Mapping Motor Inhibition: Conjunctive Brain Activations across Different Versions of Go/No-Go and Stop Tasks

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Conjunction analysis methods were used in functional magnetic resonance imaging to investigate brain regions commonly activated in subjects performing different versions of go/no-go and stop tasks, differing in probability of inhibitory signals and/or contrast conditions. Generic brain activation maps highlighted brain regions commonly activated in (a) two different go/no-go task versions, (b) three different stop task versions, and (c) all 5 inhibition task versions. Comparison between the generic activation maps of stop and go/no-go task versions revealed inhibitory mechanisms specific to go/no-go or stop task performance in 15 healthy, right-handed, male adults. In the go/no-go task a motor response had to be selectively executed or inhibited in either 50% or 30% of trials. In the stop task, the motor response to a go-stimulus had to be retracted on either 50 or 30% of trials, indicated by a stop signal, shortly (250 ms) following the go-stimulus. The shared "inhibitory" neurocognitive network by all inhibition tasks comprised mesial, medial, and inferior frontal and parietal cortices. Generic activation of the go/no-go task versions identified bilateral, but more predominantly left hemispheric mesial, medial, and inferior frontal and parietal cortices. Common activation to all stop task versions was in predominantly right hemispheric anterior cingulate, supplementary motor area, inferior prefrontal, and parietal cortices. On direct comparison between generic stop and go/no-go activation maps increased BOLD signal was observed in left hemispheric dorsolateral prefrontal, medial, and parietal cortices during the go/no-go task, presumably reflecting a left frontoparietal specialization for response selection.   © 2001 Academic Press

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INTRODUCTION

Control of behavior and impulse is a higher-order function that evolves late, phylogenetically as well as ontogenetically, and has been suggested to be subserved by the frontal lobes (Fuster, 1989). Every behavioral, cognitive, or motor act requires a finely tuned balance between initiatory and inhibitory processes to provide appropriate preparation, initiation, on-line control, and timely inhibition of this act. Inhibitory control is therefore an essential regulatory function. It develops progressively from childhood to adulthood (Williams *et al.,* 1999) and is therefore susceptible to impairment in neurodevelopmental disorders such as attention deficit hyperactivity disorder (Rubia *et al.,* 1999, 2000b), conduct disorder, antisocial personality disorder, obsessive compulsive disorder, and Tourette's syndrome (Bradshaw, 2000).

Different types of motor acts are likely to be regulated by different inhibitory processes, which may be mediated by different cortical areas. The parts of the frontal lobes specifically involved in inhibitory control may therefore depend on the type of inhibitory process and the kind of action which needs to be inhibited. Concordant with this multiple domain model, different parts of the frontal lobes have been found to be responsible for different aspects of inhibitory control. Lesions in orbitofrontal cortex can lead to behavioural and socioemotional dyscontrol (Fuster, 1989), mesial and dorsolateral prefrontal brain areas have been related to reflex inhibition in the antisaccade task (Gaymard *et al.,* 1998; O'Driscoll *et al.,* 1995; Pierrot-Deseilligny *et al.,* 1991), the supplementary motor cortex has shown to be involved in both initiation and suppression of voluntary movements (Dinner and Lueders, 1995; Kawashima *et al.,* 1996; Peterson *et al.,* 1999), dorsolateral, inferior prefrontal, and anterior cingulate cortices are activated during the more cognitive/attentional forms of "inhibiting interference" during the Stroop task (Pardo *et al.,* 1990; Bench *et al.,* 1993; Taylor *et al.,*

1997) and during the suppression of previously learned stimulus–response associations in switching tasks (Nagahama *et al.,* 1998, 1999; Konishi *et al.,* 1998b, 1999; Dove *et al.,* 2000). Inhibition of a motor response is the most direct expression of inhibitory control, as it involves (compared to the more cognitive forms of inhibitory control such as interference control) all-or-none decisions about action or non-action. Several brain areas have been related to inhibition of a motor response in stop and go/no-go tasks, including orbital, inferior, dorsolateral and mesial frontal, temporal and parietal cortices, as well as cerebellum and basal ganglia (Garavan *et al.,* 1999; Rubia *et al.,* 1997, 1999, 2000a,b,c; Konishi *et al.,* 1998a, 1999; Humberstone *et al.,* 1997; Casey *et al.,* 1997; Kawashima *et al.,* 1996; Godefroy *et al.,* 1996).

The goal of this study was to further investigate and compare the neurocognitive networks related to two different forms of motor response inhibition, namely those required by performing go/no-go and stop tasks, by use of generic brain image analysis methods similar to cognitive conjunction (Price and Friston, 1997; Friston *et al.,* 1999). Such analyses allow exploration of commonalities in activations of subject groups performing different tasks in relation to functions which are common to the tasks. In this study, these generic analysis methods enable the identification of brain regions generically activated during different versions of go/no-go and stop tasks independent of the specific effects of the particular task versions (versions differing in probability of inhibitory signals or in contrast conditions). Furthermore, the analysis of generic activation across all stop and go/no-go task versions allows the identification of brain regions related to shared inhibitory control mechanisms involved in both tasks, independent of the task-specific effects (go/no-go or stop task performance).

The go/no-go paradigm requires a response selection process between either executing or inhibiting a motor response, triggered by a go- or a no-go-stimulus. The task demands high-level cognitive functions of decision-making, response selection, and response inhibition. The stop task requires withholding a motor response, which is triggered by a stop signal shortly following the go signal, thereby converting the go-signal aposteriori to a no-go signal. It contains a higher load on response inhibition processes compared to the go/no-go task in that it involves the retraction of a response that has already been triggered by a go signal. Go/no-go tasks have a higher load on response selection, due to the apriori knowledge about whether or not to respond, provided by the categorical stimuli.

