

Individual Differences in Error Processing: A Review and Reanalysis of Three Event-related fMRI Studies Using the GO/NOGO Task

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Three previous studies using the GO/NOGO task were examined to characterize the pattern of functional activation seen during error-related processing. The large sample size ($n = 44$) also allowed investigation of the influence of individual differences in age, sex, self-reported absentmindedness and reaction speed on the level of activation. Errors were seen to activate a network of regions including the anterior cingulate cortex (ACC), pre-supplementary motor area (pre-SMA), bilateral insula, thalamus and right inferior parietal lobule. Split-half comparisons performed for each of the individual difference variables indicated greater ACC and pre-SMA activation for older subjects while slower responders showed greater activation in the parietal, lateral PFC, insula and ACC regions. Whereas males and females demonstrated equivalent levels of activation in both the ACC and insula, self-reported absentmindedness related to reduced activation in these regions. Our review of the current imaging literature on error-related activation indicates that, despite the use of a variety of other cognitive paradigms, the network of regions identified here is consistent with these previous studies, suggesting that these regions are critical to a 'general' error-related response. Furthermore, this response is, in part, influenced by individual differences in both demographic characteristics and behavioural performance.

Keywords: absentmindedness, age, cingulate, error processing, sex differences, signal averaging

Introduction

Neuroimaging evidence suggests that the neuroanatomical areas activated during error-related processing include the anterior cingulate cortex (ACC), the pre-supplementary motor area (pre-SMA), left lateral prefrontal cortex, inferior parietal lobule and bilateral insula cortex (Carter *et al.*, 1998; Kiehl *et al.*, 2000; Braver *et al.*, 2001; Menon *et al.*, 2001; Ullsperger and von Cramon, 2001, 2003; Garavan *et al.*, 2002; Rubia *et al.*, 2003). The areas detected by these studies have remained relatively consistent despite a range of different cognitive test paradigms, including GO/NOGO, stop, oddball, continuous performance and flanker tasks, being used. It would seem, therefore, that the activation observed represents a more general, rather than task-specific, error-detection network.

A controversy still exists as to the role of some of these areas, in particular the midline regions, with error-related activation foci widely dispersed throughout ACC and pre-SMA (see Fig. 1). The ACC is thought to play a central role in error processing, based largely on ERP studies that have noted an error-related negativity (ERN) 100–150 ms after a subject has made an incorrect response (Gehring *et al.*, 1993). Dipole modelling has implicated a medial-frontal generator, generally thought to be the ACC (Dehaene *et al.*, 1994). The ERN is

proposed to result from a mismatch in a comparison between the actual response and an internal representation of the correct response (Falkenstein *et al.*, 1990).

More recently it has been proposed that ACC is not involved in error detection *per se* but rather monitors for response conflict (Carter *et al.*, 1998). Response conflict is thought to arise when two competing response pathways are simultaneously activated. For example, in the GO/NOGO task conflict occurs between the GO response (responding with a button press to a stimulus) and the NOGO response (withholding a response to a particular stimulus), while in the flanker task conflict occurs between the different responses associated with the central and peripheral stimuli. Carter *et al.* (1998) noted increased levels of activation in the ACC during both incorrect trials and those involving increased amounts of response conflict. A number of other studies have also suggested that rostral ACC might be involved in error detection, whereas more dorsal ACC/pre-SMA may monitor for conflict (Ullsperger and von Cramon, 2001; Garavan *et al.*, 2003). Studies that examine error processing only can be confounded by the inherent amount of conflict associated with errors. To this end a number of fMRI studies have attempted to separate error and conflict-related processes within the one experimental paradigm (Braver *et al.*, 2001; Ullsperger and von Cramon, 2001; Garavan *et al.*, 2003). These studies appear to implicate rostral ACC in error-related processing (possibly linked to the emotional valence of an incorrect response) whereas more dorsal areas of ACC extending into pre-SMA appear to be involved in the detection of response conflict (see Fig. 2).

Individual Differences in the Error-related Neural Response

Initial investigations of individual differences have focused on the relationship between reaction time (RT), conflict monitoring and ACC activation. The studies to undertake this analysis have argued that RT provides a measure of conflict monitoring, with shorter RTs in decision-making tasks (Naito *et al.*, 2000; Mulert *et al.*, 2003) and longer RTs in the incongruent part of the Stroop task (Leung *et al.*, 2000) relating to greater ACC activation. The group comparisons from which this relationship was identified also indicate significantly greater rates of commission errors for the high ACC activation group, making it unclear whether task performance, RT or both variables in combination are influencing ACC activation. A relationship between RT and ACC activation would suggest that ACC activation provides a functional index of the monitoring being undertaken by the subject (Mulert *et al.*, 2003), and seemingly provide support for the proposal that the ACC functions to detect conflict, rather than, or in addition to,

