

Dissociation of inhibition from error processing using a parametric inhibitory task during functional magnetic resonance imaging

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Inhibition, the process that overrides and reverses the execution of a thought, action, or emotion, is important in daily life. Sixteen healthy volunteers performed a parametrically modulated motor inhibition task during functional magnetic resonance imaging. Two results were observed: (1) increased error-related anterior cingulate cortex activation and, (2) increased inferior frontal gyrus and medial prefrontal cortex activation during inhibition, irrespective of errors. Thus, the parametric nature of the task elucidated a

functional dissociation of brain structures involved in motor inhibition from those involved in error processing. Additionally, this task allowed the identification of unique areas of increased activation within specific subregions of the anterior cingulate cortex related to errors made during trials with a high (dorsal anterior cingulate cortex) and low (ventral anterior cingulate cortex) inhibitory load. *NeuroReport* 16:755–760 © 2005 Lippincott Williams & Wilkins.

Key words: Anterior cingulate cortex; Error processing; fMRI; Inhibition; Prefrontal cortex

INTRODUCTION

Inhibition, the process that overrides and reverses the execution of a thought, action, or emotion, is important in daily life. This complex process involves monitoring and stopping ongoing or planned performance, and is intimately related to error processing (i.e. failed inhibition). In order to improve our fundamental understanding, it is critical to delineate the inhibitory and error-processing mechanisms involved in inhibition of a motor act and to determine which neural substrates are involved in each of these processes.

Inhibition involves neural substrates that are important for both cognitive and emotional functions. Various functional magnetic resonance imaging (fMRI) studies in healthy populations have probed the neural circuitry of behavioral inhibition during performance of motor inhibition tasks, such as stop and no-go tasks. The inferior and middle prefrontal cortex is critically involved in motor inhibition [1–8], as are the inferior parietal lobe [1–3,5], precuneus [2,3], insula [1,2,8], and superior temporal gyrus [2,5]. Related structures such as the dorsal anterior cingulate cortex (ACC) are critically involved in error processing [9].

Inhibition is not a unitary construct and, therefore, researchers have implemented several paradigms in the attempt to measure inhibitory processes, that is, Stroop [10], stop [6], go/no-go [11], and Wisconsin Card Sorting [7] tasks. The stop task is an example of a competing motor programs paradigm, in which individuals are asked to respond with a button press to 'go' stimuli, except when a second 'stop' stimulus (typically in a different sensory dimension) is presented shortly after the initial 'go'

stimulus. By implementing a parametric stop task during functional brain imaging, one may be able to differentiate the neural substrates involved in the inhibition of a motor act from those involved in error processing.

The current study implemented a stop task with varying delays between 'go' and 'stop' stimuli that allowed manipulation of the degree to which study participants were able to successfully inhibit a motor response. The first aim of this investigation was to differentiate the neural circuitry involved in successful inhibition of a motor act from that involved when errors are made (i.e. failed inhibition). Because inhibitory deficits are necessarily associated with errors on a task, we identified error trials during both 'short inhibit' and 'long inhibit' trials (during half the trials, the stop signal was delivered a relatively short time after the 'go' stimulus, and during the other half, the stop signal was delivered a relatively long time after the 'go' stimulus; see task description below). We hypothesized that the dorsal ACC and related structures would be more active during error trials than during successful inhibition trials.

The second aim of this investigation was to determine which neural substrates would activate proportionally as the degree of inhibitory difficulty was increased, irrespective of whether errors were made. We hypothesized that the inferior frontal gyrus and the medial prefrontal cortex and related circuitry would be more active during the 'hard inhibit' trials (i.e. the most difficult trials in which the inhibit signal was given very late in the trial) relative to the 'easy inhibit' trials (i.e. the least difficult trials in which the inhibit signal was given very early in the trial).

Support for these hypotheses may contribute to the fundamental understanding of the neurobiological mechanisms that underlie motor inhibition and error-processing, processes that are critically involved in cognitive functions such as memory and attention. Additionally, inhibition is impaired in major psychiatric illnesses such as schizophrenia [6], major depression [12], and attention deficit hyperactivity disorder [13], and the degree of inhibitory dysfunction is thought to be an important behavioral marker for long-term outcome, treatment response, and possibly genetic differences among individuals with these disorders. The current study may lay the groundwork for future studies in patients with these psychiatric illnesses.

