European Journal of Neuroscience, Vol. 19, pp. 3105–3112, 2004

Prefrontal-subcortical dissociations underlying inhibitory control revealed by event-related fMRI

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Keywords: basal ganglia, executive functions, functional neuroimaging, inhibition, prefrontal cortex

Abstract

Using event-related fMRI, this study investigated the neural dynamics of response inhibition under fluctuating task demands. Fourteen participants performed a GO/NOGO task requiring inhibition of a prepotent motor response to NOGO events that occurred as part of either a Fast or Slow presentation stream of GO stimuli. We compared functional activations associated with correct withholds (Stops) required during the Fast presentation stream of stimuli to Stops required during the Slow presentation stream. A predominantly right hemispheric network was activated across conditions, consistent with previous studies. Furthermore, a functional dissociation of activations between conditions was observed. Slow Stops elicited additional activation in anterior dorsal and polar prefrontal cortex and left inferior parietal cortex. Fast Stops showed additional activation in a network that included right dorsolateral prefrontal cortex, insula and dorsal striatum. These results are discussed in terms of our understanding of the impact of preparation on the distributed network underlying response inhibition and the contribution of subcortical areas, such as the basal ganglia, to executive control processes.

Introduction

The dynamic control of behaviour is a defining feature of executive function and describes the ability to adapt one's behaviour to meet changing task or environmental demands. This type of behavioural control is critical for flexible and adaptive interaction with the world as it changes around us. One major component of the executive control of behaviour is the ability to inhibit behaviours or responses that are inappropriate in the current context (Logan *et al*., 1984; Shallice, 1988).

Inhibitory control of behaviour has typically been localized to the frontal lobes, and in particular to ventral prefrontal or orbitofrontal cortex (Fuster, 1997). However, neuroimaging studies have suggested that a number of areas in the right hemisphere, ventral/inferior and lateral prefrontal cortex (PFC) and inferior parietal cortex, along with the anterior cingulate cortex and the pre-SMA/SMA medially are the anatomical substrates of inhibitory control (Garavan *et al*., 1999; Braver *et al*., 2001; Bunge *et al*., 2001; Liddle *et al*., 2001; Garavan *et al*., 2002; Mostofsky *et al*., 2003; Sylvester *et al*., 2003). Furthermore, a number of studies have observed subcortical contributions to executive control, including inhibition (Desmond & Fiez, 1998; Middleton & Strick, 2000; Rieger *et al*., 2003; Saint-Cyr, 2003). Thus, the neural implementation of executive functions, such as inhibition, is likely to involve a distributed network including both cortical and subcortical areas and can no longer be ascribed solely to the prefrontal lobes.

One critical requirement for successful inhibitory control is that it be flexible; one must be able to adapt the level of control in response to changing task or environmental conditions, so that similar behaviour may be maintained despite changed demands. Garavan *et al*. (2002) investigated the dynamics of fluid behavioural control in a GO/NOGO task, observing a dissociation of neuroanatomical networks underlying response inhibition (Stops). They categorized each Stop as being 'difficult' or 'easy', based on the speed of a subject's responses to GO trials that immediately preceded it, hypothesizing that successful inhibitions following fast GO responses would be more difficult than Stops following relatively slower GO response times. A functional dissociation supported this hypothesis – they observed increased activation during Stops in a right hemisphere network involving dorsolateral prefrontal and right inferior parietal cortex when ongoing responses were relatively slow, while there was increased activation in the anterior cingulate cortex when ongoing response speeds were relatively fast. Garavan *et al*. (2002) suggested that the cingulate network may be involved in more difficult, urgent inhibitions, and the prefrontal-parietal network may underlie more deliberative or 'controlled' inhibitions, consistent with a role for dorsolateral prefrontal cortex (DLPFC) in response selection. Recent theories of prefrontal function have emphasized a response selection role for DLPFC (e.g. Rowe *et al*., 2000; Curtis & D'Esposito, 2003), and are supported by neuroimaging studies that show DLPFC activation underlying response selection processes (e.g. Bunge *et al*., 2002; Jiang & Kanwisher, 2003; Schumacher *et al*., 2003).