The common and distinct neural substrates of motor response inhibition in these two tasks has not previously been identified. Evidence from lesion studies points towards the involvement of the mesial frontal lobes in go/no-go tasks, especially the SMA and ante-

rior cingulate (Drewe, 1975; Leimkuhler and Mesulam, 1985; Verfaellie and Heilman, 1987), but also dorsolateral, medial prefrontal cortex, and caudate (Godefroy *et al.,* 1996). Recent modern brain imaging studies using fMRI have revealed mesial, dorsolateral, and inferior frontal and parietal involvement in this selective response inhibition process (Rubia *et al.,* 2000c; Garavan *et al.,* 1999; Humberstone *et al.,* 1997). Event related fMRI has shown that focused activation of predominantly right inferior frontal cortex correlated with no-go activity (Konishi *et al.,* 1998a, 1999), as well as pre-SMA (Humberstone *et al.,* 1997), but also inferior, mesial, and middle frontal, insular, parietal and temporal lobes (Garavan *et al.,* 1999). The motor response inhibition process involved in stop tasks has been shown to elicit predominantly right mesial and inferomedial prefrontal cortex activation in adults (Rubia *et al.,* 1997, 2000a,c) and additional caudate activation in adolescents (Rubia *et al.,* 1999, 2000a).

The goal of this paper was to investigate and compare the neurocognitive networks mediating the two types of motor inhibitory control required by go/no-go and stop tasks, independent of the specific contexts of the task variants as well as to explore shared neurocognitive processes underlying performance on both inhibition tasks.

METHODS

Subjects

Fifteen healthy right-handed male adults, aged 26 to 58 (mean age = 36 years; standard deviation (SD) = 7 years), and of average intelligence as measured by a nonverbal intelligence measure (Raven, 1960) participated in the study (mean intelligence quotient = 104 ± (SD) = 16). Subjects were divided in subgroups performing different task versions. Groups of performers did not differ in IQ or task performance (Mean performance data. Go/no-go task1: mean reaction time (MRT in ms) = 352 ± 82, mean probability of inhibition ($P(I)$ in percentage = 95 ± 8): go/no-go task2: MRT = 304 ± 87, $P(I)$ = 89 ± 9; stop task1: MRT = 664 ± 66, $P(I)$ = 93 ± 7; stop task2: MRT = 624 ± 149, $P(I)$ = 93 ± 7; stop task3: MRT = 576 ± 111, $P(I)$ = 93 ± 5). All subjects provided written informed consent. The study was approved by the Bethlem Royal and Maudsley NHS Trust Ethics (Research) Committee.

Tasks

Each paradigm consisted of two main conditions (control and activation condition), lasting 27 s each, preceded by a short visual warning cue (lasting 3 s). Control and activation condition epochs were periodically alternated five times in the course of a single experiment lasting 5 min. The control condition was

TABLE 1

Overview of Inhibition Task Versions Performed by the 15 Subjects

	Go/no-go 1	Go/no-go 2	Stop 1	Stop 2	Stop 3
Percentage of inhibition	50%	30%	50%	30%	30%
Contrast condition	Stimulus controlled	Motor controlled	Stimulus controlled	Stimulus controlled	Motor controlled
Number of subjects	5	7	8	7	7

presented first for each task. Throughout acquisition of the MR images, subjects responded to the stimuli by pressing a button with their right thumb, which was recorded by means of an MR compatible interface to a PC.

Go/no-go task 1. The go/no-go task requires selection of either a response, indicated by a go signal, or a "no-response," indicated by a no-go signal. Interstimulus-interval (ISI) was 1000 ms, including a stimulus duration of 200 ms followed by a blank screen for 800 ms (27 stimuli per epoch). Go signals (airplanes) and no-go signals (bombs) alternated with 50% probability each. Subjects had to respond to airplanes, but not to bombs. In the control condition airplanes and zeppelins alternated with a probability of 50% and subjects were instructed to press a button in response to either stimuli. This task controlled for the amount of sensory stimulation but only partially for the number of motor responses, which was higher in the control condition (by 12 responses). Five of the subjects performed go/no-go task 1.

Go/no-go task 2. This task differed from the first go/no-go task in that the no-go signals and its control signals in the control condition appeared in 30% of trials only, while the go signals appeared in 70% of trials, in both conditions. A second difference was that the ISI of the control task was 1300 ms compared to 1000 ms for the activation task, in order to control for the number of motor responses, but only partially for the number of visual stimuli, which was higher in the activation condition (by six stimuli). This task was performed by seven subjects.

Stop task 1. The stop task requires a motor response in response to the go signal, only when the go signal is not followed by a stop signal. In the activation condition (stop condition), airplanes appeared on the screen for 1000 ms, followed by a blank screen for 650 ms (18 stimuli per epoch). On 50% of trials the airplane was followed by a bomb, which appeared 250 ms after onset of the airplane, replacing it for 300 ms, and was then then followed by a blank screen for 1100 ms. The subject was required to press a button if the airplane alone appeared, but not if the airplane was followed by a bomb. The control condition was identical, except that a zeppelin instead of the bomb appeared on 50% of trials, and subjects were instructed to press the button always, whether or not the airplane was followed by a

zeppelin. This task controls for the number of visual stimuli, but only partially the number of motor responses which was higher in the control condition (by eight responses). This task was performed by eight subjects.