MATERIALS AND METHODS

Study participants: Sixteen (nine men and seven women) healthy participants, mean age 34 years (range 20–56), gave written informed consent and completed the study that was approved by the University of California San Diego (UCSD) Human Research Protection Program. All participants completed the Structured Clinical Interview for DSM IV and had no lifetime history of any Axis I DSM IV disorder.

Task: The stimuli, either an 'X' or an 'O', appeared on a black background back-projected to the magnetic resonance imaging room, subtending a visual angle of approximately 6°. Participants were instructed to press, as quickly as possible, the left button when an 'X' appeared, and the right button when an 'O' appeared. They were also instructed not to press either mouse button whenever they heard a tone during a trial. Stimuli appeared at the beginning of each of the trials. Each trial lasted 1300 ms, or until the participant responded. Trials were separated by 200-ms interstimulus intervals (blank screen). The individual response latency was used to denote the period of inhibitory processing and provided a naturally jittered reference function. Participants performed a total of 72 stop trials, which were pseudo-randomized throughout the task and counterbalanced. Six blocks were performed, each containing a total of 48 trials (12 stop and 36 nonstop trials in each block). Task instructions were presented for 12 s between blocks.

Participants, prior to scanning, performed the stop task in a behavioral testing session in order to determine their mean reaction time (RT). From this data, six different trial types were designed on the basis of the period of time after the beginning of the trial (when the 'X' or 'O' stimuli first appeared) when the stop signal was delivered, that is, when the stop signal was delivered at the participant's mean RT, and when the stop signal was delivered at 100 (RT-100), 200 (RT-200), 300 (RT-300), 400 (RT-400), or 500 (RT-500) ms less than the mean RT after the beginning of the trial.

Three separate analyses were performed. First, to probe the neural circuitry involved in processing more versus less difficult trials, we compared the brain activation pattern related to performance of 'hard' trials (both correct and incorrect) with the brain activation pattern related to performance of 'easy' trials (both correct and incorrect). During hard inhibit trials, the time from the beginning of the tone to the appearance of the next visual stimulus was equal to or 100 ms less than the participant's mean RT, calculated from performance of the task in a behavioral testing session.

During easy inhibit trials, the time from the beginning of the tone to the appearance of the next visual stimulus was 400 or 500 ms less than the participant's mean RT from behavioral testing.

In the second and third analyses, the brain regions involved in processing correct versus incorrect trials were investigated. Because the majority of errors were made during hard trials (stop signal delivered at RT or RT-100) and the majority of successful inhibits were made during the easy trials (stop signal delivered at RT-400 or RT-500), the RT-200 and RT-300 trials were also considered in the subsequent analyses of errors. Specifically, the RT-200 trials were combined with the RT-100 and RT trials in order to increase the number of correct trials in this group of 'short' trials, and the RT-300 trials were combined with the RT-400 and RT-500 trials in order to increase the number of errors in this group of 'long' trials.

In the second analysis, the brain activation pattern for incorrect relative to correct short trials (RT-200, RT-100, and RT) was examined. In the third analysis, the brain activation pattern for incorrect relative to correct long trials (RT-300, RT-400, and RT-500) was examined.

Functional magnetic resonance imaging: A fast event-related fMRI design was used. Each scanning session lasted approximately 1 h. Sessions consisted of a three-plane scout scan (10 s), a high-resolution anatomic scan covering the whole brain, a series of T2*-weighted echo-planar imaging (EPI) scans to measure blood oxygen-level dependent (BOLD) functional activity, and an EPI-based field map to correct for susceptibility induced geometric distortions. Imaging experiments were performed on a 3T General Electric scanner (T2*-weighted EPI, repetition time=2000 ms, echo time=40 ms, 64 × 64 matrix, 20 4-mm axial slices). Each run was acquired in sessions of 256 repetitions and lasted 8 min and 32 s. During the same experimental session, a T1-weighted image (MPRAGE, TR=11.4 ms, TE=4.4 ms, flip angle=10°, FOV=256 × 256, 1 mm³ voxels) was obtained for anatomical reference.