While there is therefore support for the conclusions of Garavan *et al*. (2002), the findings of that paper are based on an emergent behavioural result, rather than direct experimental manipulation. Recent work has indicated that factors other than response speed may account for the results observed. Primarily, Hester *et al*. (2004) have shown that preparation prior to the presentation of a NOGO stimulus has a significant influence on functional activations associated with

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Received 16 March 2004, accepted 23 March 2004

doi:10.1111/j.1460-9568.2004.03429.x

inhibition. They examined activations during the trials that followed a visual cue introduced 2–7 s prior to a NOGO event and observed a dissociation of areas implicated in preparation for an upcoming inhibition. There was greater activation for successful inhibitions that had been cued than those that had not in a number of areas including prefrontal and parietal regions, as well as deactivation in a number of cortical and subcortical areas. The authors take this to suggest that preparation involves activation of task-relevant cortical areas and deactivation of task-irrelevant ones. Similarly, Sohn *et al*. (2000) have suggested a dissociation of functional activations related to preparation prior to a change in cognitive task. Using a task-switching paradigm, they observed greater activation in inferior lateral PFC (BA45/46) and superior posterior parietal cortex (PPC) when subjects could prepare for an upcoming task switch, and greater activation in superior PFC (BA8) and PPC more generally when subjects had no fore-knowledge of an upcoming change of task. Taken together, these findings suggest that brain areas may respond differently based on the amount of time provided to prepare for an upcoming response. This preparation time is associated with the exertion of endogenous control or top-down influences on information processing or response selection processes (e.g. Hester *et al*., 2004; Rogers & Monsell, 1995). On the other hand, inadequate preparation may lead to suboptimal performance, or make the exertion of these control processes more demanding.

In Garavan *et al*. (2002), stimulus presentation rate was maintained at 1 Hz, which had the effect that the Slow condition, while associated with slower responses, was also associated with a shorter response-stimulus interval (RSI) than the Fast condition, where responses were faster and provided a longer time window between each subsequent response. We hypothesize that the functional activations observed may have been affected by these differential preparation times permitted by the different RSIs. This raises the possibility that, in the Slow condition, what was called into action was not a more deliberative, attentive network but rather a network necessary for response selection and the establishment of successful inhibitory control under conditions in which the subject was less well prepared to make a NOGO response.

The current investigation aimed to resolve this ambiguity by examining how changing task demands, directly affecting preparatory time, impact on the inhibitory network. We employed an experimental manipulation of presentation speeds in an event-related fMRI design to identify the functional areas activated during NOGO events that occurred as part of either a rapidly or slowly presented stream of stimuli. This manipulation allowed for the possibility that participants could maintain the same overt behaviour and performance between conditions. Equivalence in performance between conditions is desirable as it avoids the confound that differences in functional activations may reflect behavioural or performance differences between conditions, rather than the differential operation of functional areas (Murphy & Garavan, 2004).

Second, as a result of differences in the response-stimulus interval, we hypothesized that equivalent performance, including equivalent response times, across conditions would result in a between-conditions difference in the amount of time to prepare for each stimulus. While previous studies (e.g. Hester *et al*., 2004) have employed cues to examine trial-specific preparation, this manipulation permits an examination of the effect of context on the ability to inhibit. This manipulation is intended to affect the subject's level of preparedness, or state of attentiveness, to deal with the unpredictable and difficult NOGO trial. Thus, by preparation we mean the subject's general state of readiness to respond or to inhibit.

We predicted a dissociation of areas of activation within the inhibitory network between conditions corresponding to differential levels of preparation. If the activations observed in Garavan *et al*. (2002) were indeed reflective of a more attentive, deliberative network, then we would expect to see similar activations during the Slow condition. On the other hand, if those results more accurately reflected an inhibitory network called into action under conditions of less preparation then we would expect to see increased prefrontal activation in the Fast condition of the present study.

Materials and methods

Subjects and task design

Fifteen right-handed subjects (10 female, mean age 30, range 23–40), reporting no history of neurological or psychological disorders, participated in this study after providing informed and written consent. The study conforms to The Code of Ethics of the World Medical Association (Rickham, 1964). Participants completed a GO/NOGO task based on previous work (Garavan *et al*., 2002). The letters X and Y were presented serially in an alternating pattern and subjects were required to make a button press to each letter. Subjects were instructed to withhold a response to NOGO stimuli: an interruption to the alternating pattern whereby a letter was presented twice in a row (e.g. the fifth stimulus in the train X-Y-X-Y-Y-X-Y). Stimulus durations were 700 ms and 1100 ms, followed by 100 ms ISI. These durations alternated every 7–11 trials, in blocks of 313 trials, resulting in a repeating oscillation between Fast stimulus presentations and Slow stimulus presentations throughout the block. The event-related design allowed the NOGO stimuli to be distributed unpredictably throughout the stimuli stream. Subjects completed four runs comprising 1152 GOs and 100 NOGOs, equally split between Fast and Slow stimulus durations. The average interval between NOGO stimuli was 11.17 s. Reaction times, errors of commission and errors of omission were recorded.

