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# Neural substrates of the interaction of emotional stimulus processing and motor inhibitory control: An emotional linguistic *go/no-go* fMRI study

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**Neural substrates of behavioral inhibitory control have been probed in a variety of animal model, physiologic, behavioral, and imaging studies, many emphasizing the role of prefrontal circuits. Likewise, the neurocircuitry of emotion has been investigated from a variety of perspectives. Recently, neural mechanisms mediating the interaction of emotion and behavioral regulation have become the focus of intense study. To further define neurocircuitry specifically underlying the interaction between emotional processing and response inhibition, we developed an emotional linguistic *go/no-go* fMRI paradigm with a factorial block design which joins explicit inhibitory task demand (i.e., *go* or *no-go*) with task-unrelated incidental emotional stimulus valence manipulation, to probe the modulation of the former by the latter. In this study of normal subjects focusing on negative emotional processing, we hypothesized activity changes in specific frontal neocortical and limbic regions reflecting modulation of response inhibition by negative stimulus processing. We observed common fronto-limbic activations (including orbitofrontal cortical and amygdalar components) associated with the interaction of emotional stimulus processing and response suppression. Further, we found a distributed cortico-limbic network to be a candidate neural substrate for the interaction of negative valence-specific processing and inhibitory task demand. These findings have implications for elucidating neural mechanisms of emotional modulation of behavioral control, with relevance to a variety of neuropsychiatric disease states marked by behavioral dysregulation within the context of negative emotional processing.**


## Introduction

Approach and withdrawal represent fundamental behavioral tendencies. Successful adaptation requires that they be selectively invoked by a context-appropriate balance of agency and inhibition. Inhibitory control is a multi-domain executive function critical for flexible responsivity to changing task demands, and thereby an essential component of adaptive behavioral regulation. A phylogenetically and ontogenetically later-appearing function (Booth et al., 2003; Casey et al., 1997; Williams et al., 1999), inhibitory control afforded by evolutionary and maturational development may underlie human capacity for future-related thought (e.g., capacity for response inhibition enables transcendence of the "default mode" of human behavior (Mesulam 2002), permitting representation of alternative outcomes, thereby enabling meaningful behavioral decision-making) (Fuster, 2000; Goldman-Rakic, 1988). Inhibitory control is susceptible to impairment in a variety of developmental (Casey et al., 1997), degenerative (Neary et al., 2005; Royall et al., 2002; Shulman, 1997), and acquired (Damasio, 1999) processes, with potentially serious maladaptive consequences.

Neural substrates of response inhibition have been probed in animal model (Iverson and Mishkin, 1970; Roberts and Wallis, 2000), behavioral (Drewe, 1975), physiologic (e.g., Mathalon et al., 2003), and imaging studies (e.g., Fassbender et al., 2004; Garavan et al., 2002; Horn et al., 2003; Kelly et al., 2004; Konishi et al., 1999; Rubia et al., 2001). Convergent findings indicate that response inhibition is significantly mediated by prefrontal cortex (PFC) circuits (e.g., Mesulam, 2000), both dorsal (Braver et al., 2001; Miller and Cohen, 2001) and ventral. Of the latter, orbital

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frontal cortex (OFC) dysfunction has been long associated with behavioral disinhibition (e.g., Anderson et al., 1999; Rolls, 1996). An "acquired sociopathic" syndrome (e.g., impulsivity, context-dysproportionate aggression) can follow medial OFC (mOFC) damage (Bigelow, 1850; Paradiso et al., 1999; Price et al., 1990), prompting the hypothesis that mOFC dysfunction underlies behavioral dyscontrol in antisocial personality disorder (Damasio, 2000). Patients with personality disorders marked by behavioral disinhibition (e.g., borderline personality disorder) have been shown to behave similarly to OFC lesion patients on impulse control measures (Berlin et al., 2005). Neural networks combining OFC with key limbic structures (e.g., amygdala) have emerged as fundamental mediators of decision-making requiring cognitive–emotional integration (Bechara et al., 2000a).

The *go/no-go* task (Donders, 1868) has been variably adapted to neuropsychologically probe response inhibition. *Go/no-go* tasks involve execution or inhibition of a motor response, triggered by a *go*- or *no-go* stimulus, respectively. Demand to respond quickly creates a pre-potent response tone which must be inhibited when cued by a *"no-go"* stimulus. Although seemingly behaviorally simple, task performance involves multiple sub-processes, including stimulus discrimination, response selection, motor preparation, response inhibition, and error monitoring.

Imaging studies of *go/no-go* type response inhibition tasks have used a variety of methodologies (Rubia et al., 2001). Frontal regions variably identified include OFC, dorsolateral PFC (DLPFC), ventrolateral PFC (VLPFC), and anterior cingulate cortex (ACC) (e.g., Casey et al., 1997; De Zubicaray et al., 2000; Horn et al., 2003; Kawashima et al., 1996; Liddle et al., 2001; Watanabe et al., 2002). Non-frontal regions include parietal, temporal, and striatal (e.g., Garavan et al., 1999; Horn et al., 2003; Watanabe et al., 2002). *Go/no-go* imaging studies have been used to probe mechanisms of select psychiatric disorders. For example, Vollm et al. (2004) demonstrated aberrant neural activation patterns during *go/no-go* task performance by individuals with personality disorders marked by behavioral dyscontrol (e.g., antisocial personality disorder).

Inconsistencies of activation patterns across response inhibition studies have prompted some investigators to consider a "multi-domain model" of inhibitory control (Mostofsky et al., 2003) where different functions (e.g., motor versus cognitive) are at least in part regulated by different inhibitory mechanisms, correspondingly mediated by different brain regions. Accordingly, activation patterns associated with inhibitory control in part depend on the specific cognitive/behavioral inhibitory process invoked. In contrast, certain regional activations are conserved across response inhibition studies, implying relatively task-independent neural substrates of response inhibition (Wager et al., 2005). For example, Rubia et al. (2001) identified a middle-infero-mesial frontal and inferior parietal network. Others have demonstrated a supra-modal (i.e., stimulus sensory modality-independent) paralimbic/neocortical network (Laurens et al., 2005).

A successful behavioral repertoire involves not only balancing agency and inhibition, but healthy development of adaptive bi-directional modulation of emotion and cognitive control (Critchley, 2003; Davidson, 2000; Gehring and Willoughby, 2002; Lewis et al., 2006). Many psychiatric disorders involve behavioral dyscontrol which becomes prominent within certain emotional contexts (e.g., Posner et al., 2002). Integrative neurocognitive models are being applied to behavioral disorders characterized by dysfunctional interactions of emotion and behavioral control (Blair, 2005). Although the neurocircuitry of emotion has been long studied (e.g., Britton et al., 2006; Phan et al., 2002), mechanisms of the interaction of emotion and cognitive control are only recently being explored (Dolan, 2002; Zald et al., 2002), revealing complex neural interactions (e.g., Hare et al., 2005; Liberzon et al., 2000; Pessoa and Ungerleider, 2004; Phan et al., 2005; Shafritz et al., 2006), and disease-specific abnormalities (e.g., Elliott et al., 2004). Imaging studies probing neural mediation of emotion-modulated behavioral control use neuropsychological probes which join emotional manipulation with a behavioral control task (Yamasaki et al., 2002). For example, Elliott et al. (2000a) used a linguistic *go/no-go* task in which emotional valence was used to define stimulus targets, theorizing that observed neural activations reflected modulation of behavioral control by emotional valence. Others have employed similar tasks using emotional facial stimuli. Hare et al. (2005) observed slower response (interpreted as decreased approach) to negative facial targets and reduced inhibitory performance (interpreted as decreased avoidance) in response to positive non-target facial expressions. Shafritz et al. (2006) observed inferior frontal and insular activation associated with response inhibition during emotional facial expression *go/no-go* task performance, while a comparison non-emotional letter–symbol response inhibition task did not activate these regions. The investigators concluded that inhibition within an emotional context recruited neural substrates beyond those activated by non-emotional response inhibition (Shafritz et al., 2006).

