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Research Report

Individual differences in the functional neuroanatomy of inhibitory control

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ABSTRACT

We combined the data of five event-related fMRI studies of response inhibition. The re-analysis (n = 71) revealed response inhibition to be accomplished by a largely right hemisphere network of prefrontal, parietal, subcortical and midline regions, with converging evidence pointing to the particular importance of the right frontal operculum. Functional differences were observed between the sexes with greater activity in females in many of these cortical regions. Despite the relatively narrow age range (18–46), cortical activity, on the whole, tended to increase with age, echoing a pattern of functional recruitment often observed in the elderly. More absentminded subjects showed greater activity in fronto-parietal areas, while speed of Go trial responses produced a varied pattern of activation differences in more posterior and subcortical areas. Although response inhibition produces robust activation in a discrete network of brain regions, these results reveal that individual differences impact on the relative contribution made by the nodes of this network.

1. Introduction

Difficulty inhibiting inappropriate behaviours is characteristic of many psychological and psychiatric disorders ranging from the impulsivity of children with ADHD (Barkley, 1997), the loss of control exhibited by drug abusers (Fillmore and Rush, 2002; Kaufman et al., 2003), to the inappropriate stimulus-driven behaviour of brain-damaged individuals (Luria, 1966). Normal cognition is also subject to occasional inhibitory disruption as suggested by lapses in speech, action, thought and intention, wherein behaviour appears to be dictated by cue or by habit (Dempster and Brainerd, 1995). As a result of the apparent importance of this aspect of cognitive control, much effort has been expended in attempting to identify its neuroanatomical substrates. However, inhibitory control is a broad term incorporating cognitive (e.g., suppressing interference), perceptual/attention (e.g., ignoring distracters) and motor (e.g., response countermanding) domains. While the similarities and dissimilarities between these aspects of inhibition remain unclear (Bunge et al., 2002; Friedman and Miyake, 2004), it is the latter operationalisation that will be the focus here.

A substantial body of evidence on motor inhibition now exists due, in part, to the relative ease of implementing experimental tests of this function. Previous neuroimaging research has converged on a discrete number of regions thought to be implicated in motor response inhibition including dorsolateral and ventrolateral prefrontal cortex, parietal cortex, midline regions including the anterior cingulate and pre-SMA, and there is also evidence for thalamic and subcortical involvement (Aron and Poldrack, 2006; Brass et al., 2001; Braver et al., 2001; Garavan et al., 1999; Menon et al., 2001; Rubia et al., 2001; Watanabe et al., 2002). More specifically, ventral regions of the right hemisphere appear to be particularly important; the frontal operculum has been implicated

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by functional neuroimaging (Bunge et al., 2001; Konishi et al., 1998, 1999), lesion data (Aron et al., 2003) and, more recently, by TMS studies (Chambers et al., 2006). A recent meta-analysis of Go/NoGo response inhibition studies confirms substantial right prefrontal activity, incorporating both dorsal and ventral regions (Buchsbaum et al., 2005).

While research appears to converge on a discrete network of regions central to inhibitory control, a somewhat contrary set of findings have demonstrated that the functional neuroanatomy of this function can differ across individuals and across circumstances. For example, the right lateralisation of inhibitory control appears to follow a developmental timecourse, with reduced activation levels in children aged between 8 and 12 relative to adults (Bunge et al., 2002) and increased bilateral activations in the elderly (Nielson et al., 2002). Such a developmental trajectory may reflect the emergence of cortical differentiation and its subsequent decline or, with regard to the greater bilaterality of function in elderly participants, may reflect a pattern of cortical recruitment (Cabeza, 2002). Within the same experiment, the pattern of inhibition-related activation can be seen to vary in response to changes in task demands (Kelly et al., 2004) or in response to a subject's ability to prepare for an impending response inhibition (Hester et al., 2004b).

Individual differences may also exist. Within other cognitive domains such as error processing, working memory or fluid intelligence, there is evidence that activation patterns can be affected by multiple factors such as individual differences in demographics (Hester et al., 2004a), basal levels of dopamine function (Gibbs and D'Esposito, 2005), hormone levels (Maki and Resnick, 2001), extent of task practice (Kelly and Garavan, 2005) or the cognitive strategies subjects employ (Braver et al., in press; Glabus et al., 2003; Speer et al., 2003). With regard to inhibitory control, subjects with more variable response times show greater inhibition-related activity in frontal, parietal and thalamic areas; variability in response times, independent of average response time, is a putative measure of sustained attention which correlates with inhibitory success (Bellgrove et al., 2004). Differences between subjects in the speed of the response countermanding process (the stop signal response time of the STOP task paradigm) have also been shown to correlate with the magnitude of inhibition-related prefrontal and subcortical activation (Aron and Poldrack, 2006).

It is of particular interest to determine if inhibitory control is affected by the sex of the individual. Many clinical conditions characterised by impaired impulse control are more prevalent in males than females. For example, a survey with over 9000 respondents revealed that men have a higher risk of impulse control and substance use psychiatric disorders (Kessler et al., 2005) while Attention Deficit and Hyperactivity Disorder (Neuman et al., 2005) and conduct disorder (Eme and Kavanaugh, 1995) are also more prevalent in males. Whether or not such disorders, which are multi-faceted and may have multiple causes, reflect inherent differences in how males and females implement inhibitory control is unknown. While there is evidence for brain function, brain volume and brain morphometry differences between the sexes (Haier et al., 2005; Luders et al., 2004; Jung et al., 2005; Shaywitz et al., 1995; Witelson et al., 2006), it is unclear if inhibitory control differences, if they exist, will be evident in functional brain differences as assayed by a cognitive task of response inhibition. A second demographic variable of interest, age, is also worth investigating as evidence already exists for age-related changes in the functional neuroanatomy of inhibitory control (Nielson et al., 2002). However, age changes presumably reflect developmental processes that are present throughout the lifespan rather than occurring at a threshold between "young" and "old". Consequently, it is of interest to determine what age changes might occur within a younger age range.