Scanning parameters

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). All scanning was conducted on a 1.5T Siemens VISION scanner. Foam padding was used to restrict head movements within the coil. Stimuli were presented using an IFIS-SA stimulus-delivery system (MRI Devices Corp., Waukesha, Wisconsin), which was equipped with a 640×480 LCD panel. This LCD panel was mounted on the head-coil, directly in the subjects' line of vision. High-resolution T1-weighted structural MPRAGE images (FOV, 260 mm, isotropic 1 mm voxels) were acquired following functional imaging to permit subsequent activation localization and spatial normalization.

Data analysis

All data analysis was conducted using AFNI (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 3D volume registration (least-squares alignment of three translational and three rotational parameters). Activation outside the brain was removed using edge detection algorithms. One subject showed significant residual motion and was excluded from further analysis. The first five and last two images of each run were excluded from further analyses as these images were acquired during brief rest periods.

A mixed regression analysis was employed comprising five regressors. A square-wave regressor coded for the oscillating Fast-Slow pattern in a block design manner, using Slow Go trials as baseline and Fast Go trials as the ON period. Four separate haemodynamic response functions at two-second temporal resolution were calculated for

successful response inhibitions (Stops) and errors of commission (Errors) in both the Fast and Slow stimulus presentation conditions (event-related regressors). Although the subsequent event-related analyses were confined to Stops, including Errors in the multiple regression ensured that the Stop activation maps would be uncontaminated by error-related activation (Murphy & Garavan, 2004). This mixed regression analysis permitted the removal of any variance caused by a baseline shift due to differences in baseline activation between Fast Go and Slow Go trial blocks. All events of interest were time-locked to the beginning of the two-second whole-brain volume acquisition.

A nonlinear regression program determined the best-fitting gamma-variate function for Fast Stops and Slow Stops as previously described (Garavan *et al*., 1999). The area under the curve of the gamma-variate function was expressed as a percentage of the area under the baseline (in which the variance associated with any differences in activation between Fast and Slow Go trials had been removed). The percentage area (event-related activation) and percentage change (block activation) maps were re-sampled at 1 mm^3 resolution, then warped into standard Talairach space (Talairach & Tournoux, 1988), and spatially blurred with a 3 mm isotropic rms Gaussian kernel filter.

Group activation maps for each condition (Fast and Slow Stops) and for block-related activation were determined with one-sample *t*-tests against the null hypothesis of zero event-related activation. Significant voxels passed a voxelwise statistical threshold ($t = 4.6$, $P = 0.005$) and were required to be part of a larger 108 μL cluster of contiguous significant voxels. This cluster size was determined through Monte Carlo simulations and resulted in a <5% probability of a cluster surviving due to chance.

In order to conduct between-condition comparisons, the activation maps were combined to produce an OR map of Fast and Slow Stops. An OR map includes the voxels of activation indicated as significant from either of the constituent maps. To ensure an omnibus 0.05 false positive probability level, significant voxels were required to be part of a larger 117 μL cluster of contiguous significant voxels (based on 0.025 probability of a cluster surviving in either map alone due to chance). The mean activation for clusters of significant voxels in the combined maps was calculated for the purposes of a functionally defined ROI analysis, and these data were entered into ANOVAs for a series of comparisons between conditions.

Results

Behavioural results

In accordance with the aims of this study, no significant behavioural differences between conditions were observed for reaction times or errors of commission. Reaction times to Fast targets (M = 349.4) were not significantly different from those to Slow targets (M = 344.4) ($F_{1,13} = 0.23$; $P = 0.64$). Similarly, the number of errors of commission did not differ significantly between conditions with an average of 34.5% errors made in the Fast condition and 40.3% errors made in the Slow condition ($F_{1,13} = 2.46$; $P = 0.14$). The proportion of errors of omission made in each condition did reach significance ($F_{1,13} = 5.094$; $P = 0.042$), with an average of 4.8% omissions in the Fast condition compared to 2% in the Slow condition. However, this difference was primarily driven by the data of five subjects, in which there was a small number of blocks of sequential omissions (more than three omissions