All structural and functional image processing and analysis was performed with the Analysis of Functional Neuroimages (AFNI) software package [14]. In order to minimize motion artifact, echo-planar images were realigned to the 128th acquired scan. Additionally, data were time-corrected for slice acquisition order. Time series data for each individual were analyzed using a multiple regression model.

Two separate analyses were performed. First, for the analysis of task difficulty, eight regressors were entered into a regression model including two stop conditions (i.e. 'hard' and 'easy' conditions), a nonstop condition, three motion parameters (i.e. yaw, pitch, and roll), one linear drift regressor, and the baseline condition (instructions on screen). Second, for the analysis of errors, 10 regressors were entered into a regression model including four stop conditions (i.e. 'correct short' and 'incorrect short' conditions, and 'correct long' and 'incorrect long' conditions), a nonstop condition, three motion parameters (i.e. yaw, pitch, and roll), one linear drift regressor, and the baseline condition (instructions on screen). Prior to inclusion in the regression model, the task-related regressors were convolved with a modified γ variate function [15] to account for the hemodynamic delay and the slow rise and fall of the

hemodynamic response. Activation in each voxel during each specific task condition was divided by the baseline activation to obtain percent signal difference for each task condition. A 6 mm full-width at half-maximum Gaussian filter was applied to the voxel-wise percent signal difference data to account for individual variations in anatomical landmarks. Each participant's data were normalized to Talairach coordinates [16] and a whole-brain mask was applied to screen out nonbrain voxels and voxels falling within the artifact region. Before the primary analyses were performed, the nonstop trials were subtracted from the stop conditions.

The voxel-wise percent signal difference data for all participants were entered into a mixed-model two-way ANOVA with condition (hard/easy inhibit, correct short/incorrect short inhibit, or correct long/incorrect long inhibit) as a fixed factor and participants as a random factor. To determine areas that were differentially activated between hard versus easy inhibits, correct short versus incorrect short inhibits, and correct long versus incorrect long inhibits, a within-participants contrast was computed between these conditions. A threshold/cluster method was then applied. This threshold adjustment method was based on Monte-Carlo simulations and was used to guard against identifying false positive areas of activation using a 6 mm full-width at half-maximum Gaussian filter [17]. On the basis of these simulations, it was determined that a voxel-wise a priori probability of 0.05 would result in a corrected cluster-wise activation probability of 0.05 if a minimum volume of 1024 μL and a connectivity radius of 4.0 mm was considered. The average percent signal difference for each participant during each task condition was extracted from regions of activation that were found to survive this threshold/cluster method.

RESULTS

Behavioral: Participants responded with the correct button press in 97.78% (SD 2.45) of the nonstop trials. Additionally, there was a failed inhibit on 42.5% of total stop trials. Errors for each specific stop trial type are displayed in Fig. 1. Participants made significantly more errors during the hard inhibit trials than during the easy inhibit trials [$F(1,15)=51.1, p<0.001$] (Fig. 1). No difference in response latency was observed between hard error trials relative to easy error trials [$F(1,15)=2.63, \text{NS}$].

Brain activation: First, several brain regions activated proportionally as stop task difficulty was increased (Table 1). Specifically, clusters were identified in the superior frontal gyrus, lingual gyrus, inferior frontal gyrus, inferior temporal gyrus, and thalamus, which were more active during performance of hard (stop signal delivered at RT and RT-100) relative to easy (stop signal delivered at RT-400 and RT-500) trials (Fig. 2).

Second, analyses of errors revealed several brain regions that were more active during error trials relative to correct trials. Specifically, when the short trials (stop signal delivered at RT, RT-100, and RT-200) were examined (Table 2, Fig. 3), the cuneus, dorsal ACC (Fig. 4), postcentral gyrus, and fusiform gyrus were more active during errors than during correct trials.