Stop task 2. A second version of the stop task was identical to stop task 1, except that the stop stimuli and its control stimuli in the control conditions appeared with a frequency of 30% of trials instead of 50% of trials. The conditions were matched for visual stimulation, but only partially for number of motor responses, which was higher in the activation condition (by 4 responses). Go-signals appeared in 70% of trials. This task was performed by seven subjects.

Stop task 3. This stop task was identical to stop task 2, where stop stimuli and its control stimuli appeared with a frequency of 30%, except that the ISI in the control condition was 2200 ms compared to the ISI for 1650 ms of the activation condition. This task controls for the number of motor responses, but only partially for the number of visual stimuli, which was higher (by 4 stimuli) in the activation condition. This task was performed by the same seven subjects who performed stop task 2 (see Table 1).

Image Acquisition

Gradient-echo echoplanar MR images were acquired using a 1.5 Tesla GE Signa System (General Electric, Milwaukee, WI) fitted with Advanced NMR hardware and software (ANMR, Wolburn MA) at the Maudsley Hospital, London. A quadrature birdcage head coil was used for RF transmission and reception. Data were collected from 15 axial planes parallel to the anterior commissure-posterior commissure plane, ensuring that the lowermost slice lay below the inferior border of the frontal lobe. 100 T_2^*-weighted MR images depicting BOLD contrast (Ogawa *et al.,* 1990) were acquired with TE = 40 ms, TR = 3300 ms, in-plane resolution = 3.1 mm, slice thickness = 5 mm, and slice gap = 0.5 mm. Head movement was limited by foam padding within the head coil and a restraining band across the forehead. At the same session, a 43 slice, high resolution echoplanar image of the whole brain was acquired with TE = 40 ms, TI = 180 ms, TR = 16 s, in-plane resolution = 1.5 mm, slice-thickness = 3 mm, slice gap = 0.3 mm for subsequent registration of the fMRI data in

standard stereotactic space (Talairach and Tournoux, 1988).

Image Analysis

Analysis of individual subject data. Following three-dimensional correction for movement during image acquisition using standard algorithms (Bullmore *et al.,* 1999a), analysis of the individual subject data by sinusoidal regression yielded estimates for the amplitudes of the sine and cosine components of the response at the frequency of alternation between the activation and control conditions of each task. These estimates (gamma and delta) were used to compute the standardised power (fundamental power quotient or FPQ) and phase of the response at each voxel (Bullmore *et al.,* 1996). Gamma and delta were then reestimated 10 times at each voxel following random permutation of the time-series data. This facilitated construction of a distribution of FPQs under the null hypothesis of no experimentally determined response at the experimental design frequency. Tests for activation of any voxel could then be performed by obtaining the appropriate critical value from the distribution of "randomized" FPQs and accepting as activated any voxel whose FPQ exceeded this threshold (normally set at $P < 0.003$) in the current series of experiments.

Generic analyses. The data were first normalised for each subject on an inversion recovery echoplanar image obtained at twice the resolution of the fMRI data in x, y, and z. In a second stage, these were then transformed into a Talairach template (Talairach and Tournoux, 1988), constructed by manual transformation of the structural inversion recovery image from 10 subjects (5 male, 5 female) using the AFNI software (Cox, 1995) and spatially smoothed by application of a 2-D Gaussian filter (SD = 3 mm). The transformation at both stages was done by minimizing the sum of absolute image differences between the image to be transformed and the template image using an affine transformation and at the second stage by a quadratic warp algorithm. The procedure is described in detail in Brammer *et al.* (1997).

The data from the different experiments were combined and several generic analyses with non-parametric inference at a voxel-wise probability of type I error $P < 0.0007$ were performed on the motion-corrected fMRI time series at each voxel to explore commonly activated brain regions (a) in the two different versions of the go/no-go task (b) in the three different versions of the stop task, and (c) across all five task versions. Approximate Brodmann areas were assigned to the voxel with maximum FPQ in each generically activated 2-D cluster by an automated cortical parcellation scheme described in detail by Wright *et al.* (1999). Generic activations (of a, b, and c) were analyzed using a linear model to detect effects that were dependent on

and independent of the nature of the particular task/contrast condition.

The following regression model can be expressed as $FPQ_{ijk} = \alpha_{0i} + \alpha_{1i}$ Task version $+ \epsilon_{ijk}$, where FPQ_{ijk} denotes the standard power of response to the jth task (i.e., across the different experiments of (a, b, and c)) in the kth individual at the ith voxel; $\alpha_{0i} + \alpha_{1i}$ are the parameters estimated from the model; and ϵ_{ij} is the residual error at each voxel. The effect of task version membership (Task version is the classification parameter) is parameterized by α_{1i} at the ith voxel and the task version-independent (overall mean) effect by α_{0i}. This model was fitted to the Talairach transformed FPQ data obtained by random permutation of the time series (see above) as well as the FPQ data obtained by analysis of the observed time series. Fitting to the randomized FPQ data permitted construction of distributions of a_{1i} and α_{0i} under the null hypothesis that there was no experimentally determined response to periodic alternation of the different activation and control conditions of each task. The null distributions of α_{1i} and a_{0i} were then used to determine critical values of the two parameters for statistical significance at the level of probability $P < 0.0007$, allowing for 10 error voxels. As the main goal of the analysis was to identify voxels showing significant responses related to shared inhibitory processes involved in task performance across all task conditions, regardless of the particular task version, we were primarily interested in estimating and testing experiment-independent effects (a_{0i}). But since the overall mean can be inflated by a particularly salient response to one of several experiments, we included the α_{1i} term in the model to allow such responses to be identified and removed from generic activation maps. Following this conservative correction of the data, significant generic effects across task versions in (a, b, and c) were then displayed on a morphological template. The median value of gamma, indicating the phase of periodic signal change with respect to the input function, was computed for each generically activated voxel. Voxels with gamma > 0 had maximum signal during the first (control) condition, voxels with gamma < 0 had maximum signal value during the second (activation) condition. Generic brain activation maps were constructed to represent FPQ and gamma at each voxel of generic activation in (a) (go/no-go), (b) (stop), or (c) (stop and go/no-go tasks). Only voxels activated in phase with the activation condition were superimposed on a grey-scale template image to form a generic activation map depicting significant effects independent from the different task versions.