TABLE 1. Event-related activation for Fast and Slow successful response inhibitions (Stops)

Structure	Hemisphere	Brodmann's Area	Volume (μL)	Centre of Mass			Condition (sig)
				x	*y*	*z*	
Frontal lobe							
Inferior frontal gyrus	R	9/46	118	52	20	21	Fast**
Middle frontal gyrus	R	9/46	250	39	33	24	–
	R	10	131	31	55	3	Slow**
	R	10	130	40	48	5	–
	R	9	123	35	26	34	Fast*
	R	9	119	46	18	31	–
	L	9	210	−42	39	25	–
	L	10	193	−34	48	12	–
Superior frontal gyrus	R	9	185	18	52	27	Slow**
Precentral gyrus	R	44	168	52	10	6	–
Medial frontal gyrus – preSMA	R/L	24/8	154	0	22	38	–
Temporal lobe							
Middle temporal gyrus	L	22	141	−56	34	−3	–
Fusiform gyrus	L	37	121	−41	−59	−13	Fast*
Parietal lobe							
Superior parietal	R	7	119	25	−66	44	–
Inferior parietal	R	40	2200	47	−41	37	–
	L	40	236	−50	−38	41	–
	L	40	190	−45	−43	49	
	L	40	119	−58	−36	29	Slow*
Precuneus	L	7	315	−21	−57	51	Fast**
Subcortical/insula							
Insula	R	13	752	33	23	2	Fast*
	L	13	482	−31	15	0	Fast*
Striatum†	L		461	−17	4	1	Fast**
Striatum‡	R		449	21	12	−3	–

Positive values for *x*-, *y*-, and *z*-coordinates denote locations right, anterior and superior relative to the anterior commissure. The Condition column indicates the condition for which the area showed greater activation as revealed by *t*-tests for paired samples. *$P < 0.05$, **$P < 0.01$. †Includes lentiform nucleus, putamen and caudate. ‡Includes lentiform nucleus and putamen.

in a row). We consider these blocks of omissions to reflect temporary lapses of attention or disengagement from the task, rather than true omission errors, and when these sequential omissions are removed from the data the difference is not significant ($F_{1,13} = 3.35$; $P = 0.09$, Fast omissions = 4.1%, Slow = 1.8%). The overall number of omissions excluded in this way accounts for only 0.004% of the total number of trials analysed. Furthermore, the proportion of omission errors excluded is not significantly different between conditions, accounting for 10% of total omissions in the Slow condition and 15.8% of total omissions in the Fast condition ($F_{1,13} = 0.716$; $P = 0.413$).

Tonic block-related activation

The percentage change map corresponding to block-related activation failed to reveal any significant clusters of activation. The baseline used in the event-related area-under-the-curve calculations therefore did not change significantly with the Fast and Slow block-related aspects of the experimental design.

Event-related activation

Consistent with previous research, analyses revealed a widespread network of activation that was primarily right-hemisphere based and concentrated in the PFC (Table 1). Subcortical activation in the putamen, extending into the caudate nucleus was also observed.

Activation in areas of DLPFC, medial frontal cortex and inferior and superior parietal cortex bilaterally, left temporal cortex and the right putamen did not differ significantly between conditions (see Table 1). Ten areas were differentially activated by either Fast or Slow Stops (Table 1 and Fig. 1). Slow Stops showed higher levels of activation in anterior and polar sections of right dorsal PFC (superior and middle frontal gyrus, BA9/10, Fig. 1a), along with an area of the left inferior parietal cortex. In contrast, for Fast Stops there was greater activation in the left putamen and caudate (Fig. 1c and d), bilateral insula (Fig. 1b), left precuneus (BA7) and fusiform gyrus, and right middle and inferior prefrontal gyri (BA9/46, Fig. 1b). These differences in the ROI analysis were significant at $P = 0.05$, uncorrected for multiple comparisons. Using a modified Bonferroni correction for multiple comparisons (Keppel, 1991), activation in the right superior and middle frontal gyri in the Slow condition and in the left putamen/caudate, left precuneus and right inferior frontal gyrus in the Fast condition remained significant.