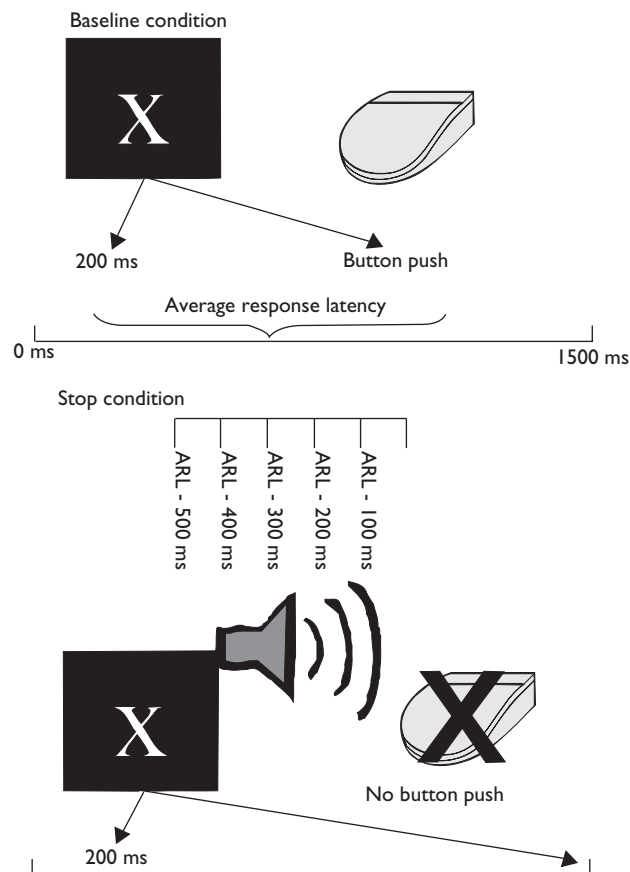


Fig. 1. Stop task trials were 1300 ms long, and separated by a 200 ms interstimulus interval (blank screen). Each stimulus appeared at the beginning of each trial and remained on the screen until the subject's response. ARL=Average Response Latency.

Table 1. Areas of activation related to hard inhibit trials relative to easy inhibit trials of a stop task.

X	Y	Z	Volume (μL)	Side	Area	Brodmann's area
29	51	26	7744	R	Superior frontal gyrus	10/9
2	14	48	6720	R/L	Superior frontal gyrus	6/32/24
-11	-83	-12	5504	L	Lingual gyrus	18/17
47	15	1	3520	R	Inferior frontal gyrus/insula	47
37	-59	2	1216	R	Inferior temporal gyrus	37
-8	-14	10	1152	L	Thalamus	

Conversely, when the long trials (stop signal delivered at RT-300, RT-400, and RT-500) were examined (Table 3, Fig. 5), the inferior parietal lobule, ventral ACC (Fig. 4), fusiform gyrus, superior temporal gyrus, posterior cingulate gyrus, inferior and superior frontal gyri, putamen, cerebellum, and insula were more active during errors than during correct trials.

DISCUSSION

In the current study, two important findings were observed that provide evidence of a functional dissociation between the brain systems involved in motor inhibition and those

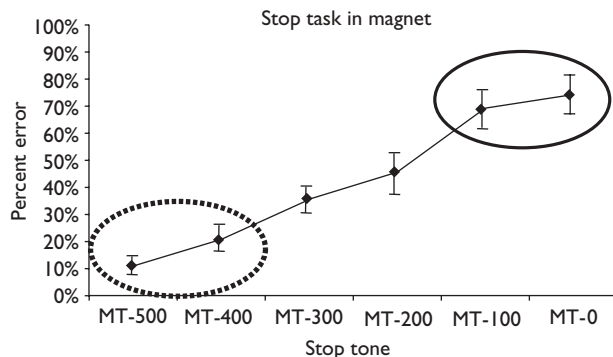


Fig. 2. During hard inhibit trials (solid circle), the stop signal was delivered at or 100 ms less than the participant's mean reaction time. During easy inhibit trials (broken circle) the stop signal was delivered at 400 or 500 ms less than the participant's reaction time. Participants ($n=16$) made significantly more errors during the hard inhibit trials than during the easy inhibit trials [$F(1,15)=51.1, p < 0.001$].

Table 2. Areas of activation related to short failed inhibit trials relative to short successful inhibit trials of a stop task.

