrontal cortex has been more consistently associated with motor response inhibition, the left ventrolateral prefrontal cortex, however, appears to be co-activated with its right hemisphere homologue in motor response inhibition tasks (see discussion above), and has been even more strongly associated with inhibitory control in functional connectivity studies of the stop task (Duann et al., 2009; Zhang et al., 2012). Furthermore, as discussed above, the left IFC has also been suggested to mediate performance monitoring, attention allocation and the updating of information and thus to have a broader more generic role in top–down attention and cognitive control that is not specific to inhibition (Chambers et al., 2009; Chao et al., 2009; Derrfuss et al., 2005; Duann et al., 2009; Hampshire et al., 2010; Rubia et al., 2011). The fact that this region was trend-wise correlated with MRT and not SSRT in females, would be in line with a

more generic attention control function of this activation cluster. The finding of enhanced putamen activation in females is interesting in light of sex-dimorphic regional basal ganglia volumes, with putamen and caudate developing earlier and being larger in girls and the globus pallidus being larger in boys (Giedd et al., 1999, 2006; Sowell et al., 2002). This sex-dimorphic dissociation between the associative basal ganglia (putamen and caudate) and their output structures (pallidum) has been suggested to underlie cognitive and behavioural sex differences. The increased putamen activation in females would reflect a similar sex-specific dissociation of basal ganglia function and be in line with evidence that males activate the globus pallidus and thalamus more than females during motor response inhibition in the stop task (Li et al., 2006). The increased activation in the anterior putamen in females, together with increased ventrolateral and superior prefrontal activation, may hence reflect underlying frontal and basal ganglia dimorphisms, and their impact on the functional development of fronto-striatal executive networks.

Inferior and superior parietal regions including the posterior cingulate and precuneus that were increased in activation in males, are crucial for visual–spatial attention and saliency detection (Mesulam et al., 2001), which are consistently activated during inhibition tasks (Chambers et al., 2009; Duann et al., 2009; Hampshire et al., 2010; Hu and Li, 2012; Rubia et al., 2003, 2007b; Zhang and Li, 2012). The inferior parietal cortex is thought to reflect visual–spatial attention functions, such as detecting and processing the rare stop signals, rather than inhibitory processes per se (Brazdil et al., 2007; Chambers et al., 2009; Corbetta & Shulman, 2002; Duann et al., 2009; Hampshire et al., 2010; Hu and Li, 2012; Serences and Yantis, 2006; Zhang and Li, 2012). Similarly, the posterior cingulate and precuneus are connected to the limbic system and visuo-motor pathways and, as discussed above, mediate the dynamic allocation of visual–spatial attention to salience, important for the processing of the rare stop signals (Mesulam et al., 2001; Mohanty et al., 2008) (Boehler et al., 2010; Chao et al., 2009). The gender difference findings could thus suggest that males and females rely on the recruitment of different brain regions when performing a motor inhibition task, with females relying more on later stage left inferior fronto-striatal, top–down inhibitory or attention control regions for task performance, and males relying more on the inferior and superior parietal visual–spatial processing areas, presumably mediating earlier stage bottom–up visual–spatial processes necessary for task performance. The findings are in line with our previous findings of similar sex-specific activation increases with age in the frontal regions in females and in the parietal regions in males during an interference inhibition and an oddball task, presumably related to similarly different performance strategies of enhanced top–down frontal inhibitory control in females and enhanced visual–spatial parietal abilities in males (Christakou et al., 2009b; Rubia et al., 2010b).

Most importantly, the age by sex interaction effects provide developmental underpinnings of the sex-dimorphic brain activation differences. The sex by age interaction effects revealed that predominantly the left hemispheric lateral frontal, striatal, thalamic and temporal regions were specifically age-correlated in females but not males, while predominantly the right hemispheric rostromedial frontal, striato-thalamic and parieto-temporal areas were gender-specifically age-correlated in males.

Importantly, the conjunction analysis showed that the same brain regions that differed between genders also differed in their sex-specific functional maturation, with exclusively female activation increases with age in the left inferior frontal cortex and exclusively male age-correlated activation increases in the right inferior parietal lobe. The findings show that sex-dimorphic activation patterns for inhibitory control are determined by sex-dimorphic changes in the functional maturation of inhibitory networks between adolescence and adulthood. This is important as it reveals for the first time that typically observed gender differences, namely of female dominance of frontal activation and male dominance of parietal activation, during a task of cognitive control, are determined by the sex-dimorphic dynamic functional maturation of these frontal and parietal regions between late childhood/adolescence and adulthood. Thus, with increasing age between adolescence and adulthood these cortical areas progressively take over function in a sex specific manner.

The findings of a steeper functional maturation in females in the left frontal regions is in line with converging evidence showing that structural developmental processes in the frontal regions, peaking during puberty and persisting through to early adulthood, take place earlier in females than in males (Giedd et al., 1999; Lenroot and Giedd, 2010). Conversely, the steeper functional maturation in males in the right parietal regions may also be related to earlier male structural maturation of these regions. Males compared to females have consistently been shown to have reduced cortical thickness and grey matter volumes in the right inferior parietal (and temporal) regions across the lifespan, between childhood and late adulthood (Allen and Courchesne, 2003; Im et al., 2006; Luders et al., 2006; Nopoulos et al., 2000; Sowell et al., 2007). Given that cortical thickness and grey matter decrease with age post-adolescence (Shaw et al., 2007; Sowell et al., 2007) due to synaptic pruning and myelination and are associated with progressive cognitive maturation, it has been suggested that the thinner cortical thickness in males may be related to an earlier structural maturation in this region for males (Luders et al., 2006; Sowell et al., 2007). Sex by age interactions have furthermore been observed for surface area, with no decrease in surface area over time in male but a decrease in female brains, suggesting sex differences in the developmental trajectories of the parietal lobes (Salinas et al., 2012). This could potentially explain well-known sex differences in cognitive functions that are mediated by the parietal lobes such as visual–spatial abilities (Sowell et al., 2007). In fact, in support of this hypothesis, a recent structural MRI study found that the increased parietal grey matter thickness in females relative to males was associated with worse performance on a mental rotation task (Koscik et al., 2009).