Task comparison. To estimate the difference between generic brain activation across all go/no-go task versions and generic activation across all stop task versions, data from all experiments were combined and fitted to the following analysis of variance (ANOVA)

model at the ith voxel generically activated by the activation condition in one or both of the tasks (referring to generic gonogo and generic stop task activations).

$$FPQ_{i,j} = \mu_i + \beta\, Task_j + \epsilon_{i,j}$$

Here, $FPQ_{i,j}$ denotes the standardized power of response by the jth individual at the ith voxel; μ_i is the overall mean power at the ith voxel; and $\epsilon_{i,j}$ is the residual term for the same individual. Task denotes a factor coding the main effect of task (generic go/no-go task activation or generic stop task activations), and $\mu_i + \beta Task_j$ denotes the mean power of response in the jth Task. The null hypothesis of zero between-task difference in mean FPQ was tested by comparing the observed coefficient β_1 to critical values of its nonparametrically ascertained null distribution. To do this, the elements of Task are randomly permuted 10 times at each voxel; β_1 is estimated at each voxel after each permutation; and these estimates are pooled over all intracerebral voxels in standard space to sample the permutation distribution of β_1. Critical values for a two-tailed test of size a = 0.01 are the $100*(\alpha/2)$th and $100*(1 - \alpha/2)$th percentiles of this distribution (Bullmore *et al.,* 1999b). Note that this uncorrected probability threshold was used to identify differentially activated voxels only within the restricted search volume of voxels generically activated in the activation conditions of the different stop task and go/no-go task versions.

Voxel clusters containing less than 4 voxels are not considered in any of the analyses and are not shown in the figures.

RESULTS

Generic Activation of Go/No-Go Task Versions

Common activation foci ($P < 0.0007$) in the different versions of the go/no-go task were in bilateral but predominantly left hemispheric middle (BA 9) and inferior frontal gyri at the border to the frontal operculum (BA 44/45), left and right mesial frontal cortex, including anterior cingulate and pre-SMA (BA 8/32/6), left inferior parietal lobe (BA 40), left precuneus (BA 7), and bilateral extrastriate cortices (BA 18/19) (see Fig. 1, Table 2a).

Generic Activation of Stop Task Versions

Common activation foci across the different stop task versions ($P < 0.0007$) were noted in bilateral, but predominantly right hemispheric inferior prefrontal/opercular cortex (BA 45), right inferior parietal lobe (BA 40), pre-SMA (BA 6), and anterior cingulate (BA 32) (see Fig. 1, Table 2b).

Shared Activation in All Inhibition Task Versions

Common foci of activation across all five go/no-go and stop task versions ($P < 0.0007$) were observed in left and right inferior (BA 47/44), right middle frontal gyrus (BA 9/6), anterior cingulate (BA 8/32), pre-SMA (BA 6), right inferior parietal lobe (BA 40), and predominantly left middle temporal cortex (BA 21) (see Fig. 2, Table 2c).

Differences between Generic Go/No-Go Task Activation and Generic Stop Task Activation

The search volume for the differences between the generic go/no-go and generic stop task activations was limited to the generic activations found in each of the two conjunctive analyses. The search volume in these regions of conjunctive activations in either go/no-go or stop tasks or both of them was 514 voxels and the voxel-wise probability of false positive test was $P < 0.01$. At this size of test we expect five false-positive tests. In fact we observed significant differences at 77 voxels. The differences were in left middle prefrontal gyrus (BA 9), in left inferior parietal lobe (BA 40), and in left medial frontal cortex (BA 32/6). In each region there was increased BOLD response during the go/no-go task compared to the stop task (see Fig. 3, Table 2d).

DISCUSSION

Concerted activation of mesial, middle, and inferior frontal and inferior parietal lobes appear to mediate performance on tasks requiring the inhibition of a motor response. While selective inhibition in a go/no-go task activates a bilateral, but more left hemispheric middle-infero-mesio-frontal and parietal network, withholding a planned motor response in a stop task elicits a predominantly right hemispheric homologue network.

Our observation of a neural network of anterior cingulate, pre-SMA, dorsolateral, and inferior frontal and inferior parietal cortices during go/no-go task performance confirms previous findings. The middle and inferior frontal foci of activation of our study are in close proximity to the middle and inferior activation foci in the event related fMRI study of Garavan *et al.* (1999) and Konishi *et al.* (1999) (in inferior frontal lobe), with the difference that the foci in middle and inferior frontal gyri were more prominent in the right hemisphere in those studies as opposed to the left hemisphere predominance in our study (inferior lobe Talairach coordinates (mm); Garavan *et al.,* 42, 40, −2; Konishi *et al.,* 41, 16, 19; this study, −49, 11, 9; middle frontal gyrus, Garavan *et al.,* 36, 23, 33; this study, −35, 19, 37). Bilateral foci in anterior cingulate as well as inferior parietal lobes were also found by Garavan *et al.*