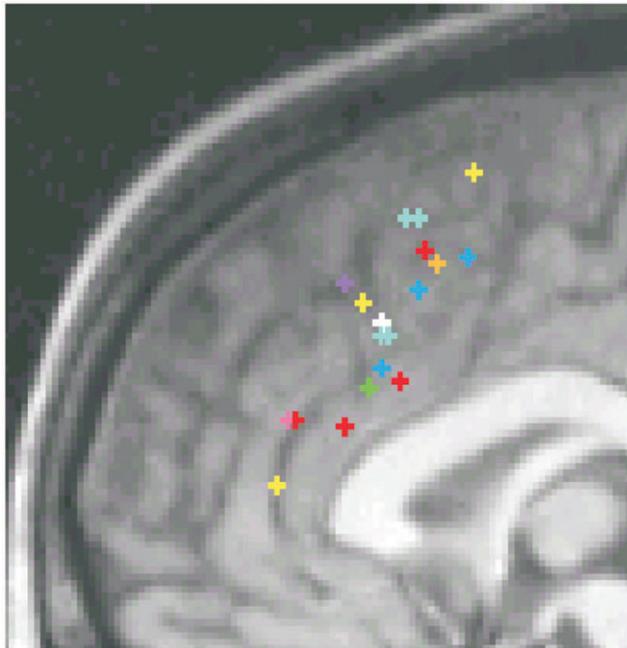


Figure 1. Eight event-related fMRI studies of error processing were selected in order to be part of the review. Foci of activation were projected onto the midline for ease of viewing. Yellow (Kiehl *et al.*, 2000); pink (Menon *et al.*, 2001); orange (Garavan *et al.*, 2002); green (Braver *et al.*, 2001); purple (Carter *et al.*, 1998); red (Garavan *et al.*, 2004); blue (Ullsperger and von Cramon, 2001); light blue (Ullsperger and von Cramon, 2003). The white point represents the average focus of error activations.

errors (Carter *et al.*, 1998; Botvinick *et al.*, 2001; van Veen and Carter, 2002).

Age has also been shown to influence the functional response of individuals to cognitive tasks (Grady, 1994; Nyberg *et al.*, 1997; Grady *et al.*, 1999; Reuter Lorenz *et al.*, 1999, 2000, 2001; Rypma and D'Esposito, 2001; Rypma *et al.*, 2001). Two studies that specifically investigated the influence of aging on functional activation in inhibitory tasks provided differing results. Milham *et al.* (2002) found decreased levels of activation in the prefrontal and parietal regions of older adults when compared with younger adults during the incongruent part of the Stroop task. In support of this, Nielson *et al.* (2002) found significant age-related decreases in right prefrontal regions during successful inhibitory trials on a GO/NOGO task. However, the Nielson *et al.* study also found the inverse, with older adults having greater bilateral prefrontal and parietal activation. Both studies also identified increased ACC and pre-SMA activation for older adults; however, the blocked fMRI design used by Milham *et al.* did not allow for discrimination between successful and failed inhibitory control. Interestingly, the increased activation in the pre-SMA, right prefrontal and inferior parietal regions seen for older adults by Nielson *et al.* (2002), persisted after adjusting for group differences in behavioural performance. This result suggests that older adults performing at the same behavioural level as younger adults required greater activation in these cortical regions.

Contrary to this hypothesis is the finding that healthy older adults show smaller ERNs than younger counterparts (Gehring and Knight, 2000; Falkenstein *et al.*, 2001; Nieuwenhuis *et al.*, 2002; Mathalon *et al.*, 2003), in the absence of any behavioural performance differences, or reductions in any other ERP amplitude measure. It has been suggested though that these reduc-

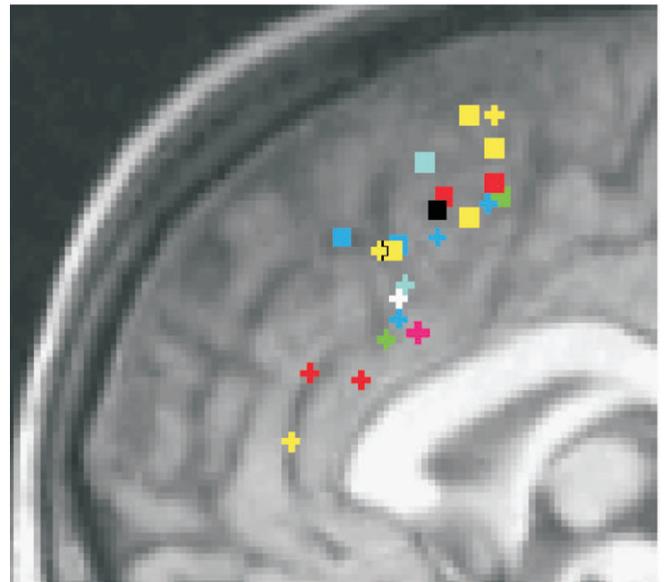


Figure 2. Five studies that attempted to separate error and conflict-related activations were included in this map. Error-related activations are shown as crosses and conflict-related activations are shown as squares: Yellow (Kiehl *et al.*, 2000); green (Braver *et al.*, 2001; red (Garavan *et al.*, 2004); blue (Ullsperger and von Cramon, 2001); light blue (Ullsperger and von Cramon, 2003). The pink point represents an activation implicated in both error detection and response conflict. The white point represents the average focus of error activations and the black square represents the average focus of conflict-related activations.

tions may be the result of older adults being more prone to 'mistakes', where the participant did not know the correct response, rather than the 'slip' response typically associated with the ERN response (Mathalon *et al.*, 2003).