Effective cognitive control requires a balance between the ability to proactively prepare (e.g., maintain task goals) and react (e.g., to an unexpected NoGo) to task circumstances. Deficiencies in either proactive or reactive control (Braver et al., in press) could account for poorer inhibitory performance: commission errors could arise from either an inability to actively attend to a task and maintain the response inhibition goal or a compromised ability to countermand an already initiated response. Previously, we have observed that those who score high on a measure of absentmindedness (Cognitive Failures Questionnaire, CFQ, Broadbent et al., 1982) showed reduced fronto-parietal activity but increased anterior cingulate activity for successful inhibitions (Garavan et al., 2002). A subsequent electrophysiological study observed larger and earlier N2 and P3 ERP components for successful inhibitions in those higher in absentmindedness (Roche et al., 2005). Combined, this suggests that absentmindedness may significantly affect inhibition-related activity levels, but it is unclear how exactly this individual difference may be realised. Finally, the functional neuroanatomy of response inhibition may be affected by the speed of Go response times. Faster responding on Go trials may increase the prepotency of responding and make inhibiting more difficult. Previously, we have shown this to be true on an intra-individual level but have not assessed inter-individual effects (Garavan et al., 2002).

On the whole, relatively little attention has been paid in the neuroimaging literature to individual differences, despite the sensitivity that neuroimaging techniques may have for revealing the cortical basis for differences. Pragmatic constraints, such as the costs associated with imaging sufficient numbers of subjects to enable an individual differences investigation, are one likely reason for this. Given this constraint, a meta-analysis (Buchsbaum et al., 2005) or a re-analysis of data combined from previous studies may be worthwhile strategies. To this end, this paper reports a re-analysis of five previous response inhibition studies that employed similar versions of an event-related Go/NoGo task. This approach, as well as providing robust statistical power for determining the functional neuroanatomy of inhibitory control, enables us to test for demographic effects on this neuroanatomy.

2. Results

2.1. *Performance measures*

The relationship between demographic characteristics and behavioural performance was examined for the entire sample, indicating that none of the performance or demographic

Table 1 – Demographic characteristics and behavioural performance of groups compared by each of the individual difference variables

	Sex		Age		CFQ		Go RT		% correct	
	M	F	M	SD	M	SD	M	SD	M	SD
Sex										
Male	26		29.1	7.6	31.7	6.8	375.6	75.7	77.3	19.0
Female		45	29.1	7.7	33.7	11.7	358.6	59.1	68.9	18.7
Age										
Young	7	11	**20.6**[a]	**1.7**	**37.1**[b]	**8.1**	352.2	60.8	69.8	19.3
Old	7	11	**39.8**	**4.0**	**27.1**	**9.8**	378.9	74.2	78.9	13.1
CFQ										
Low	5	13	**33.4**[a]	**8.5**	**21.4**[b]	**4.3**	351.9	70.1	68.9	21.5
High	4	14	**26.2**	**6.5**	**45.4**	**6.6**	362.2	60.5	69.5	16.7
Go RT										
Fast	8	10	29.0	8.6	30.8	11.0	**292.7**[b]	**19.6**	**54.7**[b]	**16.9**
Slow	9	9	30.4	8.0	31.0	9.3	**454.1**	**43.6**	**89.6**	**7.4**

Bold font identifies significant differences ([a]$P \leq 0.01$, [b] $P \leq 0.0001$, after adjusting for study).

measures was significantly influenced by sex (see Table 1). Age showed a significant negative correlation with CFQ scores ($r = -0.33$, $P \leq 0.008$), indicating that increasing age related to lower reported absentmindedness; Go RT significantly correlated with percentage of STOPS ($r = 0.56$, $P < 0.0001$), demonstrating that subjects with slower response patterns made a greater percentage of successful inhibitions.

Table 1 also presents the demographic and performance measures of each of the split-groups. For the sex split-group comparison, only the variable with which the split was made yielded a significant difference in either demographic characteristics or behavioural performance (all comparisons were adjusted for experimental design). The comparison based on age indicated that, aside from the mean age of the groups being significantly different, CFQ scores were also different, with younger subjects reporting higher levels of absentmindedness than their older counterparts, consistent with the correlational result reported above for the complete sample. A complementary pattern emerged for the high and low CFQ groups, with higher CFQ subjects having a lower mean age than the low CFQ subjects. Consistent with the overall positive correlation between Go RT and percentage of STOPS, the slow Go RT group had a significantly greater percentage of STOPS than subjects with fast Go RT (89% vs. 54%).

2.2. *Event-related activation*

The combined activation map for STOPS indicated a largely right hemisphere pattern of activation, with 20 clusters located in regions including bilateral inferior parietal, insula and middle frontal regions and right hemispheric activation in the inferior and superior frontal gyri, temporal, thalamic and lentiform areas. Significant clusters were also identified along the midline in both the anterior and posterior cingulate and pre-SMA (see Table 2 and Fig. 1 for all regions of interest).

Partial correlation analyses (adjusting for experimental procedure) examined the relationship between activation in each of the clusters from the combined STOPS map with age, CFQ score and Go RT. ANCOVA was used for gender given the dichotomous nature of the variable. Significance levels were corrected using a modified Bonferroni procedure for multiple comparisons (Keppel, 1991). Sex significantly influenced activation levels in 5 clusters, with greater activation in females in bilateral inferior parietal regions, right lentiform, precuneus and left middle frontal gyrus (BA 9) (see Table 2 for specific coordinates). Age negatively correlated with activation

Table 2 – Significant clusters of activation during STOPS for the total sample ($n = 71$)

Lobe	Hemisphere	Region	BA	Volume	x	y	z
Frontal	R	Dorsolateral/Ventrolateral PFC	9, 10, 44, 46	6811	43	19	23
	R	Middle frontal g[D]	6	353	25	−6	46
	L	Middle frontal g	6	873	−26	−9	51
	L	Middle frontal g	9, 46	180	−45	29	26
	L	Middle frontal g	9	109	−34	24	28
	L	Precentral g	6	422	−46	−2	36
	R	Anterior cingulate/Pre-SMA[A]	6, 32	2934	2	3	55
	R	Anterior cingulate	32	152	8	25	23
Parietal	R	Inferior parietal l[D]	40	9094	43	−44	40
	L	Inferior parietal l[D]	40	1484	−42	−43	41
	L	Superior parietal l[A]	7	254	−23	−60	46
	R	Precuneus	7	202	18	−63	50
Temporal	R	Middle temporal g	22	450	53	−36	−1
Subcortical	L	Insula	13	1520	−32	10	7
	R	Insula[C]	13	1307	31	14	4
	R	Lentiform/Putamen[A]		320	16	4	9
	R	White matter: corpus callosum[A,D]		224	4	−20	25
	R	Thalamus[D]		143	7	−10	4
	R	Thalamus		101	18	−14	11
	R	Lentiform/Globus pallidus		77	19	−9	3

Coordinates identify the centres-of-mass of the activated clusters, and volumes are reported in microlitres. Areas showing significant correlations are also identified: A, CFQ; B, Age; C, Go RT; D, Sex (ANCOVA). Upper case refers to positive correlations and lower case to negative correlations (for the Sex variable, upper case refers to greater activity for females and lower case to greater activity for males). Abbreviations: g, gyrus; l, lobule; SMA, supplementary motor area.

