



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.

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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

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