Sex differences in functional activation have also been demonstrated, primarily in the literature utilizing cognitive-emotional judgment tasks (Schneider *et al.*, 2000; Killgore *et al.*, 2001; Killgore and Yurgelun-Todd, 2001; Lee *et al.*, 2002), though not exclusively (Schlosser *et al.*, 1998; Gur *et al.*, 2000; Jordan *et al.*, 2002; Rossell *et al.*, 2002). There have been, as yet, no reports examining sex differences in functional activation during error processing. Given, however, the suggestion that error-related activation in the ACC may reflect an emotional response to errors (Bush *et al.*, 2000; Luu *et al.*, 2000b, 2003; Menon *et al.*, 2001), and the reported sex differences in fMRI studies of emotional processing, it remains to be seen whether the error-related activations, affective or otherwise, are influenced by sex.

Individual differences in absentmindedness have emerged as a recent interest in functional neuroimaging studies, with the primary question being whether self-reported levels of cognitive failures, relate to cortical activation. Garavan *et al.* (2002) demonstrated that successful inhibitory control in the GO/NOGO task related to individual differences on the Cognitive Failures Questionnaire (CFQ) (Broadbent *et al.*, 1982), with higher levels of self-reported absentmindedness correlating with higher levels of ACC activation, albeit a more posterior region of the ACC than typically observed in cognitive activation paradigms. This pattern of activation was seen generally for subjects when ongoing response speeds were relatively fast, suggesting that the ACC may be selectively activated for urgent inhibitions of faster or more automatic responses. This

result also provides encouragement to the idea that individual differences on self-reported measures of cognition may relate to cortical activation patterns. While this concept has been explored widely at a clinical level, the practice remains relatively unexplored with cognitive self-report measures (Gray *et al.*, 2003).

Individual differences in error-related activation has also been examined in the clinical literature, suggesting that this response is disturbed in patients with conditions such as schizophrenia, obsessive-compulsive disorder and cocaine abuse (Gehring *et al.*, 2000; Carter *et al.*, 2001; Alain *et al.*, 2002; Kaufman *et al.*, 2003; Laurens *et al.*, 2003). The influence of personality on the ERN response has also been identified, indicating that subjects low on socialization demonstrated lower ERN responses during penalized errors (Dikman and Allen, 2000), and subjects high on negative affect and emotionality larger ERNs (Luu *et al.*, 2000a). These results suggest that the cortical response to an error is not uniform and can indeed be influenced by individual differences.

To examine the existence of individual differences in error-related activation it was necessary to gather a large sample of subjects performing a single cognitive task. Given the practicalities of acquiring fMRI data, it is often difficult to obtain the large number of subjects, and hence the necessary statistical power, to examine individual differences such as sex or age. Another issue that we have encountered when analysing the results of the GO/NOGO task, is the infrequency of errors available to analyse. Huettel and McCarthy (2001) demonstrated that the spatial extent of active voxels increased exponentially as the number of events being averaged was increased from 1 to 150. The topography of activation however did not change substantially after averaging only 20 trials, and similarly the variability of the hemodynamic response asymptoted between 25 and 36 trials. Saad *et al.* (2003) demonstrated a similar pattern of results, indicating that the spatial extent of the BOLD response increased monotonically when averaging >1–22 scans; however, again the increase in spatial extent was not random with the increases forming around the original centre of mass.

To carry out the analysis of individual differences in error processing we combined the samples of three previous studies (Garavan *et al.*, 2002, 2003; Hester *et al.*, 2004) to form a group of 44 subjects, with all three samples having completed similar versions of the GO/NOGO task (Garavan *et al.*, 1999). The GO/NOGO task is a well-established measure in the cognitive literature, particularly in studies utilizing neuroimaging to characterize the pattern of activation during both correct and failed inhibitory control (Konishi *et al.*, 1998; Braver *et al.*, 2001; Garavan *et al.*, 2002; Watanabe *et al.*, 2002). The behavioural performance and cortical activation levels of the present sample were analysed to examine the influence of age, sex, self-reported absentmindedness and reaction time on error processing during the GO/NOGO task.