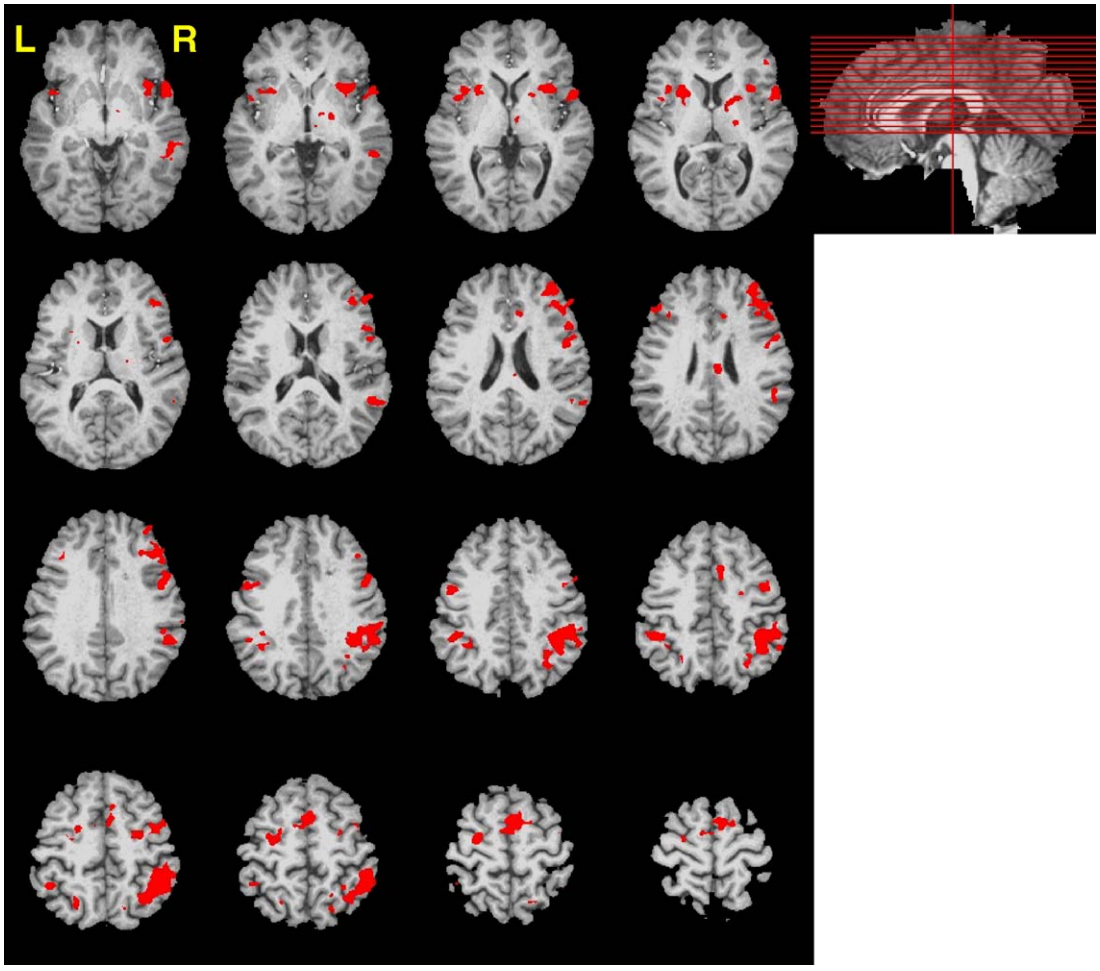

Fig. 1 – Event-related activity associated with successful response inhibitions.

in the left insula ($r = -0.47$, $P < 0.01$); Go RT negatively correlated with this same region ($r = -0.31$, $P < 0.01$) as well as the right insula ($r = -0.27$, $P < 0.05$). A subject's CFQ score positively correlated with a number of regions, including the ACC/pre-SMA ($r = 0.35$, $P < 0.01$), left superior parietal ($r = 0.26$, $P < 0.05$), posterior cingulate ($r = 0.26$, $P < 0.05$) and right precuneus ($r = 0.36$, $P < 0.01$).

2.3. *Split-group comparisons*

The examination of sex differences indicated females had significantly greater activation ($P < 0.05$ corrected) in 14 clusters located bilaterally in the middle frontal gyrus, inferior parietal lobule, right superior, middle and inferior temporal gyri, thalamus, lentiform and cerebellum (see Table 3 and Fig. 2). These activation differences arose in the absence of any sex differences in behavioural performance or other demographic characteristics. Nine other significant clusters in the OR map examining sex differences showed no difference.

For the split-group comparison based on age, the results indicated significantly greater activation for the older group in five regions, including the left inferior parietal lobule, bilateral dorsolateral prefrontal regions and bilateral inferior frontal regions (primarily BA 44). The older group also showed a significantly greater deactivation in the left pulvinar. Younger subjects showed significantly greater activation in the right insula, thalamus and lentiform (see Table 3).

The average CFQ scores for the split of subjects were 21 (low) and 45 (high), and as mentioned above, the high CFQ group was significantly younger. The results indicated significantly greater activation for the high CFQ group in 8 clusters, including bilateral inferior parietal, right middle frontal (BA 10), precuneus, putamen, anterior cingulate/pre-SMA and posterior cingulate (BA 23) and the left cerebellum (pyramis) (see Table 3).

The mean Go RT for the split of participants was 292 ms (fast) and 454 ms (slow), respectively, with the slow Go RT group having a significantly higher percentage of STOPS. The fast RT group showed significantly higher levels of activation in eight clusters including bilateral insula, right middle (BA 9) and superior frontal (BA 10), left precentral (BA 6), right superior temporal and the pre-SMA regions (see Table 3). However, the opposite pattern of greater activation for the slow RT groups was also demonstrated for 3 clusters including the right cerebellum (cerebellar tonsil), left pre-central (BA 6) and left precuneus regions. The left para-hippocampal region also showed a significant deactivation for the slow Go RT group in comparison to the baseline levels of activation for the fast RT group.