TABLE 2

Main Brain Regions Generically Activated (Omnibus $P < 0.0003$) in (a) Go/No-Go Task, (b) Stop Task, (c) Go/No-Go and Stop Task, and (d) Differences between Generic Activations in Go/No-Go and Stop Tasks (Using Region of Interest Analysis Approach at $P < 0.01$)

Cerebral region	BA	Side	x, y, z	P	N
(a) Generic Go/no-go task activation					
Middle frontal	9	L	−35, 19, 37	0.000012	43
		R	46, 22, 31	0.000012	14
Inferior frontal	44/45	L	−49, 11, 9	0.000012	44
		R	40, 3, 31	0.000012	12
Mesial frontal	8	R	3, 31, 42	0.000012	27
Anterior cingulate	24	L	−3, 0, 42	0.000012	33
Pre-SMA	6	L + R	3, 14, 48	0.000012	22
Parietal	40	L	−52, 28, 37	0.000012	15
		R	49, −50, 37	0.000089	12
Extrastriate cortex	18	L	−38, −75, −2	0.000012	17
	19	R	17, −69, 42	0.000012	27
Precuneus	7	L	−12, −64, 48	0.000024	17
(b) Generic stop task activation					
Inferior frontal/insula	44/45	R	49, 3, 4/40, 17, 9	0.000006	28
		L	−40, 11, 4	0.000006	18
Inferior parietal	40	R	49, −42, 37	0.000006	39
Pre-SMA	6	M	3, 3, 53	0.000006	16
Anterior cingulate	32	M	6, 25, 37	0.000006	8
(c) Activation common to all go/no-go and stop task versions					
Inferior frontal	44/45	L	−49, 11, 4	0.000007	39
		R	49, 3, 4	0.000007	34
Middle frontal	9/6	R	43, 3, 37	0.000007	19
Anterior cingulate	8/32	R	3, 31, 37/3, 14, 42	0.000007	40
Pre-SMA	6	R	3, 11, 48	0.000007	26
Inferior parietal	40	R	46, −42, 37	0.000007	71
Middle temporal	21	L	−49, −44, 9	0.000007	29
		R	61, −28, 4	0.000007	8
(d) Differences between generic go/no-go and stop task activations					
Middle frontal	9	L	−32, 6, 37	8	
Inferior parietal	40	L	−52, −28, 37	8	
Medial frontal	32/6	L	−6, 0, 42	8	

Note. BA, approximate Brodmann area; P, probability of maximum regional difference in fundamental power quotient (FPQ); N, number of voxels; x, y, z refer to Talairach coordinates (mm).

(1999), again more prominently right hemispheric compared to our left hemisphere predominance (Garavan *et al.,* 1999). Studies using block designed go/no-go tasks have observed activation in bilateral anterior cingulate, middle prefrontal and inferior frontal cortices (Casey *et al.,* 1997; Kawashima *et al.,* 1996; Krams *et al.,* 1999). Differences between studies in go/no-go task designs and contrast conditions may explain the differences in laterality or precise localization. Despite these differences, however, common areas of activation have been identified, especially in medial, middorsolateral, and inferior frontal lobes. From these, the most

consistent activation found across studies is in inferior frontal lobes. Right and left inferior frontal cortices are involved in a wide range of high level cognitive functions, including language processing, working memory and attention. Many of these executive functions involve aspects of inhibitory control, such as inhibition of interference in attention or working memory tasks. The inhibitory role of inferior frontal cortex therefore seems not to be limited to the motor domain. Inferior, and also occasionally middorsolateral prefrontal cortices, have been found to be activated during working memory conditions with high inhibitory demand
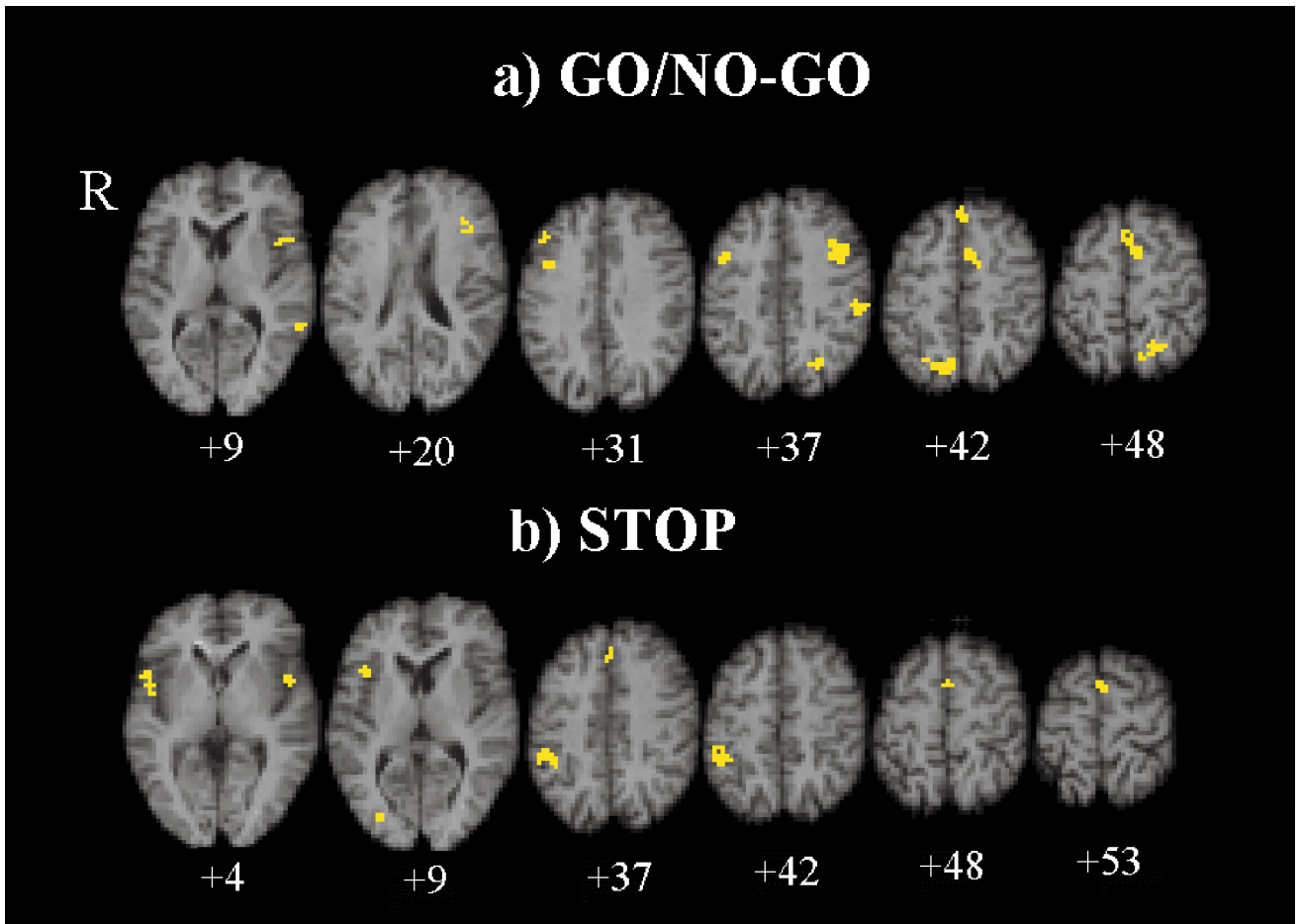
FIG. 1. Generic activation of the different task/contrast conditions of (a) go/no-go and (b) stop tasks. The right side of the brain corresponds to the left side of the image. The voxel-wise probability of Type I error is $P < 0.0007$.