Materials and Methods

Subjects and Task Design

Forty four right-handed subjects (29 female, mean age = 30 years, range = 18–46 years), reporting no history of neurological or psychological impairment, completed a GO/NOGO task based on our earlier work (Garavan *et al.*, 1999) after providing written informed consent. The task presented the letters X and Y serially in an alternating pattern at 1 Hz and subjects were required to make a button press response to

each letter. Responses and response speed were recorded. Responses were to be withheld to lure stimuli: a lure occurred when the alternation was interrupted (e.g. the fifth stimulus in the train X-Y-X-Y-X-Y). The three samples included in the reanalysis undertook the task with minor variations of on-screen presentation and inter-stimulus interval timing, varying between 900/100 (Garavan *et al.*, 2003; Hester *et al.*, 2004) and 600/400. In Garavan *et al.* (2002) pre-scanning testing identified the timing parameters that produced ~50% commission errors, by varying the timing from 600/400 to 900/100. While some other variations in the design of these tasks existed, only the commission errors made during the aforementioned design were considered, with the assumption made that the event-related analysis would minimize the influence of unrelated task variance.

The GO/NOGO task's employed an event-related fMRI design to identify the functional areas activated during successful and failed NOGO decision events. The event-related design allowed the lures to be distributed unpredictably throughout the stimuli stream. During fMRI scanning, subjects were presented with between 448 to 1180 targets (GO stimuli) and between 52 and 80 lures (NOGO stimuli). This ratio resulted in an average inter-lure interval of 12.75 s for the three studies.

All subjects were administered the Cognitive Failures Questionnaire (CFQ; 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.

Scanning Parameters and Data Analyses

Scanning for two of the studies (Garavan *et al.*, 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 ($T_E = 40$ ms; $T_R = 2000$ ms; FOV = 24 cm; 64×64 matrix; $3.75 \text{ mm} \times 3.75 \text{ mm}$ in-plane resolution). High resolution spoiled GRASS anatomic images ($T_E = 5$ ms, $T_R = 24$ ms, flip angle = 45° , FOV = 24 cm, thickness = 1.0 mm with no gap, matrix size = $256 \times 256 \times 124$) were acquired prior to functional imaging to allow subsequent activation localization and for spatial normalization. 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 third study (Hester *et al.*, 2004) was conducted using a 1.5T 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, T_2^* weighted echo planar imaging sequence ($T_E = 50$ ms; $T_R = 2000$ ms; FOV = 256 mm; 64×64 mm matrix size in-plane resolution). High-resolution T_1 -weighted structural MPRAGE images (FOV = 256 mm, isotropic 1 mm voxels) were acquired following functional imaging to allow subsequent activation localization and spatial normalization. Stimuli were delivered using an IFIS-SA stimulus-delivery system (MRI Devices Corp., Waukesha, WI), 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 subjects' line of vision.

All analyses were conducted using AFNI software (Cox, 1996). Following image reconstruction, the time-series data were time-shifted using Fourier interpolation to remove differences in slice acquisition times, and motion-corrected using 3-D 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 44 to be included.

Separate haemodynamic response functions at 2 s temporal resolution were calculated using deconvolution techniques for successful response inhibition (STOPS) and errors of commission (ERRORS), though only the ERRORS will be considered here. Although the stimulus stream was presented at 1 Hz, all events of interest were time-locked to the beginning of the two-second whole-brain volume acquisition. A multiple regression analysis was used to derive estimates for the time-point parameters of the haemodynamic response functions, by estimating the signal contributed by each individual event type to

the overall time series. In the present analysis regressors for both ERRORS and STOPS were entered, and the regression estimated the signal contributed by each of these events over and above that accounted for by the ongoing task (GO trials). The haemodynamic response functions 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. The activation map for ERRORS therefore represents the activation during failed NOGO events that is significantly greater than during the ongoing GO trials.

Given the findings of previous studies indicating that the spatial extent of activation was influenced by the numbers of events averaged (Huettel and McCarthy, 2001; Huettel *et al.*, 2001; Saad *et al.*, 2003), a split-half comparison was performed on the number of errors committed by subjects, and group activation maps for low (mean errors = 12, range = 3–23) and high ERRORS (mean = 33, range = 24–53) were determined with one-sample t-tests against the null hypothesis of zero event-related activation changes (i.e. no change relative to tonic task-related activity). Significant voxels passed a voxelwise statistical threshold ($t = 4.780$, $P < 0.0001$) and were required to be part of a larger 91 μl cluster of contiguous significant voxels. Thresholding was determined through Monte Carlo simulations and resulted in a 1% probability of a cluster surviving due to chance.

The activation maps were then combined deriving an OR map of high and low ERRORS. An OR map includes the voxels of activation indicated as significant from either of the constituent maps. The mean activation for clusters in the combined maps was calculated for the purposes of an ROI analysis, and these data were used for a series of pairwise comparisons between groups. These ROIs were also used to compare activation during STOPS and ERRORS for the purposes of identifying clusters demonstrating significantly greater activation during ERRORS. The use of the ERROR ROIs avoids the confound of motor activation which is absent from STOPS, as the ERROR ROIs were defined as regions that showed significantly greater activation than the tonic GO trial level, which did contain a motor response.