3. Discussion

3.1. *Functional neuroanatomy of response inhibition*

The present results reveal a distributed network of regions activated for successful response inhibitions. Motor response inhibition on this Go/NoGo task is largely accomplished by the right hemisphere with sizeable activations observed in fronto-parietal regions, in midline regions including the anterior cingulate and pre-SMA and in subcortical areas. Consequently, while it is perhaps safest to conclude that response inhibition is implemented by a network of regions, the challenge remains to identify the separate contributions made by each node of the network and/or to determine the circumstances that dictate the level of involvement of each

Table 3 – Significant clusters of activation from the split-group comparisons

Lobe	Hem	Region	BA	Volume	x	y	z
Sex							
Females > Males							
Frontal	R	Dorso-, ventrolateral PFC/putamen	9,10,44,46	8191	36	15	20
	L	Middle frontal g	9	520	–38	24	28
	L	Precentral g	6	327	–42	1	35
Parietal	R	Inferior parietal l	40	10025	38	–48	42
	L	Inferior parietal l	40	2012	–41	–44	39
	L	Precuneus	7	281	–11	–65	51
	L	Precuneus	7	601	–2	–66	42
Temporal	R	Superior temporal g	13	731	55	–45	18
	R	Middle temporal g	39	312	50	–55	7
	R	Superior temporal g	22	240	43	–29	–1
	R	Inferior temporal g	19	160	45	–74	–2
Subcortical	L	Lentiform		816	–24	9	6
	R	Thalamus		383	12	–7	3
	L	Cerebellum—culmen		256	–23	–49	–27
Age							
Old > Young							
Frontal	R	Middle frontal g	10	289	27	45	18
	L	Middle frontal g	9	364	–42	11	30
	R	Inferior frontal g	44	272	52	7	20
	L	Precentral g	44/13	203	–43	3	8
Parietal	L	Inferior parietal l	40	924	–42	–47	38
Subcortical	L	Thalamus—pulvinar (deactivation)		168	–2	–30	9
Young > Old							
Subcortical	R	Insula		191	44	15	–1
	R	Lentiform		163	20	9	0
	L	Thalamus		171	–11	–12	2
Absentmindedness							
High > Low							
Frontal	R	Middle frontal g	10	710	34	45	23
	R	Anterior cingulate/Pre-SMA	6,32	1067	8	5	54
	R	Cingulate G	23	377	3	–20	26
Parietal	R	Inferior parietal l	40	2531	39	–48	46
	L	Inferior parietal l	40	303	–41	–39	39
	R	Precuneus	7	177	18	–66	50
Subcortical	R	Putamen		361	15	10	2
	L	Cerebellum—pyramis		157	–10	–75	–27
Go RT							
Fast > Slow							
Frontal	L	Precentral g	6	296	–48	–4	41
	L	Precentral g	6	181	–54	1	27
	L	Pre-SMA	6	953	–8	–4	54
Temporal	R	Superior temporal g	22	329	55	–44	15
Subcortical	R	Insula	13	3043	39	13	2
Slow > Fast	L	Insula	13	1564	–35	10	3
Frontal	L	Precentral g	6	272	–36	4	26
Parietal	L	Precuneus	7	271	–24	–66	29
Temporal	L	Parahippocampal g (deactivation)	27	151	–24	–30	–8
Subcortical	R	Cerebellum—tonsil		399	8	–36	–33

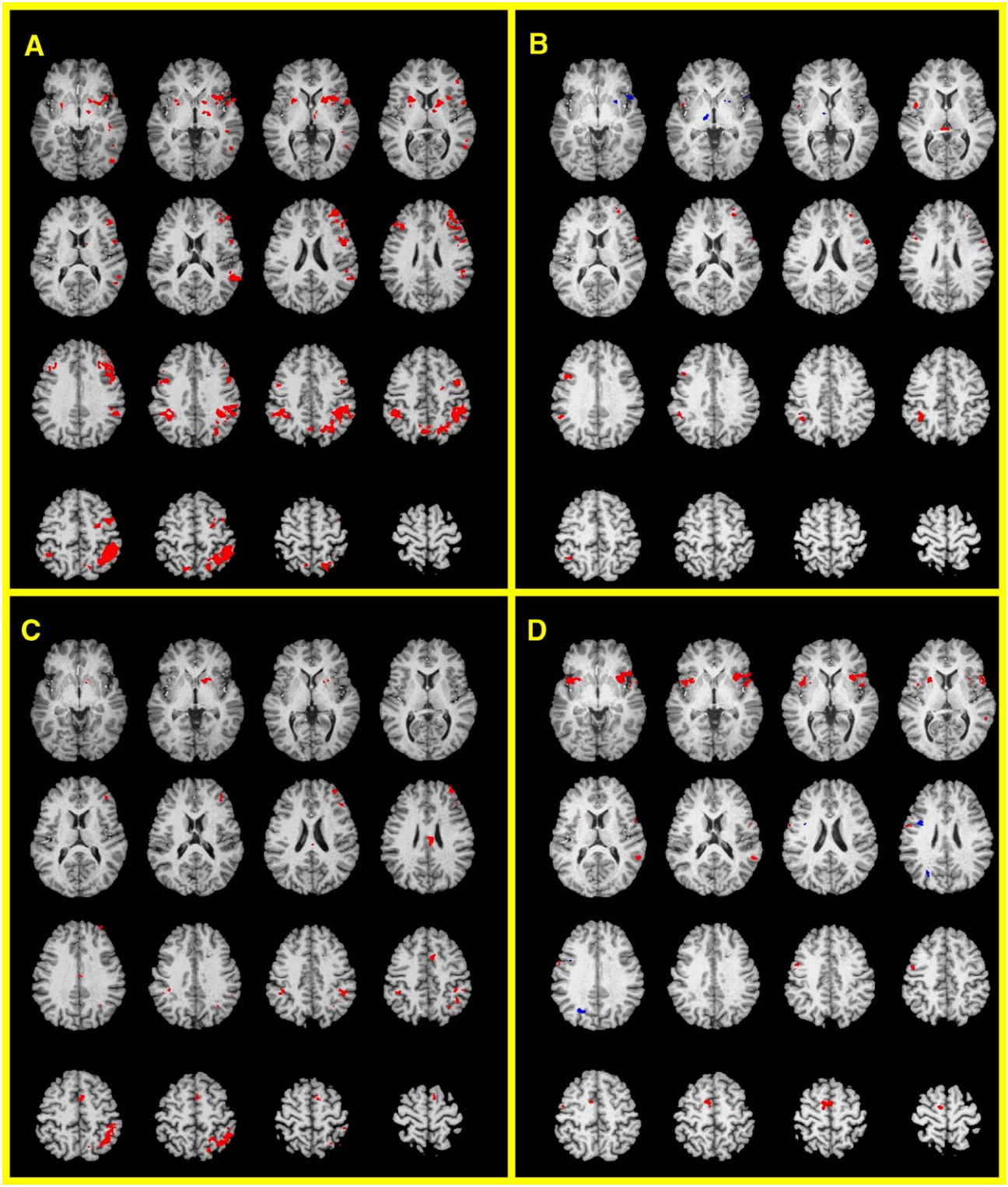

Fig. 2 – Individual differences in the functional neuroanatomy of response inhibition. The regions shown include those that were significantly greater in activity in females over males (A), in older over younger subjects (B, red) and younger over older subjects (B, blue), in high over low absentmindedness (C), in faster over slower responders (D, red) and in slower over faster responders (D, blue).