The hemispheric laterality findings of increased activation and increased age-correlation in the *left* frontal areas in females compared to males and of increased activation and increased age-correlation in the *right* parietal cortex in males relative to females are interesting. They are in line with previous sex-specific laterality findings in the frontal and parietal regions in the context of other tasks such as working memory, visual object discrimination, and interference inhibition (Christakou et al., 2009b; Georgopoulos et al., 2001; Speck et al., 2000) and with similar findings of increased left frontal age-correlations in females relative to males and increased right inferior parietal age-correlations in males relative to females during interference inhibition (Christakou et al., 2009b). The female-specific age correlation in the left putamen during motor response inhibition extends a similar finding of age by sex interaction in lenticular nucleus during an interference inhibition task which was due to a female-specific age-correlation (Marsh et al., 2006). We also observed previously an age by sex interaction in putamen during a selective attention task, although this was in the right hemisphere (Rubia et al., 2010b).

Overall, the sex by age interaction effect demonstrates that sex-specific differences in brain activation may be the result of underlying sex-dimorphic functional maturation processes. The findings are in line with the findings from our previous fMRI studies that tested for sex by age interactions of similar consistent sex-specific activation increases with age in the frontal regions in females and in the parietal regions in males during an interference inhibition, a switching and an oddball task, presumably related to similarly different performance strategies of enhanced top–down frontal inhibitory and attention control in females and enhanced visual–spatial parietal abilities in males (Christakou et al., 2009b; Rubia et al., 2010b).

Together with similar previous findings during other cognitive tasks, these developmental imaging findings therefore demonstrate that sex differences observed in task-related brain activation appear to be related to sex differences in the underlying progressive functional development of these brain regions. They demonstrate that developmental differences between males and females in the functional

brain maturation of inhibitory systems appear to be underlying the sex differences in inhibitory brain function. This underlines the importance of taking into consideration developmental imaging data when investigating gender effects on neural brain activation.

These sex-dimorphic functional maturation findings are relevant to impulsive neurodevelopmental psychiatric disorders that are associated with gender differences in prevalence. The developmental disorder of Attention Deficit Hyperactivity Disorder (ADHD), for example, has been associated with a delay in brain maturation (Shaw et al., 2007, 2012) and is more prevalent in males (Polanczyk et al., 2007). It is also associated with deficits in inhibitory and attention control (Rubia et al., 2007a; Willcutt et al., 2005) and their underlying fronto-striatal inhibitory and fronto-parietal attention networks (Cubillo et al., 2012; Hart et al., 2013; Rubia, 2011). The reduction in the recruitment of inferior fronto-striatal inhibitory networks in ADHD boys relative to healthy peers may hence reflect an immature developmental activation pattern that interacts with male-specific functional maturation patterns.

Limitations

The strengths of this study include the relatively large sample size, the use of permutation fMRI data analyses across the whole brain, and the sex by age interaction analysis of whole brain activation. In this study we primarily explored linear correlations between age and brain activation and gender effects upon these. However, non-linear developmental changes have been observed in functional imaging (Brown et al., 2005) and should be investigated in future studies of larger sample sizes. Furthermore, cross-sectional studies are confounded by cohort and gender effects and therefore functional brain development could be more thoroughly investigated using longitudinal imaging studies. Another limitation is that more males than females participated in the study. However, ANOVA analyses take into account unequal subject numbers and the subject number of 25 for females was sufficiently large to elicit statistical power for fMRI analyses, where a minimum subject number of 20 have been recommended (Thirion et al., 2007). Furthermore, the sex and sex by age interaction effects of this study were in similar sized clusters for both genders. However, it cannot be excluded that sex difference findings would have been stronger for females with larger subject numbers.

Development of brain function is likely to be closely linked to structural brain development (Olesen et al., 2003). To what extent the age-correlated BOLD changes in this and other developmental functional imaging studies are related to age-correlated grey matter volume or thickness changes needs to be established in future developmental imaging studies that combine functional and structural imaging data.

Conclusion

To our knowledge, this is the first fMRI study that tested for sex differences in brain activation of motor response inhibition in the light of underlying gender-specific effects on age-related functional brain maturation between childhood and adulthood. We provide the first evidence that the superior reliance on functional frontal mechanisms in females, and on functional parietal mechanisms in males, during inhibitory control, is determined by gender differences in the post-adolescent functional development of these brain regions. Together with our previous findings of enhanced female-specific frontal functional maturation and enhanced parietal functional maturation in males during other tasks of cognitive control and attention, the findings suggest that increased female-specific frontal activation and enhanced male-specific parietal activation during higher cognitive tasks may be due to underlying sex-dimorphic functional maturation patterns. These gender differences in functional brain maturation may also underlie aspects of differences in cognitive strategies and relative abilities between the sexes, such as superior inhibitory control in females and better visual–spatial abilities in males. This issue has important implications for the study of impulsive neurodevelopmental psychiatric disorders, which are characterised by significant sex differences in illness onset, progression and prevalence.

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Conflict of interest statement

KR has received a grant from Lilly Pharmaceutical for another project and has received speaker's honoraria from Lilly, Shire and Novartis. No other conflicts of interest need to be declared.

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