The findings of this split-half analysis prompted further comparisons using the same procedure for each of the other variables of interest (age, sex, CFQ and GO RT). Separate OR maps were made for

male/female, young/old, high/low CFQ and fast/slow GO RT comparisons, with the clusters from these maps used for ROI analysis. For example, to examine sex differences this required the production of separate activation maps for males and females, which were then combined to capture both the unique and shared cortical areas of activation. Using these clusters of significant activation, a series of ANOVA's, examined the influence of a subject's sex on activation levels. All ANOVA comparisons were adjusted for experimental procedure (unless otherwise indicated).

Results

Performance Measures

The demographic characteristics and behavioural performance of each of the groups used for comparisons are presented in Table 1.

The results from Table 1 indicate that for each of the split-half group comparisons, only the variable with which the split was made yielded a significant difference in either demographic characteristics or behavioural performance.

Event-Related Activation

The combined activation map for High and Low ERRORS indicated significant activation clusters in the ACC, pre-SMA, bilateral insula, thalamus and right inferior parietal lobule, consistent with previous error-related activation studies (Carter *et al.*, 1998; Kiehl *et al.*, 2000; Braver *et al.*, 2001; Menon *et al.*, 2001; Ullsperger and von Cramon, 2001; Garavan *et al.*, 2002). Within this OR map (see Table 2 and Fig. 3a), all eight clusters had significantly greater activation during ERRORS when compared with correct inhibitions (STOPS), suggesting that the response was specific to errors. ANOVA group comparisons (High, Low) of activation were used to compare activation for the two groups split on the basis of behavioural performance, indicating that the High group had significantly greater activation ($P < 0.01$) in six of the eight

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

	Sex		Age		CFQ		Go RT		No. of errors	
	M	F	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Errors										
High	6	16	30.0	7.2	33.6	12.2	333.3	45.1	33.9	8.9
Low	9	13	29.9	8.1	32.3	9.6	335.8	41.2	12.3	7.0
Sex										
Male	15	–	30.1	8.3	29.3	4.8	325.7	36.6	22.9	14.7
Female	–	29	29.9	7.4	34.9	12.7	339.3	45.6	23.3	13.1
Age										
Young	8	14	23.7	3.0	33.2	8.6	325.5	40.0	21.7	15.0
Old	7	15	36.3	5.1	32.6	13.1	343.2	44.4	24.5	12.2
CFQ										
Low	9	13	31.0	8.0	24.8	5.5	322.1	41.4	25.3	13.1
High	6	16	28.2	6.4	41.5	8.2	345.4	42.1	20.5	14.1
GO RT										
Fast	9	13	29.6	7.6	32.3	11.6	298.2	20.8	26.2	13.5
Slow	6	16	31.4	7.4	33.9	10.7	368.5	26.0	21.0	13.3

Bold font represents a significant comparison (at $P < 0.05$) after adjusting for experimental procedure.

Table 2
Areas activated during errors for high and low error groups

Structure	Brodmann area	Hemisphere	Volume (μ l)	Centre of mass			<i>P</i>
				<i>x</i>	<i>y</i>	<i>z</i>	
Frontal lobe							
Pre-SMA	6	R	635	11	-9	53	**
Cingulate	32	R	3196	1	-14	39	**
Parietal lobe							
Supramarginal	40	R	517	48	43	36	**
Inferior parietal	40	R	114	39	56	43	**
Temporal lobe							
Superior temporal	22	R	214	49	44	19	
Subcortical							
Insula	13	R	923	40	-13	-3	**
Insula	13	L	620	-40	-13	-2	
Thalamus		R	96	12	31	2	**

Positive values for *x*, *y* and *z* coordinates denote, respectively, locations that are right, posterior and superior relative to the anterior commissure. Significance test results indicate cortical areas of increased activation for the high error group using ANCOVA (adjusting for experimental procedure). ***P* < 0.01.

regions (see Table 2), even after adjusting for experimental procedure. Partial correlation analyses were also performed, examining the relationship between activation levels and a subject's error total (with experimental procedure adjusted for), indicating that only the level of activation in the right inferior parietal lobule correlated significantly with error total ($r = -0.44$, $P < 0.01$).

Partial correlation analyses (adjusting for experimental procedure) examined the relationship between activation in each of the clusters from the combined high/low ERROR map with age, CFQ score, and GO RT. ANCOVA was used for sex given the dichotomous nature of the variable. Age, sex and CFQ scores did not significantly influence activation levels in any of the 8 clusters, however, GO RT positively correlated with activation in the inferior parietal region ($r = 0.35$, $P < 0.05$).