node. For example, Mostofsky and colleagues have demonstrated that, in a simple Go/NoGo task in which subjects responded to green stimuli and inhibited to red stimuli, activation was restricted to a pre-SMA region similar to that observed here (Mostofsky et al., 2003). Right dorsolateral prefrontal activity for inhibitions was observed when subjects

had to inhibit to just those red stimuli preceded by an even number of green stimuli. The increased demands of the counting condition may have required additional "resources" to accomplish the inhibition: parametric increases in working memory demands have been shown to increase activity levels in inhibition-related areas (Hester et al., 2004c). Similar flexibility in the relative contribution of prefrontal and subcortical regions to inhibitory control has been observed to depend on the extent to which subjects can prepare for each stimulus (Kelly et al., 2004). These dynamics demonstrate that the act of inhibiting a response may not be accomplished by a dedicated inhibition-related cortical region or regions but instead suggest that motor countermanding is accomplished with differential contributions from different regions dependent upon the circumstances in which that inhibition is required.

The preceding conclusion notwithstanding, there is converging evidence for particular importance of the right inferior frontal gyrus in response inhibition (Fig. 3). The activity observed in this study encompassed the frontal operculum region identified through lesion studies as necessary for response inhibition (Aron et al., 2003). Furthermore, a recent TMS study observed that pre-test stimulation over this region produced significant deficits on a STOP task (Chambers et al., 2006). The TMS study is notable in that it showed no impairment with similar TMS stimulation over the more dorsal right prefrontal or right parietal regions also observed in the present data. The converging evidence from the lesion and TMS studies is particularly valuable given the inherent ambiguities of functional neuroimaging; the different methodologies complement each other well as lesion and TMS studies may reveal areas that are necessary but not sufficient for inhibition while neuroimaging may reveal regions that are sufficient but not necessary.

The STOP tasks used in both the lesion and TMS studies varied the delay between the choice stimulus and the signal to withhold responding, thereby ensuring high rates of commission errors. Thus, this task makes inhibiting quite difficult and may be most sensitive to detecting a "brake" mechanism, proposed to be mediated by right inferior frontal cortex. In contrast, one speculation is that the dorsal right frontal activity may be associated with a more deliberative response selection process (Rowe et al., 2002) wherein the inhibition "response" is selected rather than a Go response being countermanded. If this is the case, then one might predict increased dorsal and reduced ventral prefrontal activity as inhibitions require less response countermanding, for example, for shorter intervals between the choice stimulus and the signal to withhold responding. Another possibility, given the similarity to sustained, or vigilant, attention functional patterns (Robertson and Garavan, 2004), is that the right dorsal prefrontal and parietal activations may reflect phasic increases in attentional processes triggered by the NoGo trial. In theory, one might thus expect the amount of dorsolateral

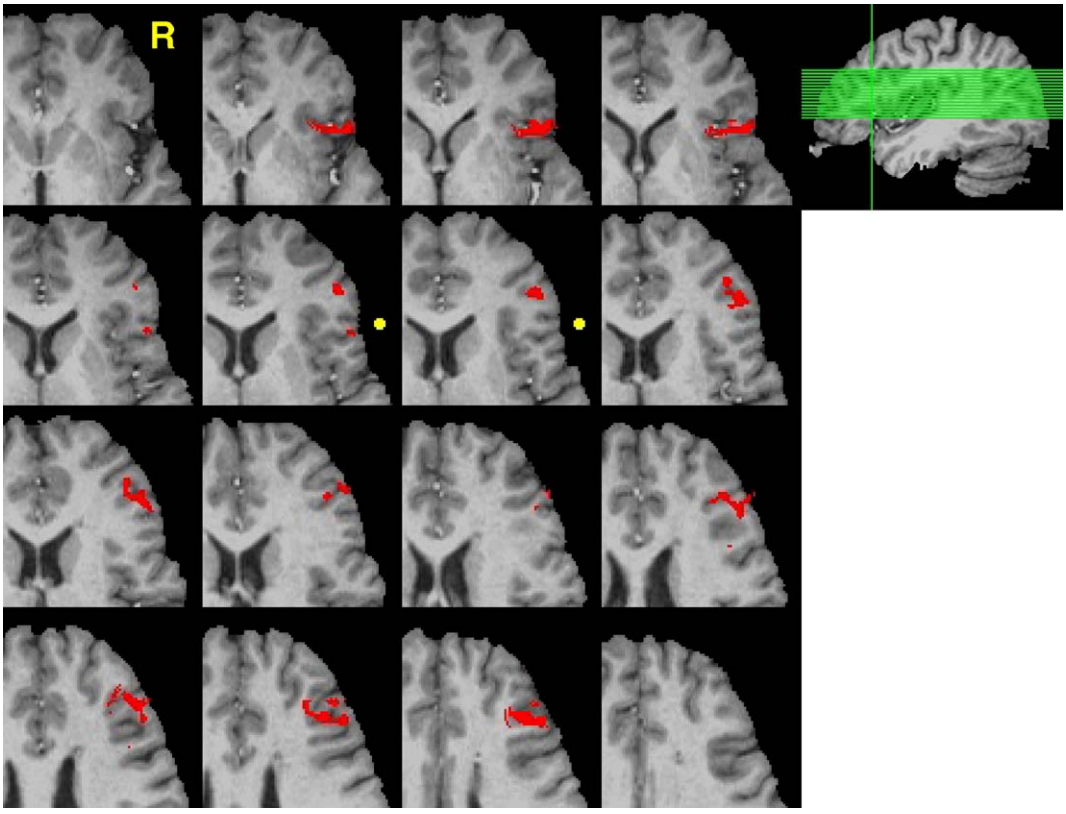

Fig. 3 – Converging evidence for the importance of right inferior frontal regions for response inhibition. The highlighted region is the overlap between the functional activation for inhibitions and the frontal operculum region identified through lesion studies as critical for inhibitory control (Aron et al., 2003). The yellow circle (3 mm radius) identifies the location of TMS stimulation that significantly impaired response inhibition (Chambers et al., 2006).

prefrontal cortex activity that precedes a NoGo to be inversely related to activity levels for the inhibition itself.