To confirm the apparent dissociations we conducted two 2 (Region) × 2 (Fast/Slow) ANOVAs. In the first, the Region factor comprised a weighted average of the activation magnitudes for the two anterior prefrontal areas showing greater activation in the Slow condition and a weighted average of the two dorsolateral prefrontal areas showing greater activation in the Fast condition. There were no main effects, but the interaction was significant ($F_{1,13} = 59.859$, $P \leq 0.001$). Consistent with the *t*-tests above, a (Newman–Keuls) *posthoc* analysis of the interaction revealed that the weighted average of the anterior PFC areas was significantly more active for Slow than Fast ($P \leq 0.001$), and the weighted average of the dorsolateral PFC areas was significantly more active for Fast than Slow ($P \leq 0.001$; Fig. 1e).

The second 2 (Region) × 2 (Fast/Slow) ANOVA examined activation magnitudes for the same weighted average of the two anterior prefrontal areas showing greater activation in the Slow condition and the left putamen/caudate, observed to be more significant in the Fast condition. Again, there were no main effects ($P \geq 0.05$), but the interaction was significant ($F_{1,13} = 43.398$, $P = 0.001$). A Newman–Keuls *posthoc* analysis of the interaction revealed that the left putamen/caudate was significantly more active for Fast than Slow ($P \leq 0.001$; Fig. 1e).

Discussion

In the present study we elucidated the neural dynamics of response inhibition under conditions of changing task demands. We compared successful inhibitions to NOGO stimuli (Stops) occurring as part of a slowly presented stream of stimuli, which provided greater preparation time for each subsequent stimulus, to those Stops occurring as part of a rapidly presented stream of stimuli, which reduced the opportunity for such preparation to occur. We observed a pattern of activation that included both a common network of activations, and a dissociation of areas underlying task performance. Across conditions, there was equivalent activation of areas of PFC, medial frontal cortex and parietal cortex bilaterally, left temporal cortex and the right putamen. Thus, although a number of areas throughout the brain made differential contributions to task performance, there were some core areas active across conditions, consistent with the network of regions previously observed to underlie inhibitory control (Garavan *et al*., 1999; Liddle *et al*., 2001; Garavan *et al*., 2002; Sylvester *et al*., 2003).

The between-conditions comparison revealed that when NOGO events occurred as part of a rapidly presented stream of stimuli, there were significantly higher levels of activation in the right DLPFC, left putamen and caudate, left precuneus and fusiform gyrus. We suggest the prefrontal and subcortical activations are primarily reflective of increased demand on response selection processes occurring under conditions in which there was little time to prepare for the upcoming response. This is consistent with theories of prefrontal cortical function that emphasize response selection processes (Curtis & D'Esposito, 2003; Rowe *et al*., 2000), and studies demonstrating PFC activity related to response selection in working memory paradigms (Garavan *et al*., 2000; Rowe *et al*., 2000; Rowe & Passingham, 2001). The subcortical activation, which extended from the putamen into the caudate, is also consistent with previous research demonstrating the involvement of these areas in inhibitory tasks (e.g. Casey *et al*., 1997; Rieger *et al*., 2003) as well as their implication in various clinical syndromes that feature inhibitory deficits. On the other hand, when stimuli were presented at a slower rate, different areas of the inhibitory network were active, with higher levels of activation in anterior and polar regions of the right superior and middle frontal gyrus and in left inferior parietal cortex. We suggest that these activations correspond to more deliberative, controlled response selection and inhibitory processes, associated with the greater degree of preparation permitted in the slow condition.