(Smith and Jonides, 1996; Jonides *et al.,* 1998), during control of distraction (Chao and Knight, 1995), during inhibition of habitual responses in Stroop tasks (Pardo *et al.,* 1990; Bench *et al.,* 1993; Taylor *et al.,* 1997; Carter *et al.,* 1999a), and during inhibition of previously learned stimulus–response associations in
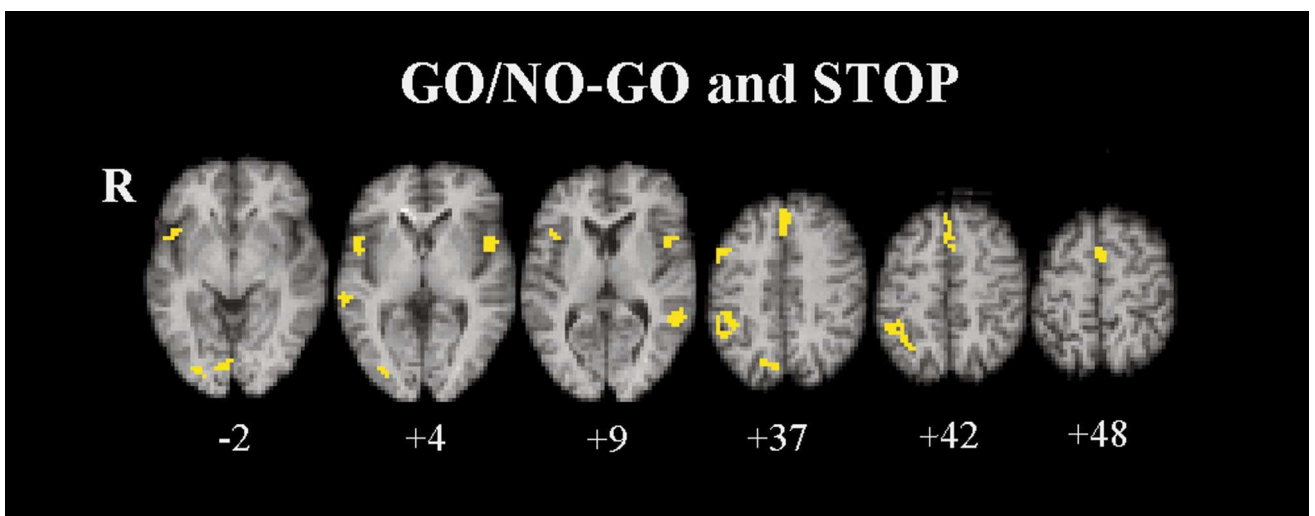