While its exact role in cognitive control is still a matter of debate, the anterior cingulate activity may reflect the processing of error likelihood, given that the NoGo trials very often produce errors of commission (Brown and Braver, 2005). Activity here may also reflect conflict monitoring processes given the competing Go and NoGo response demands activated on NoGo trials (Botvinick et al., 2001). The activation observed in subcortical regions is consistent with an increasing appreciation of subcortical involvement in cognitive control and, particularly, in inhibitory control (Middleton and Strick, 2000; Rieger et al., 2003; Saint-Cyr, 2003).

In summary, in keeping with an emerging understanding of the topography of control functions (Fassbender et al., 2004), we hypothesise that activations associated with response inhibition reflect fronto-parietal attentional or response selection mechanisms, midline-mediated performance monitoring processes and an inferior frontal region central to a response countermanding function. Subcortical regions may reflect an autonomic response (bilateral insula) and motor control functions. In order to confirm which components of the activated network reflect autonomic arousal responses, a suggestion would be for concurrent physiological monitoring enabling one, for example, to test if insular activity correlates with the peripheral physiological measures. Finally, although activation was largely associated with the right hemisphere, it should be noted that this functional lateralisation is most likely one of degree rather than of absolutes, as is likely the case with most functional localisations in the prefrontal cortex (Duncan, 2001; Duncan and Miller, 2002). Smaller volumes of activation were observed in left prefrontal and parietal regions (consistent with the meta-analysis of Buchsbaum et al., 2005), and a role in inhibitory control in these regions is consistent with their recruitment in elderly subjects (Nielson et al., 2002). Similarly, data on a split-brain patient show that, although the patient's right hemisphere is superior at inhibiting prepotent responses, the performance of the left hemisphere is far from catastrophically poor (Funnell et al., 2004). In this study, the capability of each hemisphere to inhibit a prepotent response was assessed with lateralised presentation of stimuli in both a Go/NoGo task and a STOP task (Logan and Cowan, 1984). The right hemisphere successfully inhibited more often than the left hemisphere in both tasks, confirming its superiority for inhibitory control. However, the left hemisphere, although worse, still successfully inhibited on the majority of trials confirming that the ability to inhibit is not unique to the right hemisphere.

3.2. *Individual differences*

As well as showing robust activations associated with response inhibition, the present results also reveal that activity levels within these regions are affected by individual differences. The results underscore the value of brain imaging for providing, at a minimum, a novel dependent variable for understanding behaviour insofar as the group differences in activation were observed in the absence of performance differences.

3.3. *Age*

Within a quite restricted adult age range (18 to 46), greater cortical activity was observed with increasing age. It is notable that the regions more active for the older subjects were the same left hemisphere regions that were present in the complete-group analysis; these regions are largely left-hemisphere homologues of the more substantial right hemisphere activations. This is indicative of an age-related reduction in the hemispheric asymmetry of this cognitive process. A similar effect using a similar Go/NoGo task has been observed in a much greater age range (18 to 78, Nielson et al., 2002), indicating, as has been shown with brain volumetric measures (Good et al., 2001), that age-related changes are continuous across the adult lifespan and can thus be observed in a younger age group. If so, then it might be argued that the mechanisms of functional recruitment, thought to underlie the greater bilateral activity of elderly subjects (Cabeza, 2002), are already operating in the young adult age range. Conversely, a number of smaller subcortical areas showed an opposite effect, being more active in the younger subjects. While this may relate to age-related changes in dopamine function, more evidence will be needed to determine the mechanisms and functional consequences of these differences.

3.4. *Sex*

Greater activity was observed in numerous cortical areas, but not in midline areas, in females relative to males. The functional significance of activation differences in cognitive tasks is often not straightforward as greater activity might reflect greater effort, less neural efficiency or, alternatively, an appropriate marshalling of resources for a difficult trial. It is difficult to adjudicate between these alternatives as males and females did not differ in performance. Other research suggests that superior performance on cognitive tasks may be characterised by low tonic levels of activity combined with greater phasic, event-related activity levels (Gray et al., 2003; Haier et al., 1992; Pessoa et al., 2002; Rypma et al., 2002), and this is a pattern that has also been observed to result from practice on a task that combines working memory and response inhibitory demands (Kelly et al., in press). Unfortunately, the present data did not provide measures of tonic activity. Despite its uncertainty, this observation of greater inhibition-related activity in females, which was quite substantial being present in most of the task-related brain regions (compare Fig. 1 to 2A), may warrant further investigation.

The regionally widespread sex effects in activation levels suggest a systems-wide male–female difference. Increased gyrification and fissuration of the cortical surface have been reported for fronto-parietal areas in females relative to males with the suggestion that this may be a compensatory response for the smaller intracranial volumes of females (Luders et al., 2004). Notably, these male–female differences were greater in the right hemisphere. In keeping with the findings of higher grey matter percentages in females (Gur et al., 1999), these findings may suggest a neuroanatomical basis to our functional effects in that the greater, largely right hemispheric activity in females may reflect a higher density of neurons. If the present findings are relevant to the higher prevalence of

impulse control disorders in males (Kessler et al., 2005), then this would imply that the functional differences in females, and perhaps the associated neuroanatomical differences, are protective against the development of these disorders.

Previous studies have suggested that women may have less hemispheric specialisation than males (Hiscock et al., 2001; Shaywitz et al., 1995; Witelson 1976). The present results, relevant to this issue given the strong hemispheric specialisation of response inhibition, are inconsistent with this suggestion as the regions in which women showed greater activity than males were largely in the right hemisphere. This can be contrasted with a prediction that women, if less hemispherically specialised than men, would show greater left hemisphere activation accompanied by reduced right hemisphere activations, a pattern that clearly was not observed.