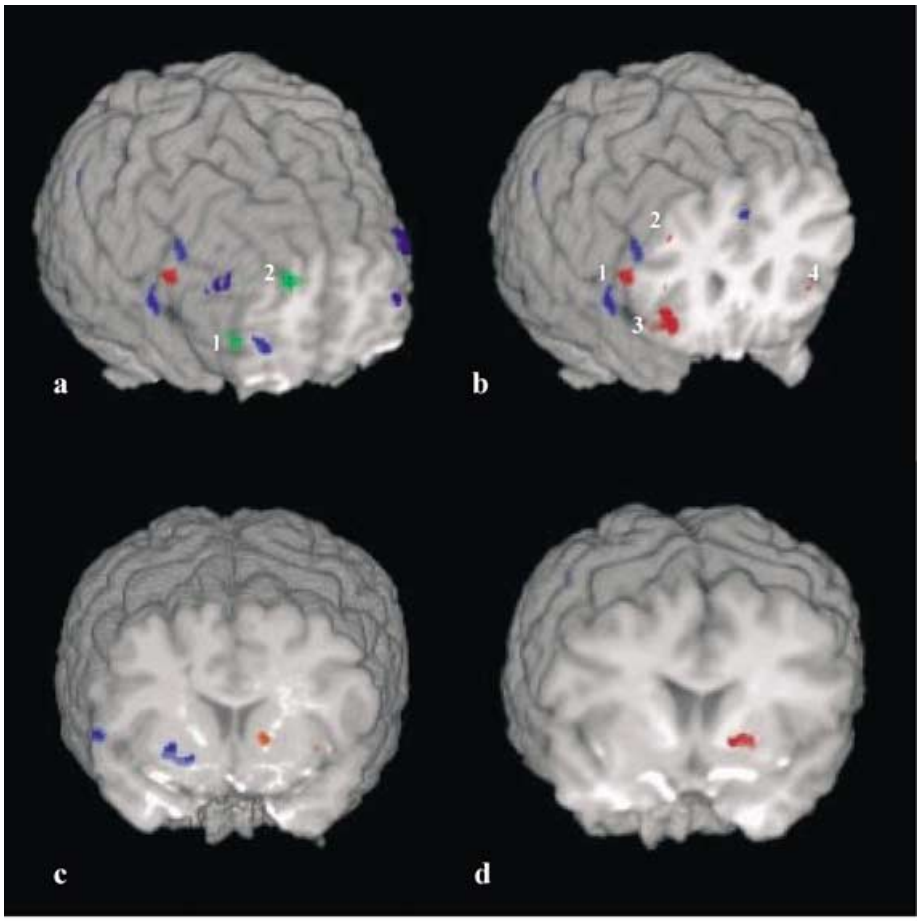
Importantly, these differences in activation occurred in the absence of performance differences between conditions, indicating that the brain can fluidly adapt to changing task demands with no overt behavioural indication that it is doing so. A number of other studies utilizing parametric manipulations of the GO/NOGO paradigm have also observed differences in brain activity in the absence of performance differences between conditions (de Zubicaray *et al*., 2000; Casey *et al*., 2001). This finding also indicates that both sets of brain areas were equally capable of implementing inhibitory control, despite the differences in preparation afforded by the different demand conditions.

The response inhibition network

Robust activations common to both experimental conditions were observed in DLPFC and the inferior parietal lobe (BA40) consistent with a role for these areas in response selection and visuospatial attentional aspects of GO/NOGO task performance (Bunge *et al*., 2002; Rubia *et al*., 2001b; Garavan *et al*., 2002). The area of significant activation in the medial frontal lobe overlaps with that defined as the

pre-SMA (e.g. Humberstone *et al*., 1997; Luppino & Rizzolatti, 2000), an area associated with conflict monitoring, error detection and response selection aspects of behavioural control (Humberstone *et al*., 1997; Braver *et al*., 2001; Rubia *et al*., 2001b; Ullsperger & von Cramon, 2001; Mostofsky *et al*., 2003), and therefore likely to reflect the response conflict inherent in a NOGO trial (Garavan *et al*., 2003), common to both conditions.

There was also equivalent activation of the right putamen across conditions. This is consistent with suggestions that prefrontal cortex achieves motor and behavioural inhibition in association with subcortical structures, such as the basal ganglia (Sasaki *et al*., 1989; Mink, 1996; Band & van Boxtel, 1999; Rieger *et al*., 2003), and with studies associating abnormalities in striatal structures, such as the caudate and putamen, with the inhibitory deficits observed in a number of clinical