X	Y	Z	Volume (μ L)	Side	Area	Brodmann's area
-19	-83	30	3264	L	Cuneus	19
2	29	30	2880	R/L	Dorsal anterior cingulate	32
-28	-21	37	2816	L	Postcentral gyrus	3
38	-19	32	1344	R	Postcentral gyrus	3
40	-48	-15	1152	R	Fusiform gyrus	37
7	-88	28	1152	R	Cuneus	19

involved in error processing. Consistent with prior studies, increased error-related ACC activation was observed, and a network of medial prefrontal cortical structures activated proportionally as the degree of inhibitory difficulty increased, irrespective of whether errors were made. The parametric nature of the task allowed these processes to be clearly delineated, and an analysis of particular types of errors to be made. Specifically, the dorsal ACC was more active during failed short inhibitory trials relative to successful short inhibitory trials, and the ventral ACC was more active during failed long inhibitory trials relative to successful long inhibitory trials. Prior research has revealed that inferior and medial prefrontal structures are critically involved in performance of stop tasks [4]. In one study that implemented go/no-go tasks in a parametric design, the greater the number of go trials (three or more) that preceded a no-go trial (i.e. the more difficult the inhibition), the greater the activation in the inferior frontal gyrus [Brodmann's area (BA) 9/44, 44/46], the anterior and posterior cingulate (BA 32, 23/31), and the superior parietal cortex (BA 7) [4]. In the current study, similar brain structures, including the inferior frontal gyrus and the superior and middle prefrontal cortex, were activated as stop task difficulty increased, supporting the role of the inferior frontal gyrus and related structures in inhibition of a motor act in stop paradigms.

Performance of the stop task involves multiple subprocesses that span both cognitive and emotional domains. In order to understand the neural circuitry involved in these subprocesses, we considered the duration (i.e. difficulty)

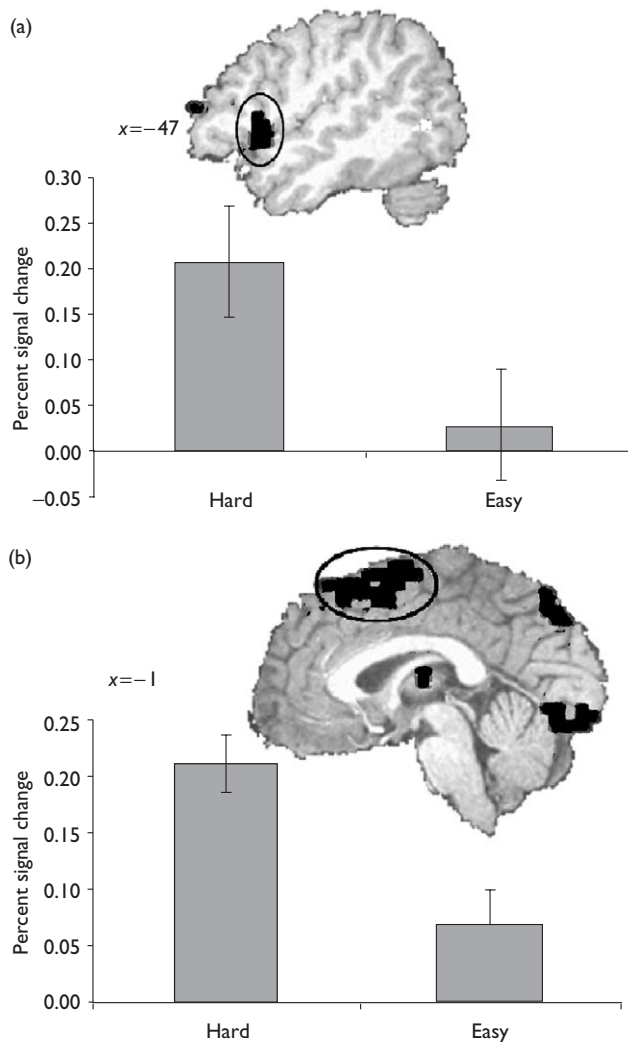


Fig. 3. (a) Inferior frontal gyrus (circled) and (b) superior frontal gyrus (circled). Activation related to hard inhibit trials compared with easy inhibit trials of a stop task.