3.5. *Absentmindedness*

There was greater inhibition-related activity in frontal, parietal and subcortical regions in those subjects who reported being higher in absentmindedness. These results share similarities with a previous individual differences investigation in which subjects who were more variable in their Go response times also showed greater fronto-parietal activity when inhibiting (Bellgrove et al., 2004). As the ability to sustain attention is relatively poor in absentminded subjects (Porter and Robertson, 2002) and is likely to underlie differences in response variability, it is plausible that diminished attention to the task resulted in inhibiting requiring greater phasic increases in the fronto-parietal areas that may reflect the attentional demands of the task. These results speak to the context selectivity of the inhibitory network as poorer levels of preparatory attention (or proactive control, Braver et al., in press) influence the demands placed on the individual to exercise control reactively.

It is perhaps surprising that increased levels of absentmindedness were not associated with poorer performance or with greater inhibition-related activity in the ventral prefrontal region which we have characterised as constituting a "brake" mechanism and has been shown to be necessary for motor inhibition (Aron et al., 2003; Chambers et al., 2006). Instead, the greatest volumes of increased activity were in the right parietal lobe and medial prefrontal areas (including the ACC but largely in the pre-SMA). The parietal lobe effect suggests that absentmindedness impacts primarily on the attentional response to the task. Mostofsky and colleagues have demonstrated unique inhibition-related activity in the pre-SMA in a simple Go/NoGo task that the authors attempted to strip of extraneous cognitive processes (Mostofsky et al., 2003). Although robust pre-SMA activity was recently observed by Aron and colleagues for motor inhibition, it was the inferior frontal cortex and subthalamic nucleus that correlated with stop signal reaction time, a measure of the speed with which a subject can inhibit a response (Aron and Poldrack, 2006). Thus, if it is these regions that block thalamocortical motor output, then the pre-SMA either constitutes another node in motor output in which motor signals can be countermanded or reflects other processes incidental to inhibition such as response conflict (Garavan et al., 2003; Ullsperger and von Cramon, 2001). It is plausible that the more absentminded subjects may experience greater conflict between the NoGo requirement and the prepotent Go response if their absentmindedness results in poorer attention to the task.

In passing, it is notable that the effects that absentmindedness has on inhibition-related activity are opposite to those seen for error-related activity (see Hester et al., 2004a). The more absentminded subjects had greater inhibition-related activity but lower error-related activity in the anterior cingulate, leading to the tempting speculation that absentmindedness results from poorer monitoring of behaviour and, consequently, results in greater efforts required to inhibit.

3.6. *Go response time*

The context for inhibiting can also be driven by the subject's Go response times. The most striking result was the greater bilateral insula activity of faster responders which may reflect a greater autonomic arousal reaction to the unpredictable NoGo trials in those who are faster in responding on the more frequent Go trials. Similar to the absentmindedness findings, it is notable that neither dorsal nor inferior prefrontal activity discriminated fast and slow responders as one might expect inhibiting to be more difficult for faster responders. This stands in contrast to the effects of individual differences in variability (Bellgrove et al., 2004) suggesting that the fluctuation in a subject's response speeds rather than the subject's average speed is the more relevant modulator of the involvement of these cognitive control centres. Faster responders also had greater inhibition-related activity in the left precentral gyrus (although slower responders showed greater activity in a different left precentral region) and in the pre-SMA. As with the absentmindedness results, the pre-SMA activity might reflect inhibitory processes per se or incidental processes such as response conflict monitoring. On the whole, the Go response time split-group effects are more difficult to interpret as opposite effects (i.e., greater activity in slower responders) were also observed including opposite effects in similar cortical regions (e.g., left precentral gyrus). It may be the case that the effects of differences in mean Go response time are more likely to be reflected in processes that occur over the duration of the task and would thus be better assayed by tonic activity levels rather than by the phasic, event-related activity measures reported here.

3.7. *Summary*

The influence of individual differences on inhibition-related activity levels demonstrates that functional neuroanatomy is not static but varies between those who differ across demographic, performance and trait measures. Although we have offered possible explanations for the particular effects of these individual differences, it should be acknowledged that these suggestions require further hypothesis-driven investigation. This caveat notwithstanding, the present empirical observations of individual differences impacting on cognitive control functions such as inhibitory control raise the possibility that control functions and their functional neuroanatomy can be altered through interventions such as training. For

example, brief practice on a similar Go/NoGo task not only produces sizeable activity changes but can also change the activation patterns of poorer inhibitors to look, following practice, like those of better inhibitors (Kelly et al., in press). That such flexibility exists bodes well for therapeutic interventions in clinical populations (Klingberg et al., 2005; Posner and Rothbart, 2005).

4. Experimental procedures

4.1. *Subjects and task design*

Seventy-one right-handed subjects (45 female, mean age 29, range: 18–46), reporting no history of neurological or psychological impairment, completed a Go/NoGo task after providing written informed consent. The initial design for the XY Go/NoGo task is described in Garavan et al. (1999), and slight modifications were made in four subsequent studies. In each study, subjects were presented with a serial stream of letters in which frequent Go stimuli (the letters X and Y) were presented in alternating order with subjects instructed to inhibit responding when the alternation was interrupted (e.g., the fifth stimulus in the train X–Y–X–Y–Y–X–Y). In the initial study (Garavan et al., 1999), an average of seven distracter letters (random letters of the alphabet) separated the presentation of X and Y stimuli. There were no distracters in the subsequent studies.

The five samples included in this re-analysis undertook the task with minor variations of on-screen presentation and inter-stimulus interval timing, varying between 900 ms on-screen presentation with a 100 ms ISI (Garavan et al., 2003; Hester et al., 2004b), 600 ms presentation with a 400 ms ISI (Garavan et al., 2002; Fassbender et al., submitted for publication) and 500 ms presentation with no ISI (Garavan et al., 1999). In two of the studies (Garavan et al., 2002; Fassbender et al., submitted for publication), pre-scanning testing identified the timing parameters that produced approximately 50% commission errors. This was accomplished by presenting the stimuli for durations of 600, 700, 800 or 900 ms with accompanying ISIs of 400, 300, 200 or 100 ms, respectively; when combined with the instruction to respond while the stimulus is on-screen, shorter durations produce faster responses and, consequently, more commission errors. While some other variations in the design of these tasks existed, only the successful response inhibitions (STOPS) are addressed in this re-analysis, with the assumption made that the event-related design in which phasic activity time-locked to STOPS can be isolated would minimise the influence of unrelated task variance. In a separate re-analysis of these data (including all studies except Fassbender et al., submitted for publication), we have shown that activation differences between the studies were no greater than what would be predicted based on the sample sizes of the studies, indicating no additional task-associated variance (Murphy and Garavan, 2004).