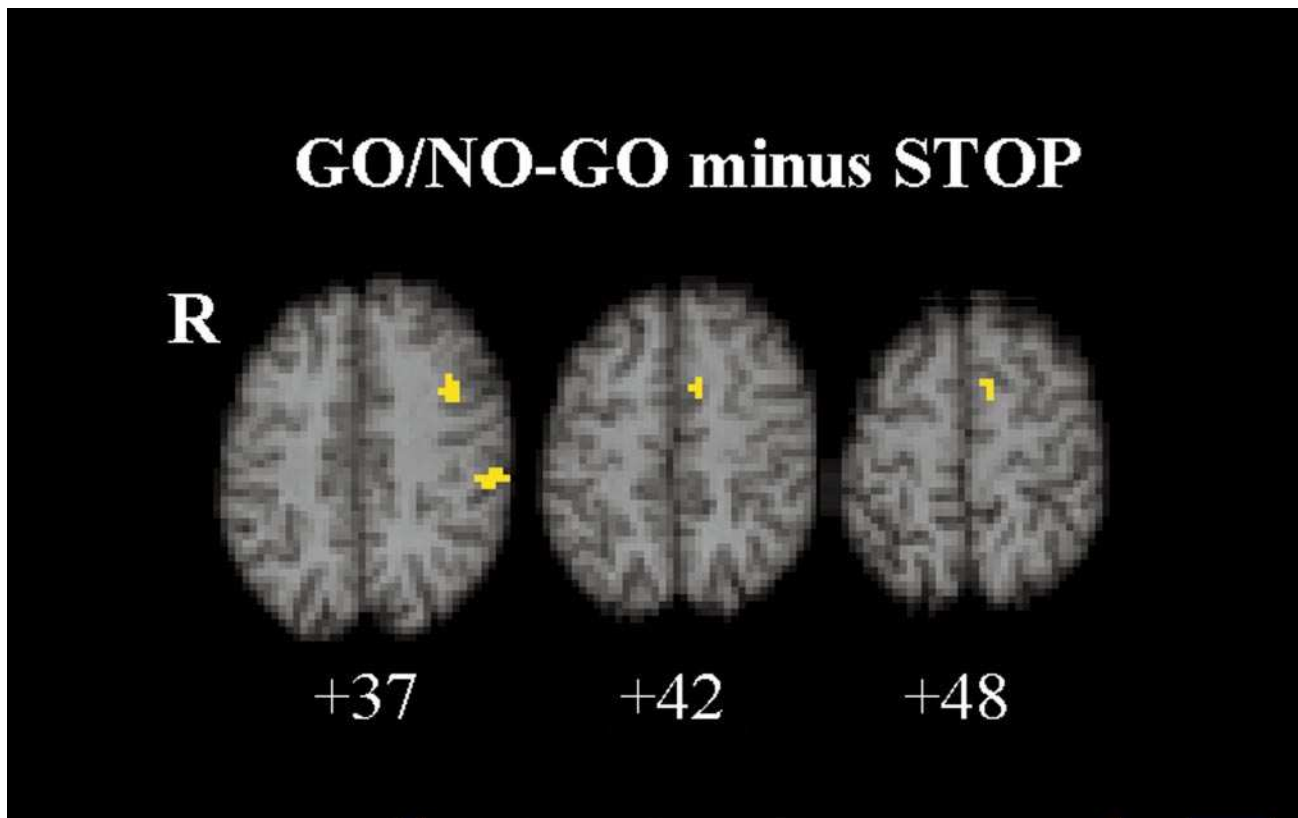**FIG. 2.** Generic activation across all 5 go/no-go and stop task versions. $P < 0.0007$.

FIG. 3. Areas of significant increased power of BOLD signal response during go/no-go compared to stop task performance. The search volume was restricted to generically activated voxels in the 2 go/no-go or the 3 stop tasks (ANOVA map). The voxel-wise probability of Type I error is $P < 0.01$.

switching tasks (Konishi *et al.,* 1998a, 1999; Naga-hama *et al.,* 1998, 1999; Dove *et al.,* 2000).

Lesion studies have traditionally implicated the adjacent orbito-frontal lobes in behavioral and emotional inhibition in animals (Fuster, 1989; Brutkowski *et al.,* 1964; Iverson and Mishkin, 1970) and in humans (Fuster, 1989; Stuss and Benson, 1986; Rolls *et al.,* 1994; Malloy *et al.,* 1993). Susceptibility effects at the air–tissue interface in the perinasal sinuses can make it difficult to observe orbitofrontal activation in fMRI; while it is conceivable that orbitofrontal cortex is more prominently related to behavioral and emotional rather than motor inhibition, we can, however, not exclude a potential role of orbitofrontal cortex in inhibitory motor control based on fMRI data.

The middorsolateral prefrontal focus could be related to other noninhibitory functions, which were not optimally controlled for by the executive control conditions, such as selective attention, conflict monitoring, motor preparation, and response selection. Dorsolateral prefrontal cortex has been attributed a role in selective attention and response selection (Decary and Richter, 1995; Sakai *et al.,* 2000; Passingham, 1993; Deiber *et al.,* 1996; Jueptner *et al.,* 1997; Rubia *et al.,* 1998). The implication of dorsolateral prefrontal cortex

in response selection is supported by the fact that the main dorsolateral prefrontal focus was during the go/no-go task, which has a higher load on response selection compared to the stop task.

Pre-SMA and the proximal, closely connected rostral anterior cingulate have reciprocal anatomical connections with lateral prefrontal and parietal brain regions (Bates and Goldman-Rakic, 1993; Picard and Strick, 1996). As stated above, these medial frontal brain areas have been shown by several studies to be involved in situations where motor responses need to be inhibited, based on modern neuroimaging (see above), electrophysiological (Brandeis *et al.,* 1998; Naito and Matsamura, 1996), and lesion data (Drewe, 1975; Leimkuhler and Mesulam, 1985; Verfaellie and Heilman, 1987). It is conceivable, however, that the role of medial frontal cortex during inhibition task performance is not restricted to the process of inhibition itself. Evidence exists for a more general, metamotor, attentional control function of medial frontal cortex, required for, but not specific to complex motor inhibition task situations. Neuroimaging studies have attributed a wide range of executive supervisory and attentional control functions to pre-SMA and rostral anterior cingulate, such as attention for action, re-