Split-half Group Comparisons

The examination of sex differences indicated females had significantly greater activation ($P < 0.01$) in clusters located bilaterally in the inferior parietal lobule, and the right middle frontal gyrus (BA 6) (see Fig. 3b), however activation in the insula, cingulate and pre-SMA regions was not significantly different for males and females. These activation differences arose in the absence of any sex differences in behavioural performance or other demographic characteristics. Given the unexpected nature of this finding and exploratory nature of this investigation, we examined whether adjusting for the other individual difference variables (age, CFQ, no. of errors, GO RT) ameliorated the effect of sex. A comparison of male and female activation in the inferior parietal and middle frontal regions was examined with ANCOVA, revealing that the significant sex differences remained ($P < 0.05$) even after adjusting for all of the other individual difference variables.

For the split-half comparison based on age, the results indicated significantly greater activation for the older group in the ACC [$F(1,41) = 5.60$, $P < 0.05$] and the pre-SMA region [$F(1, 41) = 5.73$, $P < 0.05$] (see Fig. 3c). These differences were observed despite the older adults being on average only 36 years of age and having no other demographic or behavioural performance differences (see Table 1).

The average CFQ scores for the median split of subjects was 24 (low) and 41 (high), and no significant differences in behavioural performance or demographic characteristics was evident. The results indicated significantly greater activation ($P < 0.01$) for the high CFQ subjects in the right middle frontal and inferior parietal regions, and significantly lower activation in the right insula and ACC (see Fig. 3d,e) when compared with their low CFQ counterparts.

The mean GO RT for the split of subjects was 298 ms (fast) and 368 ms (slow) respectively, with the slow GO RT group having significantly greater activation in bilateral parietal, insula, middle frontal regions, and within the cingulate region (see Fig. 3f,g). However, the pre-SMA region displayed an opposite pattern, with fast GO RT subjects showing the greater level of activation. A repeated measures ANOVA using region as the within subjects variable (ACC, Pre-SMA) and GO RT group (fast, slow) as the between subjects variable, indicated a significant interaction between region and group [$F(1,42) = 7.32$, $P < 0.01$]. The mean activation levels indicated a pattern of low ACC and high pre-SMA activation for the fast GO RT group, and the opposite pattern for the slow group.

Discussion

Individual differences in age, sex, speed of responding and self-reported absentmindedness influenced the level of activation seen during the error-response to a failed inhibitory event. The error-related activation pattern seen in the present study indicated regions in the ACC, pre-SMA, bilateral insula, thalamus and right inferior parietal lobule to be significantly activated, consistent with the small number of previous studies that had examined error-related activation in cognitive tasks (Carter *et al.*, 1998; Kiehl *et al.*, 2000; Braver *et al.*, 2001; Menon *et al.*, 2001; Ullsperger and von Cramon, 2001; Garavan *et al.*, 2002). The activation identified in these regions also appeared specific to errors, rather than the result of a stimulus property (e.g. high response conflict trials), as activation was significantly greater during errors when compared with correct inhibitions.

The number of errors committed during the GO/NOGO task also appeared to influence the variance in the activation pattern for inhibitory errors. A split-half group analysis showed gross differences when comparing the activation level for subjects with large and small numbers of errors. This result is consistent with the studies demonstrating that over 20 events need to be averaged to obtain a spatially 'reliable' event-related fMRI activation map (Huettel and McCarthy, 2001; Saad *et al.*, 2003). The results from the present study also suggest that if the spatial regions of interest (ROI) are defined based upon such a map, the level of activation within these regions, with the exception of the right inferior parietal lobule, did not discretely relate to the number of errors an individual makes. Therefore, examining the level of functional activation for subjects who have only a small number of errors (events) with which to average, should only be carried out if the ROIs are