The Go/NoGo tasks employed an event-related fMRI design to identify the functional areas activated for STOPS and NoGo commission errors. The event-related design allowed the NoGo trials to be distributed unpredictably throughout the stimuli stream, thereby enabling a response prepotency to be maintained. During fMRI scanning, subjects were presented with between 448 and 1180 Go stimuli and between 25 and 80 NoGo stimuli. This ratio resulted in an average inter-NoGo interval of 16.4 s for the five studies.

Sixty-five of the subjects were administered the Cognitive Failures Questionnaire (Broadbent et al., 1982), which provides a self-report measure of everyday absentmindedness. The test comprises 25 items, and scores range between 0 and 100, with higher scores indicative of greater absentmindedness.

4.2. *Scanning parameters*

Scanning for three of the studies (Garavan et al., 1999, 2002, 2003) was conducted using contiguous 7 mm sagittal slices covering the entire brain from a 1.5 T GE Signa scanner using a blipped gradient-echo, echo planar pulse sequence (TE = 40 ms; TR = 2000 ms; FOV = 24 cm; 64 × 64 matrix; 3.75 mm × 3.75 mm in-plane resolution). High resolution spoiled GRASS anatomic images (TR = 24 ms, TE = 5 ms, flip angle = 45°, FOV = 24 cm, thickness = 1.0 mm with no gap, matrix size = 256 × 256 × 124) were acquired prior to functional imaging to enable subsequent activation localisation and spatial normalisation. Foam padding was used to limit head movements within the coil. Stimuli were back-projected onto a screen at the subject's feet and were viewed with the aid of prism glasses attached to the inside of the radio-frequency head-coil.

Scanning for the fourth study (Hester et al., 2004b) was conducted using a 1.5 T Siemens VISION scanner in which foam padding was used to restrict head movements. Contiguous 5 mm sagittal slices covering the entire brain were collected using a single-shot, T2*-weighted echo planar imaging sequence (TE = 50 ms; TR = 2000 ms; FOV = 256 mm; 64 × 64 mm matrix size in-plane resolution). High-resolution T1-weighted structural MPRAGE images (FOV = 256 mm, isotropic 1 mm voxels) were acquired following functional imaging for subsequent activation localisation and spatial normalisation. Stimuli were delivered using an IFIS-SA stimulus delivery system (MRI Devices Corp., Waukesha, Wisconsin), which was equipped with a head-coil-mounted 640 × 480 LCD panel. This shielded LCD screen is mounted on the head-coil, directly in the subject's line of vision.

Scanning for the fifth study (Fassbender et al., submitted for publication) was conducted using a 1.5 T Siemens scanner. Functional images were single-shot, T2*-weighted, echo planar imaging sequences. Twenty sagittal slices (7 mm slice thickness) were acquired for each subject (TR = 2000 ms, flip angle = 90°, 128 mm × 128 mm matrix size, field of view = 240 mm). High-resolution T1-weighted sagittal slices were acquired for each subject (slice thickness = 1 mm, field of view = 250 mm).

4.3. *Data analyses*

Analyses were conducted using AFNI software (Cox, 1996; http://afni.nimh.nih.gov/). Following image reconstruction, the time series data were time-shifted using Fourier interpolation to remove differences in slice acquisition times and

motion-corrected using 3D volume registration (least squares alignment of three translational and three rotational parameters). Activation outside the brain was also removed using edge detection techniques. No subjects showed significant residual motion, thus allowing all 71 to be included.

Separate hemodynamic response functions (HRFs) at 2-s temporal resolution were calculated using deconvolution techniques for successful response inhibitions (STOPS) and errors of commission (ERRORS), though only the STOPS are considered here. All events of interest were time-locked to the beginning of the 2-s whole-brain volume acquisition. A multiple regression analysis was used to derive estimates for the time-point parameters of the HRFs by estimating the signal contributed by each individual event type to the overall time series. The HRFs were then modelled voxelwise with a gamma-variate function using non-linear regression (Ward et al., 1998; Garavan et al., 1999). An area-under-the-curve measure of the gamma-variate model was expressed as a percentage of the tonic baseline activity and served as the activation measure for the event-related responses (Murphy and Garavan, 2005). The activation map for STOPS therefore represents activation during successful NoGo events that is significantly greater than during the baseline of ongoing Go trials. One advantage of the curve fitting technique is that a best fitting HRF is calculated for each individual voxel which can thereby accommodate differences in HRFs across brain regions and across individuals.

4.4. *Group analyses*

Activation maps were resampled to 1 μl and warped into standard Talairach space (Talairach and Tourneaux, 1988) and spatially blurred using a 3 mm isotropic rms Gaussian blur. A one-sample *t* test against the null hypothesis of zero event-related activation changes (i.e., no change relative to tonic task-related activity) was performed voxel by voxel on the percentage area-under-the-curve measure. Significant voxels passed a voxelwise statistical threshold ($t = 4.762$, $P < 0.00001$) and were required to be part of a larger 71 μl cluster of contiguous significant voxels. Thresholding was determined through Monte Carlo simulations and resulted in a 0.1% probability of a cluster surviving due to chance. The mean activation for clusters in this group map was calculated for the purposes of an ROI analysis, and these data were used for a series of comparisons between groups.

The interest in individual differences also prompted a series of split-group analyses, where activation maps were made for groups divided by the variable of interest, selecting the top and bottom quartiles ($n = 18$ in each group), or in the case of sex, creating separate maps for males and females. The top and bottom quartiles were compared as this enabled us to compare groups that clearly differed on the variable of interest while keeping sample sizes relatively high. These group maps were also determined with one-sample *t* tests against the null hypothesis of zero event-related activation, in which significant voxels passed a voxelwise statistical threshold ($t = 3.965$, $P < 0.001$) and were required to be part of a larger 142 μl cluster of contiguous significant voxels resulting in a 5% probability of a cluster surviving due to chance. The activation maps were then combined within variables, deriving OR maps of male/female, young/old, high/low CFQ and fast/slow Go RT, with the clusters from these maps used for ROI analysis. For example, the examination of sex differences required separate activation maps to be produced for males and females, which were then combined into an OR map (a voxel was included if significant in either map) to identify both the unique and shared cortical areas of activation. Using these clusters of significant activation, a series of ANOVAs examined the influence of a subject's sex on activation levels. This procedure exploits the fact that *t* tests against the null hypothesis of no activation change are more powerful than direct contrasts between groups. By OR'ing significantly active clusters across groups before proceeding to the cluster-level analysis, one ensures no bias for one group over another. All ANOVA comparisons included as a nuisance covariate the study from which the data came.

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