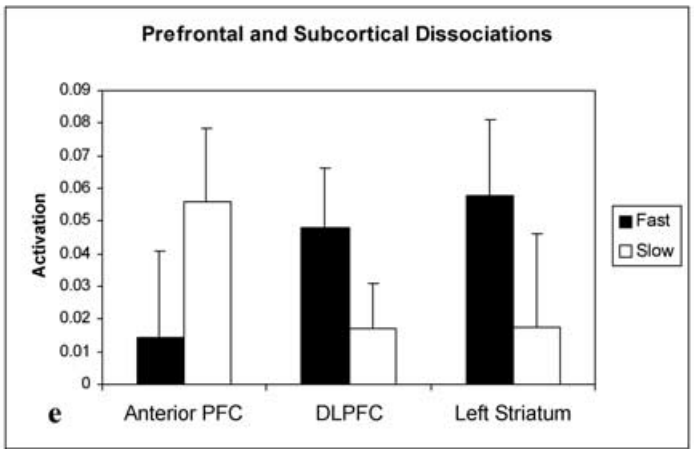


FIG. 1. Event-related activation maps for Fast and Slow successful response inhibitions (Stops) and statistical dissociation of activations. The event-related activation maps depict the dissociation of areas activated in the Fast (red) and Slow (green) conditions. Blue indicates clusters of activation common to both conditions. (a) Illustrates the two right anterior prefrontal areas (1, 2) more active in the Slow condition and which formed the basis for comparison as a weighted average in (e). (b) Shows the two right dorsolateral prefrontal areas (1, 2) more active in the Fast condition and which formed the basis of the weighted average DLPFC area. Activation magnitudes for this area are shown in (e). (b) Also shows the insular activations (3, 4) which were significantly higher in the Fast condition. (c) Shows the left caudate region and (d) shows the left putamen region that were significantly more active in the Fast condition and activation for which is also depicted in (e). The graph in (e) depicts the statistical dissociations reported in the ANOVAs.

conditions such as ADHD (Casey *et al*., 1997), OCD (Rosenberg *et al*., 1996), schizophrenia (Rubia *et al*., 2001a), Parkinson's Disease (Cools *et al*., 2003) and Huntington's Disease (Lawrence *et al*., 1998; Aron *et al*., 2003).

Functional dissociations in inhibitory control

The present study revealed a functional dissociation of areas contributing to inhibitory control under changing task conditions when those conditions impacted on the subjects' levels of preparedness to respond. While reaction time was equivalent across conditions, the slow rate of stimulus presentation was associated with a longer RSI, affording greater preparation time prior to the onset of each stimulus, whereas the rapid rate of stimulus presentation was associated with a shorter RSI, resulting in less well-prepared inhibitions.

In the Slow condition, there was increased right anterior prefrontal cortical activation, typically associated with decision-making and problem solving processes (Fuster, 1997; Wood & Grafman, 2003), and 'cognitive branching', that is, maintaining a task goal while performing a concurrent task (Koechlin *et al*., 1999). There was also additional activation in the left inferior parietal cortex. We suggest that the additional preparation time provided by the Slow presentation rate enabled a more deliberative, endogenous and controlled route for response selection, resulting in more top-down control over inhibitions. Left parietal cortex has previously been implicated in response selection processes (e.g. Bunge *et al*., 2002) and anterior prefrontal activations (BA9 and BA10) have been seen in a number of studies employing GO/NOGO tasks (e.g. Garavan *et al*., 1999; de Zubicaray *et al*., 2000; Watanabe *et al*., 2002). In particular, de Zubicaray *et al*. (2000) observed this anterior PFC activation when the GO/NOGO ratio approached 1 : 1, supporting a role for this area in attentive, controlled response selection processes. These data are also consistent with Sakai & Passingham (2003), who observed activation in the anterior PFC during preparation for a working memory task. They associated this activation with endogenous control and the establishment of task set.

By contrast, increased activation in areas of DLPFC, the dorsal striatum, precuneus, and, less robustly, the insula and fusiform gyrus in the Fast condition suggests a response inhibition network that achieved successful inhibitory control under conditions that prevented the same level of preparation as in the Slow condition. This is consistent with Durston *et al*. (2002) who observed increasing activation in the inhibitory network as inhibition became more demanding, that is, as there was an increased prepotency to respond to the NOGO stimulus. It appears that, without preparation, more widespread activation in the inhibitory network, which also includes the striatum and insula, was necessary in order to ensure successful inhibition of the response to the NOGO stimulus.

The prefrontal-subcortical dissociation reported here lends support to reports that subcortical areas are, in conjunction with the PFC, engaged in response selection processes. For example, Lawrence *et al*. (1998) suggest that the neuropsychological profile associated with Huntington's disease results from a breakdown in the mechanisms of response selection, which may be directly linked to the loss of specific corticostriatal pathways caused by cell degeneration in the striatum. Similarly, Manoach *et al*. (2003) observed widespread activation in regions including DLPFC, insula, thalamus and basal ganglia, exclusively associated with the probe (rather than the encoding or delay) epoch of a Sternberg working memory task. They argue that the subcortical activation during the probe epoch reflects processes related to the selection of an appropriate response based on the contents of working memory, and that these findings indicate a role for frontostriatal circuitry in response selection processes. A critical aspect of the working memory paradigm used by Manoach *et al*. (2003) was that it did not permit planning or preparation of a specific motor response prior to the appearance of the probe, and in this way, is highly similar to the Fast condition of the present study. Similar effects of preparation on striatal activation have been observed by Sohn *et al*. (2000). In an examination of areas involved in preparation for an upcoming task switch, there was greater striatal activation when the subject was unprepared for the task switch than when they were forewarned of the upcoming switch, a pattern consistent with the present data. They suggest an endogenous–exogenous cueing effect such that without preparation, activations reflect exogenously triggered response selection processes. The current data therefore suggest that corticostriatal circuits are involved in the implementation of inhibitory control under conditions of reduced preparation.