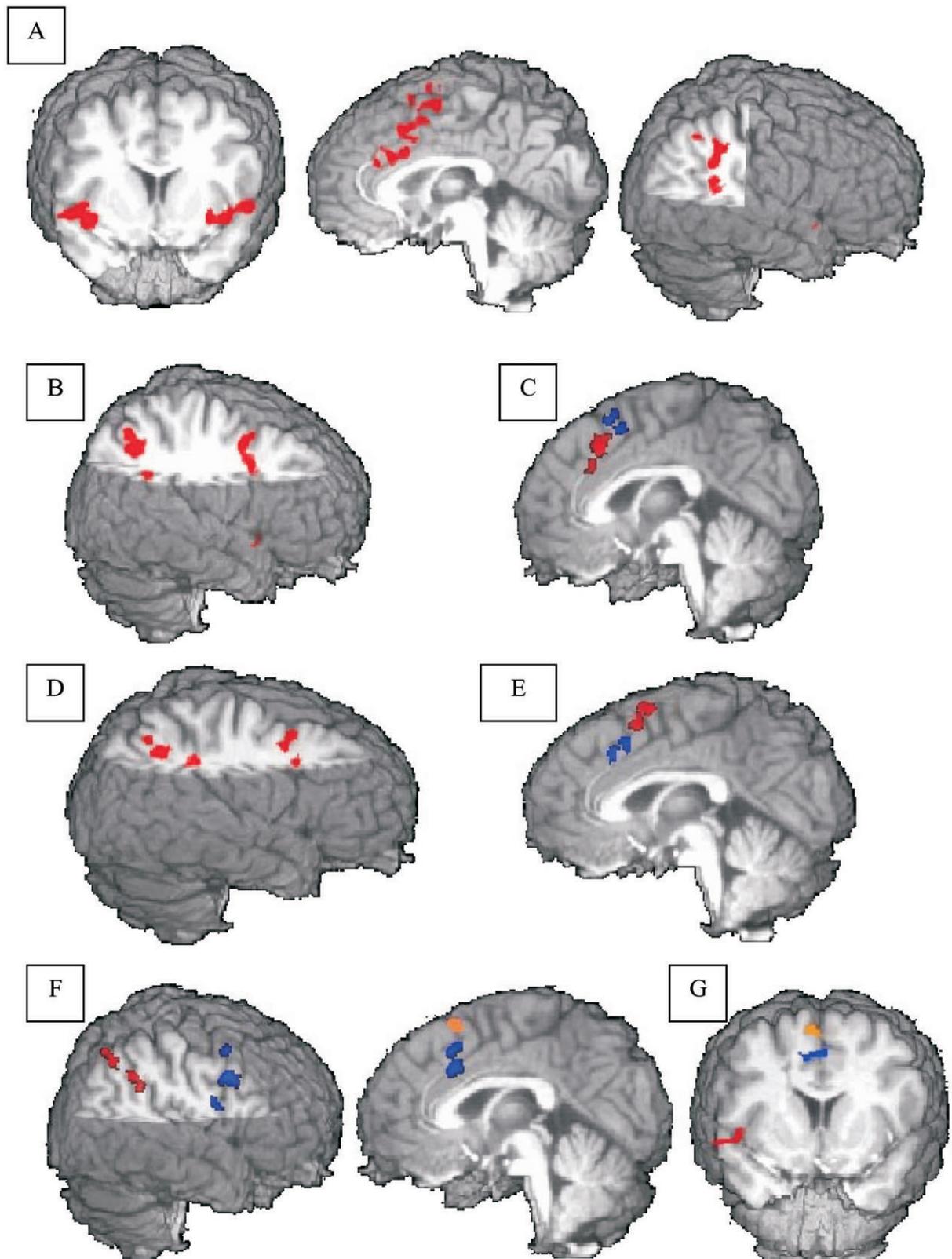


Figure 3. (A) The combined activation map (OR map) for high and low error groups. (B) Inferior parietal and middle frontal regions showing significantly greater activation for females than for males. (C) The ACC (red) and pre-SMA (blue) regions showing significantly greater activation with increasing age of subjects. (D) The right inferior parietal and middle frontal regions showing significantly greater activation for low CFQ subjects. (E) The ACC region (blue) showing significantly lower activation for high CFQ subjects. (F) The inferior parietal and middle frontal areas showing significantly greater activation for slow GO RT subjects. (G) The right insula (red) and ACC (blue) regions showing significantly greater activation, and the pre-SMA (orange) significantly less activation for the slow GO RT group.

defined by averaging a group of subjects with a larger number of events, or if there is a strong a priori expectation of error activation in that ROI. This finding may prove useful to studies where only a few events of interest are available, because group differences might still be examined if the ROIs from a related study where the number of events was greater can be used.

Influence of Individual Differences

Speed of responding was found to influence the error-related neural activation response, with slower responders showing significantly greater activation in the parietal, lateral PFC, insula and ACC regions. The prefrontal regions have been seen previously in error-processing (Carter *et al.*, 1998; Kiehl *et al.*, 2000; Ullsperger and von Cramon, 2001; Garavan *et al.*, 2002), and Ullsperger and von Cramon (2001) argued that prefrontal activation, particularly left lateralized, was not specific to errors *per se*, but reflective of task-set maintenance. Similarly, Garavan *et al.* (2002) showed that left DLPFC was associated with adjustment to ongoing behaviour following an error, rather than to simply all errors equally. The relationship between slower speed of responding and greater activation in the lateral PFC regions seen here would appear consistent with this argument, if RT is considered a measure of attention to task. In support of this hypothesis, subjects with greater attentiveness, as defined by low self-reported absentmindedness, also showed greater activation in the lateral PFC and parietal regions.