When interpreting results of experimental designs that probe the interaction of emotion and behavioral control by using explicit emotion as motor response ("target") signifier, it is relevant to note that the presumed emotional component of such a task may represent more a categorization (i.e. deciding if a stimulus is "happy" or "sad") than an emotional task (Elliott et al., 2000a,b). Evidence suggests that explicit labeling of affect has distinct neural correlates (Crosson et al., 2002; Hariri et al., 2003; Teasdale et al., 1999; Taylor et al., 2003).

We developed an emotional linguistic *go/no-go* fMRI paradigm with a factorial block design to specifically investigate neural substrates of the interaction of emotional stimulus processing and inhibitory control in both normal subjects and patient populations. This paradigm introduces stimulus emotional valence *incidentally* relative to the explicit behavioral task demand (i.e., *go* or *no-go*). It is thought that such interaction better approximates that operating in many real-world socio-behavioral contexts. Sufficiency of incidental emotional stimuli to modulate neural activity is supported by diverse data (e.g., Isenberg et al., 1999; Perlstein et al., 2002; Whalen et al., 1998). Rather than requiring subjects explicitly use emotional stimulus content to guide performance on a behavioral task, this paradigm joins task demand (i.e., *go* or *no-go*) with concomitant task-unrelated emotional stimulus valence manipulation, to probe the modulation of the former by the latter.

Building on coalescing knowledge of the functional neuroanatomy of cognitive control, and accumulating evidence of the interaction of emotion and response inhibition, we hypothesized functional changes in prefrontal (e.g., mOFC) and anterior limbic (e.g., amygdala) sites reflecting the modulation of behavioral inhibitory control by emotional stimulus processing. Further, we hypothesized valence-distinct activity variations enabling identification of negative valence-specific neural substrates of the

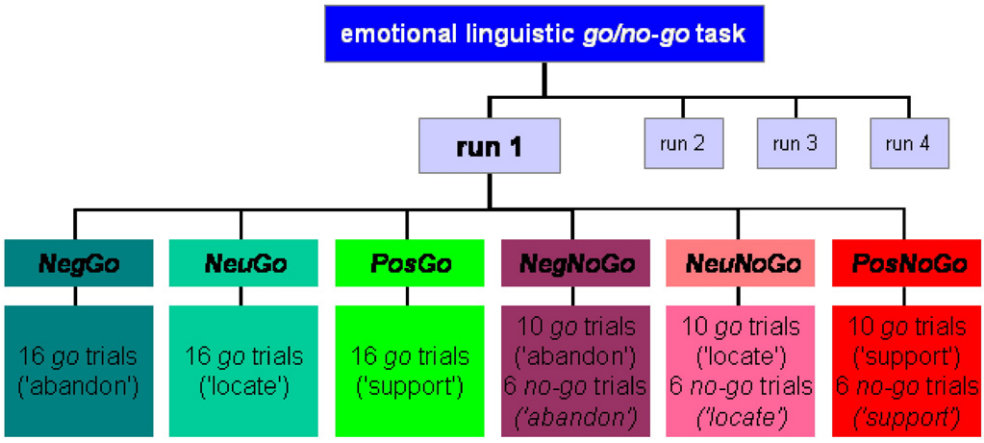


Fig. 1. Neuropsychological activation paradigm architecture (for clarity, only one of four runs is shown).

interaction of emotional stimulus processing and response inhibition.

## Methods

### *Subjects*

Fourteen healthy subjects (10 females; mean age 23.9 years, range 18–31; 12 right-handed (Edinburgh Handedness Inventory; Oldfield, 1971)) participated in the study. All were screened using the Structured Clinical Interview for DSM-IV (First et al., 1996); exclusion criteria included any psychiatric, neurological, or medical condition, either current or past. No subjects were taking psychotropic medications; two subjects were using oral contraceptives. All subjects met acceptable limits of head motion ($<1/3$ voxel size of $3.75\times3.75\times6$ mm$^3$) during scanning. All subjects gave informed consent prior to participation, which was part of a protocol approved by the Institutional Review Board of Weill Medical College of Cornell University.

### *Neuropsychological activation paradigm*

Behavioral response was prompted by orthographically-based cues. Subjects were instructed to perform a right index finger button-press immediately after silently reading a word stimulus appearing in normal font (*go* trial) and to inhibit this response after reading a word presented in italicized font (*no-go* trial). We used 64 negative and 64 positive valence words reflecting themes salient for individuals with borderline personality disorder (while still relevant for normal individuals), since we planned to study this patient population in future investigations. Stimuli were selected from a larger group of potential words after being rated for relevance and suitability by a panel of 4 experienced clinicians (representative negative words: "enraged", "worthless", "abandon"; representative positive: "cheerful", "support", "tranquil"). We also used a set of 64 neutral words to enable delineation of those neural responses underlying motor inhibition in the absence of emotional context, thereby facilitating identification of neural function attendant to inhibition within emotional contexts. Thus, a novel set of 192 linguistic stimuli was used (64 positive, 64 negative, 64 neutral). Stimuli were balanced across all valence conditions for frequency, word length, part of speech, and imageability (complete word set is available from the corresponding author). For counter-balancing, each word stimulus was presented twice, both as a *go* trial and a *no-go* trial.

Each stimulus block was composed of 16 univalent individual word trials. *Go* blocks contained 16 *go* trials (100% *go* trials); *No-Go* blocks contained 10 *go* trials (trials) and 6 *no-go* trials (37.5% *no-go* trials) presented in pseudo-randomized order to establish pre-potent motor response (62.5% *go* trials) yet have ample *no-go* stimuli. Blocks were presented in runs of 6, representing the 6 main conditions (neutral *Go*, neutral *No-Go*, negative *Go*, negative *No-Go*, positive *Go*, positive *No-Go*), counterbalanced to control for order and time effects across runs. There were 4 total runs (therefore 24 total blocks). In total, 4 blocks of each condition were presented (therefore 64 trials per condition, 384 total trials per

Notes to Table 1:
- *NeuPos*=combined neutral and positive conditions.
- *Neg vs. Neu*×*NoGo vs. Go*=[*NegativeNoGo* vs. *NegativeGo*] vs. [*NeutralNoGo* vs. *NeutralGo*].
- *Neg vs NeuPos*×*NoGo Vs. Go*=[*NegativeNoGo* vs. *NegativeGo*] vs. [*NeutralPositiveNoGo* vs. *NeutraPositiveGo*].
- *Pos* vs. *Neu*×*NoGo* vs. *Go*=[*PositiveNoGo* vs. *Positive Go*] vs. [*NeutralNoGo* vs. *NeutralGo*].
- Blue denotes fronto-limbic regions.
- **Bold** denotes a *priori* ROI.
- *Italics* denote sub_maximal peaks within same cluster region.
- [a] *p* corrected =
  - small volume correction (SVC) for *a priori* ROIs using AAL masks (gyrus rectus and amygdala).
  - whole brain false discovery rate (FDR) correction for regions not of *a priori* interest.
- [b] cluster volumes at
  - $p<0.005$ for *a priori* ROIs.
  - $p<0.001$ for regions not of *a priori* interest, spatial extent $>80$ mm$^3$.

complete study session). A rest period followed each block, serving to minimize emotional/task demand carryover among blocks (Garrett and Maddock, 2001). Paradigm architecture is summarized in Fig. 1.