sponse monitoring and motor preparation; while the more caudal parts of anterior cingulate and SMA have been found to be involved in motor execution itself (for overview see Picard and Strick, 1996; Passingham, 1996; Posner and Digirolamo, 1997). Both areas have thus been found to be activated in complex and novel versus simple and learned performance (Paus *et al.,* 1993; Jenkins *et al.,* 1994), in motor preparation and initiation (Jenkins *et al.,* 2000; Warburton *et al.,* 1998; Abdullaev and Posner, 1998; D'Eposito *et al.,* 1995; Deiber *et al.,* 1996, 1999), in response selection (Paus *et al.,* 1993; Devinsky *et al.,* 1995; Elliott and Dolan, 1998; Peterson *et al.,* 1999) and in motor timing (Rao *et al.,* 1997; Rubia *et al.,* 1998). Most recently, anterior cingulate has been attributed a role in the high-level cognitive functions of task switching (Nagahama *et al.,* 1999) and monitoring response competition (Carter *et al.,* 1999b; Botvinick *et al.,* 1999), both of which are required by go/no-go and stop tasks. A more general meta-motor control function of medial frontal cortex is also supported by findings of studies using inhibition tasks. We have observed a biphasic response of anterior cingulate during delay and stop tasks in the activation and their fMRI contrast conditions (Rubia *et al.,* 1998, 1999). Anterior cingulate activation disappears if a go/no-go task is subtracted from a response selection task (Kawashima *et al.,* 1996) and is equally engaged in the processes of response inhibition, response selection and target detection in different modifications of go/no-go-like tasks (Braver *et al.,* 2000). In the Stroop task, anterior cingulate activation has been shown to be related to response selection and selective attention processes rather than to interference inhibition (Taylor *et al.,* 1997). Pre-SMA has found to be activated during both "go" and "no-go" trials in go/no-go tasks (Humberstone *et al.,* 1997). Thus, medial prefrontal activation during inhibition tasks may not necessarily reflect an inhibitory function, but a multipurpose and metamotor attentional control function in a multifunctional network necessary for performance of inhibition tasks, involving selective attention, conflict monitoring, response selection and ultimately response inhibition. Alternatively, it is also conceivable that particular subregions in pre-SMA and in anterior cingulate are responsible for inhibition of motor responses, while other parts are mediating response execution (Dinner and Lueders, 1995; Peterson *et al.,* 1999).

The stop task has rarely been used in functional imaging. The predominantly right hemispheric network of medial and inferior prefrontal cortex found here is strikingly similar to the network we observed previously in healthy adults (Rubia *et al.,* 1997, 2000c) and adolescents (Rubia *et al.,* 1999, 2000a,b), with the exception of an additional caudate activation found in adolescents, possibly reflecting a reliance on subcortical structures in younger subjects. The medial prefrontal focus is in line with electrophysiological activity found over frontocentral brain areas during stop task performance, assumed to lie close to the SMA (DeJong *et al.,* 1990, 1995; Naito and Matsamura, 1996; Brandeis *et al.,* 1998).

Left inferior parietal activation in our go/no-go task and the right parietal homologue in the stop task are in close proximity to the bilateral inferior parietal activations in Garavan's study (Garavan *et al.,* 1999). Parietal activation is also unlikely to be related to motor inhibition per se, but rather to movement-related visuospatial attentional demands which might have been higher in the inhibition tasks compared to their executive control conditions. Although visual stimulation was controlled for, the conflict situation of either execution or inhibition, depending on the signal context, may have produced the activation in inferior parietal brain regions. The anterior part of inferior parietal cortex, closely connected to the other areas activated in this study, has been related to motor attention/motor control (Rushworth *et al.,* 1997) and to preparation for movements (Decety *et al.,* 1992; Deiber *et al.,* 1991, 1996), especially in situations where visual cues need to be integrated into movement preparation and selection (Grafton *et al.,* 1992). Stop and go/no-go task performance may thus produce a high load on this "sensorimotor interface" role of the inferior parietal cortex (Mattingley *et al.,* 1998).

The left hemispheric medial, dorsolateral and parietal activation specific to go/no-go task performance may be related to the role of these left-hemispheric regions in higher level motor planning and response selection (Kimura, 1993; Rushworth *et al.,* 1997, 1998), which is in greater demand in the go/no-go compared to the stop task. Specifically left anterior cingulate (Elliott and Dolan, 1998; Badgaiyan and Posner, 1998), left pre-SMA (Stephan *et al.,* 1995; Rubia *et al.,* 1998), and left dorsolateral prefrontal cortex (Stephan *et al.,* 1995; Thompson-Schill *et al.,* 1997; Desmond *et al.,* 1998; Rushworth *et al.,* 1998; Rubia *et al.,* 1998) have been found to be involved in response selection; left inferior parietal lobe has been shown to play a role in movement preparation and fine-motor control (Rushworth *et al.,* 1997).

In conclusion, using a range of conjunctive brain activation and ANOVA analysis methods we have shown that the neurocognitive network subserving motor response inhibition involves bilateral middle and inferior frontal gyri, anterior cingulate, pre-SMA, and inferior parietal cortex. Inferior frontal cortex may be specifically related to motor response inhibition, while dorsolateral, medial prefrontal, and parietal cortices are possibly mediating more general metamotor executive control functions such as motor attention, conflict monitoring, and response selection, necessary for inhibition task performance. While activations during stop task performance were more right-hemispheric, the go/no-go task with lower load on inhibition elicited

specific left hemispheric dorsolateral, medial prefrontal, and parietal activations, presumably responsible for response selection.

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