The pattern of activation seen in the ACC and pre-SMA regions for fast responders also appears consistent with one interpretation of the function of these regions. Fast responders had higher levels of pre-SMA activation than slow responders, whereas slower responders had higher levels of ACC activation. Fast responding on a GO/NOGO task would typically be associated with greater levels of response conflict, on NOGO trials in which subjects are required to withhold their response. The greater level of activation in the pre-SMA region therefore appears consistent with the studies where increased pre-SMA activation was associated with greater levels of response conflict, rather than error detection *per se* (Braver *et al.*, 2001; Ullsperger and von Cramon, 2001; Garavan *et al.*, 2003). These studies also suggest that the ACC monitors responses, in particular error responses, and adjusts behavioural strategies on the basis of erroneous responses; for example, more controlled response patterns (Pailing *et al.*, 2002) and greater post-error slowing (Gehring *et al.*, 1993; Scheffers *et al.*, 1996) have been associated with larger ACC responses.

The greater ACC activation observed here for slow responders might suggest that slow responders have greater opportunity for, or are undertaking more monitoring for errors, or that the greater activation is related to their more controlled response pattern. Both of these interpretations suggest that slower responders are attending more readily to the task. This interpretation is consistent with the relationship between self-reported absentmindedness and error-related processing in which the more absentminded subjects had reduced activation in the ACC and insula regions, and greater activation in the parietal and prefrontal regions. These results suggest that absentmindedness may contribute to, or be the result of reduced error-related response monitoring.

The influence of age on error-related processing appears on one level to be consistent with the compensatory hypothesis in the aging literature (Reuter Lorenz *et al.*, 1999, 2000, 2001; Rypma and D'Esposito, 2000, 2001). The compensatory hypothesis suggests that with increasing age, recruitment of additional cortex is necessary to maintain the same level of behavioural performance. The results of the present study indicate that despite equivalent levels of behavioural performance, a group comparison of younger (mean age = 23 years) and older (mean = 36 years) adults indicated significantly greater activation of both the ACC and pre-SMA areas for older subjects. This result supports the findings of Nielson *et al.* (2002) who demonstrated greater levels of activation with aging in the ACC and pre-SMA regions for correct inhibitions on the GO/NOGO task. The challenge for this interpretation is why additional cortex is recruited for error processing, given that the increased activation after the error has been committed would not serve to improve performance. One suggestion is that age-related neurovasculature changes are responsible, or alternatively, that performance feedback mechanisms such as error processing are also required to increase their level of activation with aging in order to maintain performance.

Another surprising aspect of the present finding, particularly when compared with the Nielson study where the age of subjects varied between 18 and 78, was the small age range required to observe a group difference. This finding may be an example of the greater sensitivity to subtle activation changes afforded to the present study as a consequence of the larger than usual sample sizes. It also provides a note of caution for researchers using functional imaging to be aware of even seemingly inconsequential demographic differences when undertaking group comparisons.

The increase in ACC activation with age also initially appears contradictory to the ERN literature identifying decreases in error negativity with increasing age (Falkenstein *et al.*, 2001; Nieuwenhuis *et al.*, 2002; Mathalon *et al.*, 2003). In these studies the age-related ERN amplitude difference was greatest when the ratio of 'mistakes' (subjects do not know the correct response) to 'slips' (subjects know the right answer but fail to provide it) increased. The ERN response is specifically associated with 'slips' (Dehaene *et al.*, 1994; Pailing *et al.*, 2002), and consequently the age-related weakening of the ERN may be due to an increase in 'mistakes' made by older participants, a suggestion supported by the finding that subjects diagnosed with Alzheimer's disease display a similar pattern when making a high proportion of mistakes due to disease-related loss of knowledge (Mathalon *et al.*, 2003). Participant's own reports during the present task suggest that almost all errors were 'slips' rather than 'mistakes', suggesting that this particular influence reported in the ERN studies may contribute to the difference in findings.

The examination of sex differences in error-related processing was undertaken due to the suggestion that error processing may involve an emotional response to the error, and previous studies had identified sex differences in emotional processing. The present study's results suggest that the regions typically associated with both emotional and error processing; the ACC and insula, did not show any sex related activation differences. Increased error-related activation was seen in the inferior parietal and middle frontal regions for females, though the basis for this difference is uncertain.

Previous studies reporting sex differences in the magnitude of activation for the parietal and prefrontal regions have not provided a consistent pattern of findings (Gur *et al.*, 2000; Speck *et al.*, 2000; Jordan *et al.*, 2002; Rossell *et al.*, 2002), even within the same cognitive task domain. A further confound for this analysis was the large discrepancy in samples for males and females, which might have influenced the validity of the group comparison.

Conclusion

These results have shown that error-related activations are quite robust, particularly in producing midline activations along the ACC, consistent with the extant functional brain imaging literature. This general conclusion notwithstanding, individual differences do affect the magnitude of activation. Whereas older subjects produced greater levels of midline activation and males and females equivalent levels of activation, the less attentive subjects (i.e. those with faster RTs and scoring higher in absentmindedness) produced smaller midline activation. The relative hypoactivity in the less attentive subjects may speak to the importance of midline performance monitoring structures in engaging appropriate top-down attentional control. The findings of this meta-analysis reveal a degree of functional variability in a brain system that has frequently been observed to be altered in different clinical groups.

Notes

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