Each word was presented individually in white letters on dark background for 1.5 s followed by a 0.75 s inter-stimulus interval (total block duration = 36 s). Each block was followed by a 20 s duration fixation cross. Each run started and ended with a 20 s rest period. Stimulus presentation and response acquisition were performed within the IFIS SA/E-Prime environment (IFIS-SA, Integrated Functional Imaging System, MRI Devices Corporation, Waukesha, WI; Psychology Software

Table 1
Regional activations revealed by valence × response condition interaction analyses

| Contrast | Cluster region | Brodmann area | Peak coordinate (*x*,*y*,*z*) | Peak *Z*-score | *p* uncorr. | *p* corr. | Volume[a] ($mm^3$) |
|---|---|---|---|---|---|---|---|
| *Neg* vs. *Neu* | **L posterior mOFC** | **11/25** | **−9, 27, −18** | **3.61** | **0.0002** | **0.011** | **918** |
| × | **R posterior mOFC** | **11/25** | **6, 15, −21** | **3.60** | **0.0002** | **0.01** | **810** |
| *NoGo* vs. *Go* | **L amygdala** | | **−21, 0, −15** | **3.10** | **0.001** | **0.015** | **675** |
| | R DLPFC | 9 | 48, 6, 33 | 3.65 | 0.0001 | 0.047 | 810 |
| | L pre-motor cortex | 6 | −42, −6, 24 | 3.49 | 0.0002 | 0.049 | 216 |
| | R dorsal ACC | 24 | 9, −3, 36 | 3.50 | 0.0002 | 0.049 | 81 |
| | L posterior cingulate | 31 | −12, −24, 36 | 3.53 | 0.0002 | 0.049 | 135 |
| | L fusiform gyrus/ | 20/36/37 | −27, −30, −15 | 3.87 | 0.0001 | 0.042 | 2403 |
| | hippocampus/ | | *−36, −33, −18* | 3.72 | *0.0001* | 0.045 | |
| | parahippocampus | | | | | | |
| | R fusiform gyrus/ | 20/36/37 | 42, −30, −18 | 4.07 | <0.0001 | 0.039 | 2835 |
| | hippocampus/ | | *39, −48, −18* | 3.51 | *0.0002* | 0.049 | |
| | parahippocampus | | | | | | |
| | L inferior parietal lobule/ | 22/40/41/42 | −66, −51, 24 | 4.80 | <0.0001 | 0.036 | 7830 |
| | supramarginal gyrus/ | | *−57, −45, 18* | 4.48 | *<0.0001* | 0.036 | |
| | superior/tranverse temporal gyrus | | *−54, −24, 9* | 4.28 | *<0.0001* | 0.036 | |
| | R inferior parietal lobule/ | 39/40 | 45, −45, 27 | 3.60 | 0.0002 | 0.047 | 1269 |
| | supramarginal gyrus | | | | | | |
| | R superior temporal gyrus | 22/41/42 | 66, −27, 9 | 4.20 | <0.0001 | 0.036 | 2322 |
| | | | *57, −18, 6* | 4.13 | *<0.0001* | 0.039 | |
| | R middle temporal gyrus | 21 | 75, −27, −9 | 3.68 | 0.0001 | 0.046 | 81 |
| *Neg* vs. *NeuPos* | **L posterior mOFC** | **11/25** | **−9, 27, −21** | **3.40** | **0.0003** | **0.021** | **459** |
| × | **R posterior mOFC** | **11/25** | **6, 30, −21** | **3.32** | **0.0005** | **0.024** | **297** |
| *NoGo* vs. *Go* | R DLPFC | 9/45/46 | 54, 15, 24 | 3.95 | <0.0001 | 0.026 | 3807 |
| | | | *48, 9, 30* | 3.52 | *0.0002* | 0.037 | |
| | R inferior frontal gyrus | | 27, 36, 9 | 3.82 | 0.0001 | 0.032 | 270 |
| | L inferior frontal gyrus | 45 | −54, 6, 21 | 3.26 | 0.0006 | 0.042 | 189 |
| | L caudate | | −15, 18, 15 | 3.23 | 0.0006 | 0.043 | 297 |
| | L parahippocampus | 36 | −36,−33−18 | 3.36 | 0.0004 | 0.035 | 108 |
| | R fusiform gyrus/ | 20/36/37 | 39, −30, −18 | 4.49 | *<0.0001* | 0.019 | 2862 |
| | hippocampus/ | | *39, -45, -15* | 3.69 | *0.0001* | *0.033* | |
| | parahippocampus | | | | | | |
| | R superior temporal | 6/44 | 60, 6, 9 | 3.29 | 0.0005 | 0.041 | 297 |
| | gyrus/premotor | | | | | | |
| | L inferior parietal lobule/ | 22/40/41/42 | −66, −45, 21 | 4.75 | <0.0001 | 0.019 | 9693 |
| | supramarginal gyrus/ | | *−57, −48, 15* | *4.46* | *<0.0001* | *0.019* | |
| | superior/transverse temporal gyrus | | *−54, −24, 9* | *4.38* | *<0.0001* | *0.019* | |
| | R precuneus | | 21, −57, 33 | 3.65 | 0.0001 | 0.034 | 1836 |
| | | | *15, −63, 24* | *3.49* | *0.0002* | 0.038 | |
| | L posterior cingulate | 23 | −12, −24, 33 | 3.79 | 0.0001 | 0.032 | 891 |
| | R posterior cingulate | 23 | 9, −6, 36 | 3.65 | 0.0001 | 0.034 | 1242 |
| | | | *9, −24, 27* | *3.63* | *0.0001* | 0.034 | |
| | | | *9, −9, 27* | *3.58* | *0.0002* | 0.037 | |
| | L middle temporal gyrus | 39 | −42, −66, 15 | 3.34 | 0.0004 | 0.04 | 216 |
| | L superior temporal gyrus | 22 | −51, −3, −6 | 3.31 | 0.0005 | 0.04 | 216 |
| | R superior/middle/transverse | 22/39/40/ 41/42 | 39, −66, 27 | 4.07 | <0.0001 | 0.023 | 6750 |
| | temporal gyrus/ | | *75, −27, −9* | *4.04* | *<0.0001* | 0.024 | |
| *Pos* vs. *Neu* | inferior parietal lobule/ | | *69, -30, 6* | *3.94* | *<0.0001* | 0.026 | |
| × | supramarginal gyrus | | | | | | |
| *NoGo* vs. *Go* | **L amygdala** | | **−27, 0, −18** | **4.03** | **<0.0001** | **0.001** | **1163** |
| | **R amygdala** | | **21, −6, −15** | **2.88** | **0.002** | **0.029** | **135** |
| | **L posterior mOFC** | **11/25** | **−9, 21, −18** | **3.39** | **<0.0001** | **0.02** | **189** |
| | **R posterior mOFC** | **11/25** | **12, 15, −15** | **2.99** | **0.001** | **0.05** | **243** |

Tools, Inc., Pittsburgh, PA). Stimuli were presented on a 640×480 pixel MRI compatible LCD screen (Sharp Electronics, NJ, USA) with display area 130.6×97 mm, viewing distance=41 cm (±6.7 cm).