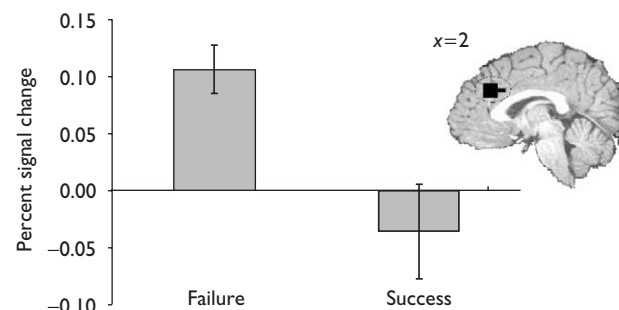
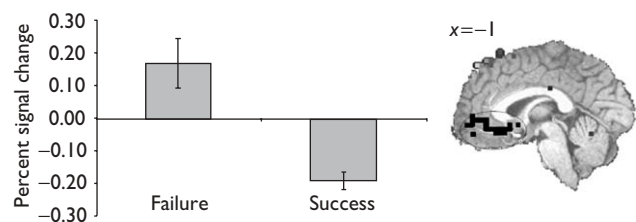


Fig. 4. Dorsal anterior cingulate activation (circled) related to short failed inhibit trials compared with short successful inhibit trials of a stop task.

and outcome (successful/failed) of the inhibitory trials of this task. In the current study, greater activation was observed in the dorsal ACC during failed short inhibitory trials relative to successful short inhibitory trials. The dorsal ACC is intimately involved in error processing and conflict

Table 3. Areas of activation related to long failed inhibit trials relative to long successful inhibit trials of a stop task.

X	Y	Z	Volume (μ L)	Side	Area	Brodmann's area
33	-54	38	12096	R	Inferior parietal lobule	40/19
-1	32	-6	11840	R/L	Ventral anterior cingulate	25
-43	-52	38	7424	L	Inferior parietal lobule	40/19
16	-48	-10	4928	R	Fusiform gyrus	36
-55	-35	13	3968	L	Superior temporal gyrus	22/42/13
-24	-41	-12	2944	L	Fusiform gyrus	36
-11	-26	34	2240	L	Posterior cingulate	31
12	-29	42	2048	R	Posterior cingulate	31
-47	4	29	1792	L	Middle frontal gyrus/precentral gyrus	9
0	36	52	1600	R/L	Superior frontal gyrus	8
-20	59	-2	1536	L	Superior frontal gyrus	10
56	-26	29	1472	R	Inferior parietal lobule	40
-23	1	11	1408	L	Putamen	
-13	-73	-23	1344	L	Cerebellum	
33	-24	20	1216	R	Insula	
-28	-35	25	1216	L	Posterior insula/internal capsule	
22	3	3	1088	R	Putamen	
13	59	21	1088	R	Superior frontal gyrus	10

**Fig. 5.** Ventral anterior cingulate activation (circled) related to long failed inhibit trials compared with long successful inhibit trials of a stop task.

monitoring [9] and also in motor control [18] and response selection [19]. Consistent with our initial hypotheses, failed relative to successful short inhibitory trials engaged more error-monitoring resources, and it is not surprising that the dorsal ACC was more active during failed than during successful short inhibitory trials. For long trials, the ventral ACC was more active during failed inhibit trials than during successful inhibit trials. During the long trials, participants had more time for outcome processing, and we speculate that errors made during these trials may have been attributed to an internal, or 'self' source. Although data are not available to support this hypothesis, it is conceivable that errors made during long trials were more emotionally evocative and brain structures such as the ventral ACC, a structure that is critically involved in emotional processing [20] were engaged. This assertion is reinforced by findings that the ventral ACC is more active when there is an internal focus rather than an external focus [21].

CONCLUSION

By using a parametrically modulated motor inhibition task, we were able to delineate the neural substrates involved in motor inhibition from those involved in error processing. These findings may contribute to the fundamental understanding of inhibition, a mechanism that is central to cognitive functions such as memory and attention. This study may also lay the groundwork for future studies in patients with various psychiatric disorders that may

contribute to understanding the neurobiological underpinnings of the inhibitory dysfunction seen in these patients.

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