There is, however, a possibility that the RSI manipulation produced between-condition effects other than differences in the subjects' level of preparedness. One possibility is that in the Fast condition there exists some dynamic between response prepotency and preparation, such that the faster presentation rate, shorter RSI and more frequent responding are associated with an increased response prepotency as well as lower levels of preparation. The functional activations observed in the Fast condition may therefore reflect either of these processes, as the design of the present study does not permit us to disentangle prepotency from preparation. These two processes have been distinguished at a behavioural and electrophysiological level, demonstrating differential behavioural effects depending on the influence of factors such as RSI and practice (e.g. Soetens *et al*., 1985; Matt *et al*., 1992; Leuthold & Sommer, 1993). However, the current behavioural data do not support a prepotency explanation, as there were equivalent RTs and accuracy rates across conditions. Furthermore, both increased prepotency and reduced preparation presumably lead to more difficult inhibitions, and we have associated the prefrontal and subcortical activations observed in the Fast condition with the greater effort required to enact inhibitory control under such conditions of increased demand. It is desirable that future studies focus on disentangling these two processes and resolving any differential influence they might have on the functional activations underlying inhibitory control.

The explanation put forward in the current paper does, however, call for some re-interpretation of previous findings. Primarily, the results of Garavan *et al*. (2002) must be qualified by the effect of preparation time on response selection and inhibitory processes. In the introduction we hypothesized that if the activations observed during the Slow condition of Garavan *et al*. (2002) were indeed reflective of a more attentive, deliberative network, then we would expect to see similar activations during the Slow condition here. Alternatively, if those results more accurately reflected an inhibitory network called into action under conditions of less preparation then we would expect to see more similar activations in the Fast condition of the present study. The latter prediction was supported by the data. Thus, we may conclude that it is the shorter response-stimulus interval, and associated reduced preparedness, that accounts for the dorsolateral prefrontal activation in that previous study. Furthermore, the current study suggests that the response selection processes implemented in DLPFC under conditions of reduced preparation are carried out in conjunction with the insula and striatum, a suggestion that is supported by the literature, as discussed above.

Summary and implications

The present study has provided evidence for a widespread cortical and subcortical network underlying response inhibition combined with a dissociation of functional activations during inhibition of a prepotent response, directly related to the amount of preparation time permitted

ahead of each subsequent response. In addition, these data support conjunctive roles for prefrontal and striatal areas in response selection processes during the implementation of inhibitory control.

These results are consistent with a 'multiple domain' model of inhibitory control, which views its neural implementation in terms of a distributed network (Dias *et al*., 1997; Rubia *et al*., 2001b; Mostofsky *et al*., 2003) but in which there exist different inhibitory processes for different types of acts (motor, cognitive or affective). Different cortical areas mediate these different inhibitory processes. This model is supported and extended by the present study, by demonstrating within-domain dissociations, consistent with previous studies (Casey *et al*., 1997; de Zubicaray *et al*., 2000; Durston *et al*., 2002; Garavan *et al*., 2002). Furthermore, this study highlights how the dissociation of executive functions such as inhibition into separable components can aid in the characterization of their neural implementation (Curtis & D'Esposito, 2003) and contribute to the development or expansion of theories of brain function. These data also emphasize the need for further investigations of how subcortical areas contribute, both normally, and across a number of clinical conditions, to executive control functions such as inhibition.

Acknowledgements

This research was supported by USPHS grant DA14100 and GCRC M01 RR00058, and NIMH grants MH63434 and MH65350. The assistance of Patrick O'Donnell and Deirdre M. Foxe in the collection of the functional data is gratefully acknowledged. The authors would also like to thank two anonymous reviewers for helpful comments and suggestions on previous drafts of this paper.

Abbreviations

DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex; PPC, posterior parietal cortex; RSI, response-stimulus interval.

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