Task instructions were given to subjects at the beginning of the experiment, and then again at the start of each run. Subjects were told to read each word silently to themselves, and then respond according to orthographic cues as described above. Instructions for rest periods were to look at the fixation cross and "keep your mind either blank or floating freely". A shortened practice run preceded experimental runs in order to ensure subject task instruction understanding. Button-press responses and reaction times were recorded.

On completion of imaging, subjects were removed from the scanner, and instructed to complete a word recognition task. Subjects were given a list of the 192 stimulus words (targets) randomly interspersed with 48 distracter words (equally divided among negative, positive, and neutral categories, balanced for the same linguistic qualities as targets), and asked to circle those words believed to have been seen during scanning session. Subjects were then given a word valence rating task (also involving a list of both targets and distracters) in which they were asked to rate the valence of each word on a Likert-like scale (−3=very negative, 0=neutral, +3=very positive).

### *Image acquisition*

Image data were acquired with a research-dedicated GE Signa 3 Tesla MRI scanner (maximum gradient strength 40 mT/m, max gradient slew rate 150 T/m/s) (General Electric Company, WI, USA) at the Weill Medical College of Cornell University. Structural images were acquired with a high-resolution T1-weighted SPGR sequence (resolution $0.9375\times0.9375\times1$ mm$^3$) for subsequent anatomic localization. T2*-weighted echo planar imaging (EPI) was used to obtain blood oxygen level dependent (BOLD) axial functional images (Logothetis, 2002; Ogawa et al., 1990). After shimming to maximize homogeneity, fMRI scans were acquired (TR=1200 ms; TE=30 ms; flip angle=70°; FoV=240 mm; 15 slices; 5 mm slice thickness; 1 mm inter-slice distance; matrix=64×64) with a z-shimming algorithm to reduce susceptibility artifact at base of brain (modified from Gu et al., 2002). Head movement was minimized using bilateral padding.

### *Image processing and data analysis*

Prior to analysis, customized SPM 99 software (Friston, Frackowiak et al., Wellcome Dept. of Imaging Neuroscience) was implemented within MATLAB (Mathworks, Inc., MA, USA) to realign functional EPI scans to correct for slight head motion; co-register functional images to individual subject anatomical images; perform stereotactic normalization to the Montreal Neurologic Institute (MNI) version of the standardized coordinate space of Talairach and Tournoux (1988); and spatially smooth with an isotropic Gaussian kernel (FWHM=7.5 mm) to increase signal-to-noise ratio.

A multiple linear regression model was employed at the single subject level. Regressors of interest were stimulus onset times convolved with a prototypic hemodynamic response function; covariates of no interest were global signal, realignment parameters, and scanning periods (Andersson et al., 2001; Desjardins et al., 2001; McGonigle et al., 2000). Effects at each voxel were estimated by a least squares algorithm, and regionally specific effects were then compared using linear contrasts. The resulting set of contrast images were then entered into group analyses, where we employed a random-effects model which accounts for inter-subject variability, allowing population-based inferences to be drawn (Worsley et al., 2002). For each subject, a contrast image for each main condition (i.e. condition against resting state) was generated; these were then combined in a series of linear contrasts to assess group effects, using demographic data (age, gender, and handedness) as covariates in an ANOVA setting. These comparisons generated statistical parametric maps (SPMs) of the $t$ statistic (SPM{$t$}) (Friston et al., 1995), which were then transformed to a unit normal distribution (SPM{Z}). Per convention, a statistically significant difference in BOLD signal response is termed "activation."

Although multiple fronto-limbic sites were of conceptual interest as substrates of the interaction of motor inhibition and emotional stimulus processing, specific *a priori* regions of interest (ROIs) were restricted to mOFC and amygdala (because of their established individual involvement in behavioral control and emotional processing respectively), as defined by automated anatomic labeling (AAL) masks created in MNI space by Tzourio-Mazoyer et al. (2002). For predicted peaks within *a priori* ROIs, comparisons based on one-tailed $t$-tests were considered significant if initial voxel-wise $p<0.005$ and family-wise error small volume corrected (SVC) $p<0.05$ within AAL masks. For unspecified peaks within non *a priori* ROIs, comparisons were considered significant if initial voxel-wise $p<0.001$ and false-discovery-rate corrected $p<0.05$ across entire brain volume (see Tables 1 and 2).

Behavioral data (response times, error rates, recognition rates, valence ratings) were analyzed using Wilcoxon signed rank-sum testing to identify performance differences across conditions. Response times (RTs) were calculated on the basis of *go* trial responses (i.e., for *No-Go* blocks, mean RTs were calculated on the basis of *go* trial RTs, excluding *no-go* error of commission RTs).

## Results

### *Behavioral*

Valence ratings (Fig. 2) revealed significant differences among negative, neutral, and positive word ratings ($p<0.001$, respectively). Response times (Fig. 3) were significantly slower in *no-go* versus *go* blocks within negative and positive valence conditions ($p<0.01$), with a trend toward such difference within neutral valence ($p=0.066$). There were no significant valence-dependent differences in total mean response times (i.e., mean RT of all responses within all *Go*- and *No-Go* blocks of a particular valence). High accuracy rates were seen across all conditions (mean commission error rate=0.89%; mean omission error rate=0.37%). No significant response error rate differences were observed among conditions except for a lower omission error rate within negative versus positive conditions ($p<0.05$).

As also shown in Fig. 2, recognition rates, corrected for distracter words (i.e., adjusted for subject tendency to false-recognize distracters), for emotional (negative and positive) words were significantly higher than the recognition rate for neutral words ($p<0.05$). There was no significant difference between recognition rates of words appearing in *Go* versus *NoGo* blocks.

Table 2
Regional activations revealed by between-condition contrasts

| Contrast | Cluster region | Brodmann area | Peak coordinate (*x*,*y*,*z*) | Peak *Z*-score | *p* uncorr. | *p* corr. | Volume[a] ($mm^3$) |
|---|---|---|---|---|---|---|---|
| *NegNoGo* | **L posterior mOFC** | **11/25** | **0, 27, −21** | **3.06** | **0.001** | **0.047** | **243** |
| vs. *NeuNoGo* | **R posterior mOFC** | **11/25** | **3, 21, −18** | **3.72** | **0.0001** | **0.007** | **594** |
| | **L posterior mOFC** | **11** | **−9, 33, −18** | **4.03** | **0.0001** | **0.003** | **729** |
| *NegNoGo* | **R posterior mOFC** | **11** | **3, 24, −18** | **3.22** | **0.0006** | **0.033** | **351** |
| vs. *NegGo* | R mid OFC | 11 | 21, 42, −12 | 3.65 | 0.0001 | 0.033 | 459 |
| | L dorso-rostal PFC | 9/10 | −33, 60, 24 | 3.41 | 0.0003 | 0.037 | 1107 |
| | R dorso-rostral PFC | 10 | 33, 69, 15 | 4.50 | <0.0001 | 0.017 | 405 |
| | R DLPFC | 9/45/46 | 51, 21, 27 | 4.71 | <0.0001 | 0.017 | 6264 |
| | | | *42, 30, 30* | *4.18* | *<0.0001* | *0.019* | |
| | R inferior frontal gyrus/anterior | 47 | 33, 24, −3 | 3.50 | 0.0002 | 0.033 | 729 |
| | insula | 45/47 | | | | | 1107 |
| | L inferior frontal gyrus/ | | −36, 27, −6 | 4.26 | <0.0001 | 0.017 | |
| | anterior insula | | *−36, 24, 6* | *3.22* | *0.0006* | *0.04* | 297 |
| | R thalamus/putamen | | 15, 0, 9 | 3.38 | 0.0004 | 0.037 | 4536 |
| | R inferior parietal lobule, | 39 | 39, −66, 27 | 5.03 | <0.0001 | 0.013 | |
| | precuneus/ supramarginal gyrus/ | | *24, −60, 30* | *4.46* | *<0.0001* | *0.017* | |
| | middle temporal gyrus/ | | *30, −48, 36* | *3.61* | *0.0002* | *0.033* | |
| | angular gyrus | | | | | | |
| | L posterior cingulate | 23 | −12, −24, 33 | 4.15 | <0.0001 | 0.019 | 1026 |
| | R posterior cingulate | 23 | 9, −21, 36 | 4.09 | <0.0001 | 0.019 | 1026 |
| | | | *12, −24, 27* | *3.66* | *0.0001* | *0.032* | |
| | | | *12, −9, 36* | *3.49* | *0.0002* | *0.033* | |
| | L middle temporal sulcus | 20 | −57, −24, −18 | 3.90 | <0.0001 | 0.024 | 216 |
| | R posterior superior temporal | 22/40/42 | 54, −51, 15 | 4.42 | <0.0001 | 0.017 | 4266 |
| | sulcus/ inferior parietal lobule | | *57, −39, 18* | *3.65* | *0.0001* | *0.033* | |
| | | | *48, −45, 24* | *3.62* | *0.0001* | *0.033* | |
| | L superior/middle temporal gyrus | 21/22 | −66, −51, 9 | 3.58 | 0.0002 | 0.033 | 351 |
| | L fusiform gyrus | 20/37 | −39, −33, −21 | 3.65 | 0.0001 | 0.032 | 378 |
| | R fusiform gyrus/ | 37 | 42, −51, −15 | 3.87 | 0.0001 | 0.025 | 4779 |
| | middle occipital gyrus/ | | *45, −63, −9* | *3.66* | *0.0001* | *0.032* | |
| | middle/inferior temporal gyrus | 19 | −33, −84, 18 | 3.64 | 0.0001 | 0.033 | 1188 |
| | L occipitalL occipital | 19 | −51, −78, −3 | 3.53 | 0.0002 | 0.033 | 756 |
| | L fusiform gyrus | 37 | −33, −60, −18 | 3.20 | 0.0007 | 0.041 | 459 |
| *NeuNoGo* | **L posterior mOFC** | **11** | **−9, 24, −18** | **−3.66** | **0.0001** | **0.009** | **324** |
| vs. *NeuGo* | **R posterior mOFC** | **11** | **15, 15, −12** | **−3.85** | **<0.0001** | **0.005** | **756** |
| *PosNoGo* | **L amygdala** | | **−27, 0, −18** | **2.90** | **0.002** | **0.028** | **81** |
| vs. *PosGo* | | | | | | | |
| *PosNoGo* | **R posterior mOFC** | **11** | **6, 24, -21** | **3.17** | **0.0008** | **0.038** | **297** |
| vs. *NeuNoGo* | | | | | | | |

*Notes.*

- *Neu*=neutral; *Neg*=negative; *Pos*=positive; DLPFC=dorso_lateral prefrontal cortex; mOFC=medial orbito_frontal cortex; PFC=prefrontal cortex.
- Blue denotes fronto-limbic regions.
- **Bold** denotes a *priori* ROI.
- *Italics* denote sub-maximal peaks within same cluster region.
- Pink denotes deactivation.
- [a] *p* corrected =
  - small volume correction (SVC) for *a priori* ROIs using AAL masks (gyrus rectus and amygdala).
  - whole brain false discovery rate (FDR) correction for regions not of *a priori* interest.
- [b] cluster volumes at
  - $p < 0.005$ for *a priori* ROIs.
  - $p < 0.001$ for regions not of *a priori* interest, spatial extent $> 80$ $mm^3$.

During post-experiment de-briefing, subjects acknowledged inferring that words of similar valence were grouped in their presentation. However, subjects did not apparently consciously infer (as evidenced by spontaneous report or response to explicit inquiry) any grouping of response conditions (i.e., *Go* or *NoGo* blocks).

### *Imaging*

Principal contrasts relevant to identifying neural substrates of the *interaction* of emotional stimulus processing and response inhibition are (a) for negative valence: [(*Negative* vs. *Neutral*)× (*NoGo* vs. *Go*)], and (b) for positive valence: [(*Positive* vs. *Neu-*

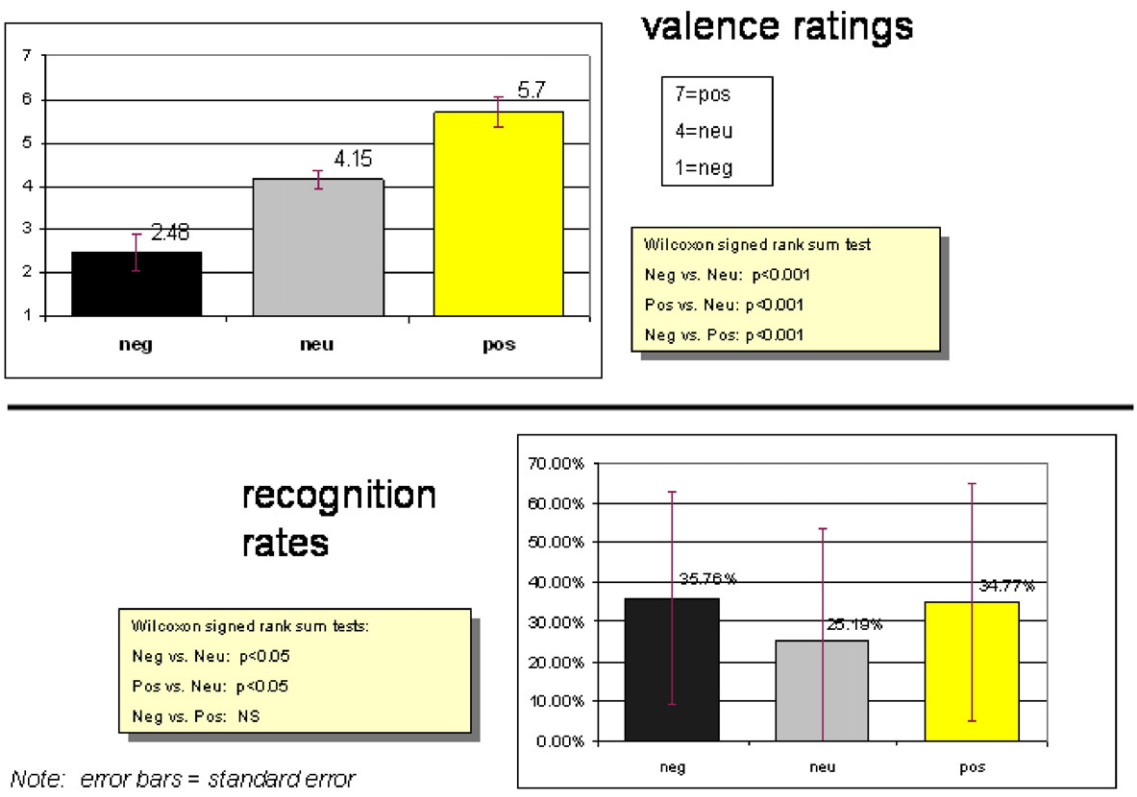


Fig. 2. (a) Mean subject ratings of word stimulus valence; (b) subject recognition, by percentage, of target word stimuli among target and distractor words (see Methods section for further description).

*tral*)×(*NoGo* vs. *Go*)]. Since we were especially interested in emotional processing influences on inhibitory control specific to negative valence, we also consider the interaction contrast of [(*Negative* vs. *NeutralPositive*)×(*NoGo* vs. *Go*)] to ascertain negative-specificity of findings (i.e., negative versus combined neutral and positive interactions). Contrasts of main conditions informing interpretation of these interactions were also performed (e.g., *NegativeNoGo* vs. *NeutralNoGo* (i.e., between valence, within response condition)).

*(Negative vs. Neutral)×(NoGo vs. Go)*

Testing the interaction of negative relative to neutral valence with motor inhibition vs. expression [(*NegNoGo*−*NegGo*)−(*NeuNoGo*−*NeuGo*)] revealed activation of *a priori* ROIs including bilateral mOFC and L amygdala; non *a priori* fronto-limbic activations included R DLPFC, R dorsal ACC, and L premotor PFC. See Fig. 4 for representative activation pattern and Table 1 for full cluster inventory.

*[Negative vs. NeutralPositive]×[NoGo vs. Go]*

Testing the interaction of negative relative to non-negative (i.e., neutral and positive) valence with motor inhibition vs. expression [(*NegNoGo*−*NegGo*)−(*NeuPosNoGo*−*NeuPosGo*)] demonstrated activations in *a priori* ROI bilateral mOFC, as well as R DLPFC and bilateral posterior cingulate, among other regions (see Table 1).

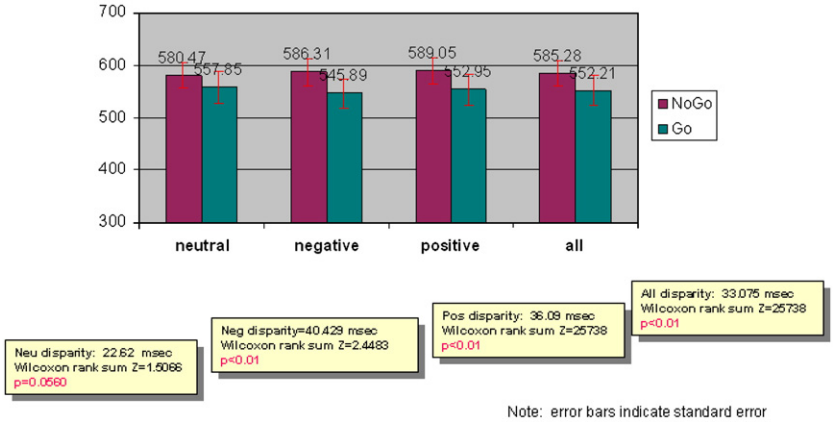


Fig. 3. Mean subject response times by word stimulus valence.

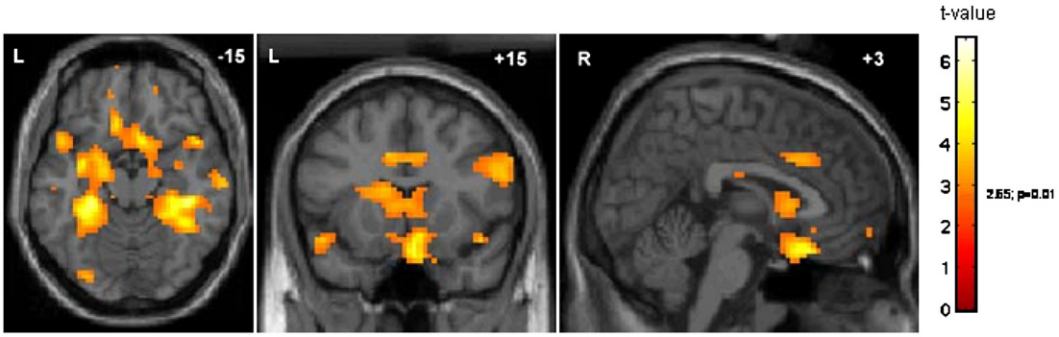


Fig. 4. Statistical parametric map of interaction contrast [(*Negative* vs. *Neutral*)] × (*NoGo* vs. *Go*)] showing regional BOLD differences present at $p < 0.01$ (see Table 1 for complete cluster description).

*[Positive vs. Neutral] × [NoGo vs. Go]*

Testing the interaction of positive relative to neutral valence with motor inhibition vs. expression [(*PosNoGo* − *PosGo*) − (*NeuNoGo* − *NeuGo*)] revealed activations in *a priori* ROI bilateral mOFC and bilateral amygdala (see Table 1).

*NegativeNoGo vs. NeutralNoGo*

Contrasting response inhibition within negative vs. neutral valence solely revealed activations within *a priori* ROI bilateral mOFC (see Fig. 5 and Table 2).

*NegativeNoGo vs. NegativeGo*

Within negative valence, contrasting response inhibition vs. expression revealed bilateral mOFC activation; see Fig. 6 for representative activation pattern and Table 2 for complete cluster inventory.

*NeutralNoGo vs. NeutralGo*

Within neutral valence, contrasting response inhibition vs. expression solely revealed *deactivations* within bilateral mOFC (see Table 2).

*PositiveNoGo vs. PositiveGo*

Within positive valence, contrasting response inhibition vs. expression solely revealed L amygdala activation (see Table 2).

*PositiveNoGo vs. NeutralNoGo*

Contrasting response inhibition within negative versus neutral valence solely revealed R posterior mOFC activation (see Table 2).

Medial OFC function varied across main conditions, notable for activation in *NegativeNoGo* relative to all other conditions (see Fig. 7).

## Discussion

Results overall indicate support for hypotheses regarding fronto-limbic activity changes associated with, and valence-distinct variation in the neural network engaged by, the interaction of emotional stimulus processing and behavioral inhibitory task demand. Because of its relevance to pathologic disturbances of the human behavioral repertoire, we contextualize results with special attention to findings revealed by those contrasts highlighting negative valence-specific behavioral inhibition, hereafter referred to as "***NegativeNoGo***".

*Behavioral findings*

Valence ratings indicated intended stimulus valence perception. Increased mean response time in *no-go* vs. *go* blocks suggests successful induction of inhibitory tone in *no-go* conditions (Miller et al., 2001). Higher recognition rates for emotional (both negative and positive) compared to neutral words is consistent with prior findings demonstrating enhanced memory performance for emotional stimuli (Burke et al., 1992). Low overall error rate suggests that error detection was not a major paradigm processing task and commensurately lessens this as a confound when interpreting imaging results. Also, low error of commission rate suggests that impulsivity was not significantly elicited by the paradigm task.

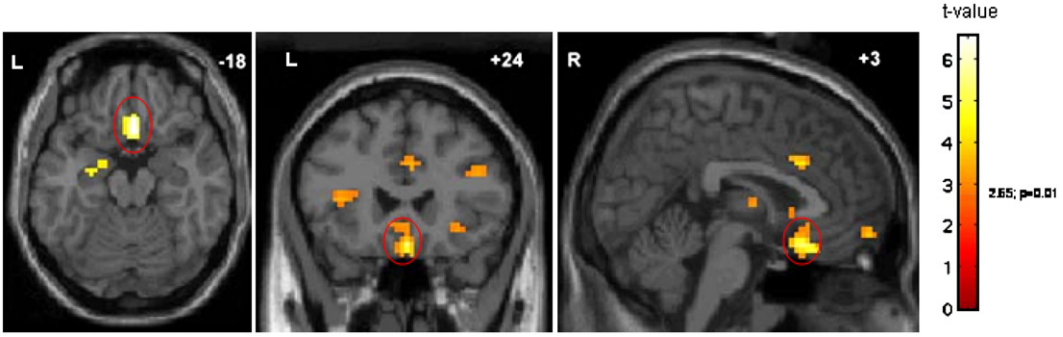


Fig. 5. Statistical parametric map contrasting *NegativeNoGo* vs. *NeutralNoGo* showing regional BOLD differences present at $p < 0.01$; activations surviving correction for multiple comparisons indicated by red oval, here bilateral mOFC; see Table 2 for complete cluster description.

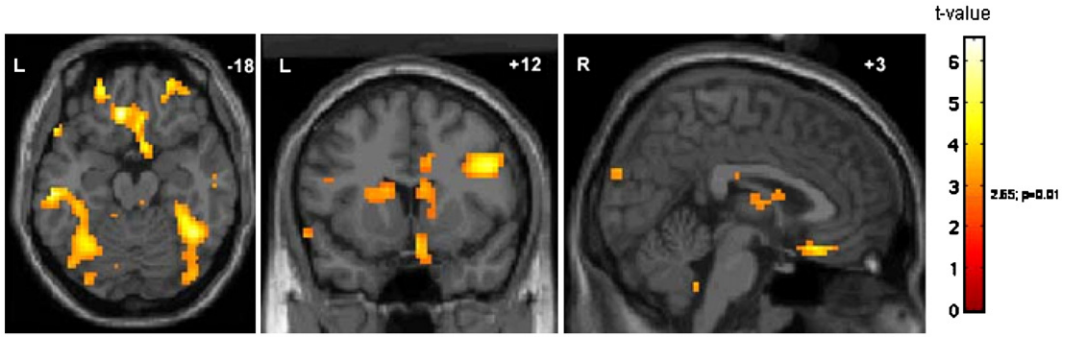


Fig. 6. Statistical parametric map contrasting *NegativeNoGo* vs. *NegativeGo* showing regional BOLD differences present at $p < 0.01$ (see Table 2 for complete cluster description).

*Neural mediation of the interaction of emotional stimulus processing and response inhibition*

*Bilateral medial orbitofrontal cortex (mOFC)*

All contrasts of the interaction of emotion and behavioral inhibition revealed greater bilateral mOFC activation during emotionally-valenced relative to emotionally-neutral response suppression, strongly supporting a bilateral mOFC role in mediating response inhibition during emotional stimulus processing. Moreover, contrasting the interaction of response inhibition within negative as compared to both positive and neutral valences demonstrated significantly greater bilateral mOFC function associated with *NegativeNoGo*.

OFC has been strongly implicated in emotion-influenced decision-making (Rolls, 1996), including integrating motivational states with task performance goals (Dolan, 1999; Hurliman et al., 2005; Schoenbaum and Setlow, 2001). Building on James–Lange conceptualizations of emotion, Damasio (1999) and others (e.g., Bechara et al., 2000a) incorporated hypotheses regarding OFC's role in processing viscero-somatic afferent input into the somatic marker hypothesis (SMH). Per SMH, neural representations regarding somatic (including visceral) arousal associated with an emotional stimulus can bias response selection by their integration into response selection processing (Damasio, 1999). OFC is hypothesized to be a key functional repository of these representations. Impaired integration of emotional information into response selection processes may underlie socio-behavioral regulatory deficits in patients with OFC lesions (Bechara et al., 2000b; Damasio, 2000; Dolan, 1999; Mitchell et al., 2002; Shamay-Tsoory et al., 2003). Similarly, failure of OFC-mediated modulation of behavioral control may underlie the behavioral dysregulation characteristic of certain personality disorders (Berlin et al., 2005).

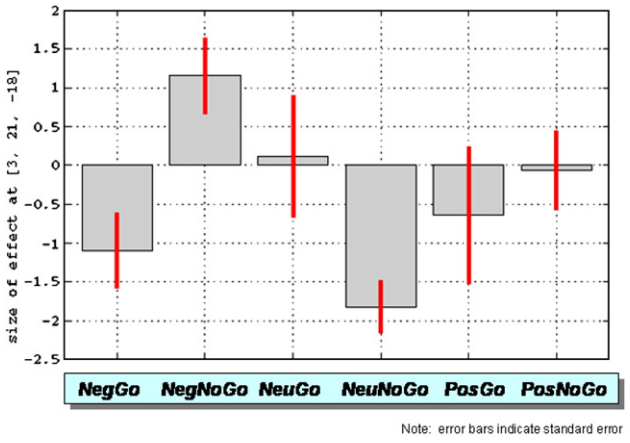


Fig. 7. Histogram of relative BOLD signal change by condition at right medial OFC ($x=3$, $y=21$, $z=-18$, of MNI version of Talairach and Tournoux coordinate space).

Greater mOFC activity revealed by all interaction contrasts is therefore consistent with presumed OFC participation in somatic marker theory's linkage of emotional processing and behavioral control. Valence-dependent variation of mOFC activity across inhibition conditions (Fig. 7), with uniquely negative valence-specific activation, further informs evolving understanding of OFC's relevance to behavioral disorders marked by regulatory failure within the context of *NegativeNoGo*-type task demand.

Medial–lateral functional segregation within the OFC remains a target of extensive inquiry (Elliott et al., 2000b); medial OFC functional variation in particular within the present study therefore also potentially contributes to evolving neurocognitive models defining this segregation.

Of note, contrasting response inhibition vs. expression within solely neutral valence (*NeuNoGo* vs. *NeuGo*) demonstrated bilateral mOFC *deactivation*; the significance of this is discussed below.

*Right dorsolateral prefrontal cortex (DLPFC)*

Prominent R DLPFC activation associated with *NegativeNoGo* is consistent with findings of prior studies of response inhibition (Rubia et al., 2001), and can be interpreted within various cognitive control models. Right lateralization in particular is consistent with prior data suggesting right frontal mediation of behavioral inhibition within negative-avoidance affect (Demaree et al., 2005; Garavan et al., 1999).

DLPFC has been implicated as a key substrate mediating a variety of executive functions, including: representation of task demand (Hartley and Speer, 2000); working memory (e.g., Levy and Goldman-Rakic, 2000); response selection (Rowe et al., 2000); response switching (Garavan et al., 2002); pre-potent response inhibition per se (e.g., Garavan et al., 2002; Horn et al., 2003); proactive control of interference (e.g., suppression of task-extraneous information) (Bunge et al., 2001); and voluntary suppression of sadness (Phan et al., 2005). Thus, DLPFC activation specific to *NegativeNoGo* may be demonstrating that behavioral inhibitory task demand bestows greater operational task management processing load within the context of negative emotion. Supporting this, DLPFC activation has been associated

with the interaction of working memory task demand and response suppression (Nathaniel-James and Frith, 2002).

This finding may also be demonstrating an instance of cognitive–emotional neural integration. Whereas identifying functional *localization* by demonstrating *fractionation* of mentation by double dissociation relies on the logic of subtraction analysis, identifying *integration* involves identifying neural *convergence* of sub-functions (Gray et al., 2002). Accordingly, identifying emotional and cognitive control *integration* requires demonstrating functional convergence at a brain region by crossover interaction of emotion and cognitive control, thereby implying joint influences, while simultaneously demonstrating absence of main effect of either emotion or cognitive control on the same region (Friston, 1998; Gray et al., 2002). Thus increased R DLPFC activity within *NegativeNoGo*, and absence of such activity solely by main effect of negative valence or inhibitory task demand, implicate R DLPFC participation in mediating the *interaction* of response inhibition and negative emotional stimulus processing.

Prior studies have also suggested DLPFC as an emotional–cognitive integration site. For example, Gray et al. (2002) found DLPFC regions to demonstrate functional crossover interaction of emotion and cognitive task demand, without cognitive or emotional main effects. Perlstein et al. (2002) found DLPFC function to be modulated by emotional valence only when DLPFC was recruited by task demand. Other studies have implicated *right* DLPFC in particular as a potential substrate of emotional–cognitive integration, especially for negative affect (Liotti and Mayberg, 2001). The present finding thus extends conceptualization of R DLPFC as a potential neural nexus of negative emotional stimulus processing and behavioral inhibitory control.

This finding may also offer insight into the neural mechanisms of psychiatric states marked by behavioral regulatory failure within negative socio-emotional contexts. For example, DLPFC-related cognitive dysfunction has been implicated as part of the neuropsychological profile of antisocial personality disorder (Dolan and Park, 2002).

*Anterior cingulate cortex (ACC)*

Extensive data indicate that ACC subserves an array of meta-regulatory cognitive functions (Fernandez-Duque et al., 2000). Accordingly, dorsal ACC activity in *NegativeNoGo* (though solely revealed in the interaction contrast [(*Neg* vs. *Neu*)×(*NoGo* vs. *Go*)]) can be understood within several models of ACC function.

*Response inhibition.* ACC has been implicated as a component substrate of an inhibitory system thought to be activated in contexts requiring *difficult* inhibitory control (De Zubicaray et al., 2000; Garavan et al., 2002). Increased ACC activity in *NegativeNoGo* therefore suggests that response inhibition is a more demanding task demand within negative relative to neutral stimulus processing.

*Cognitive interference/conflict monitoring.* ACC activation is a frequent finding in studies of interference tasks (Carter et al., 2000; Milham and Banich, 2005). Dorsal ACC in particular appears activated by competing information streams (Hester et al., 2004). For example, ACC activity is associated with incongruent trials of Stroop tasks (Gruber et al., 2002; Laird et al., 2005), a cognitive interference-induction method (Stroop, 1935). Consequently, increased dorsal ACC activity in *NegativeNoGo* suggests that inhibitory task demand during negative stimulus processing generates conflict.

There are two levels at which such conflict can potentially exist. An affective attribute can generate processing interference at the *stimulus* level (e.g., as in an "emotional Stroop" task) (Whalen et al., 1998). In contrast, several investigators have proposed that ACC function includes detection of competition among processes conflicting at the *response* level (Botvinick et al., 2001; van Veen et al., 2001). If we interpret increased dorsal ACC activity in *NegativeNoGo* as indicating a conflict between inhibitory task demand and negative emotional stimulus processing, since there should be no intrinsic stimulus-based conflict (i.e., orthographic stimulus properties alone should not interfere with negative emotion), this task would appear to generate conflict at the *response* stage.

*Meta-cognitive control.* "Effortful control theory" distinguishes between relatively "attended" and "automated" behavioral pathways (Posner et al., 2003). Within this model, ACC participates in a processing path invoked when effortful control is required (Gehring and Knight, 2000; Paus et al., 1998), including that control necessitated by conflict (Kerns et al., 2004). Thus ACC activation in *NegativeNoGo* may be indicating greater effortful control, including any permutation of meta-motor control functions required for motor inhibition (Carter et al., 2000; Peterson et al., 1999). That is, increased dorsal ACC activity in *NegativeNoGo* further suggests that, during negative emotional stimulus processing, response suppression is more cognitively demanding than response expression. Complementing data suggesting ACC as a component neural substrate of emotional–cognitive interface (Allman et al., 2001; Bush et al., 2000; Paus, 2001), Ochsner et al. (2004) found a positive correlation between dorsal ACC activity and decreased negative affect. Thus it is possible that dorsal ACC recruitment in *NegativeNoGo* could reflect increased cognitive control related to reciprocal emotional suppression (Drevets and Raichle, 1998; Mayberg et al., 1999).

*Posterior cingulate cortex (PCC)*

PCC function has been variably associated with emotional, cognitive, and physiologic control operations (e.g., Gianaros et al., 2005). PCC has been specifically implicated in emotional evaluation (Vogt et al., 1992), particularly negative valence (Maddock et al., 2003). During *go/no-go* task performance, Laurens et al. (2005) observed PCC participation within a neural network thought to be associated with "task-relevant" stimulus processing. Strong PCC activation associated with *NegativeNoGo* would thereby appear to extend emotional evaluative and task-relevant stimulus detection conceptualizations of PCC function to include *inhibitory* task demand within negative stimulus processing.

*Temporal*

*Medial temporal (corticoid and mesocortical)*

*Amygdala.* Although moderately greater L amygdala activity was noted in the [*PosNoGo* vs. *PosGo*] main condition contrast, there were no other significant amygdala activity differences among main conditions, suggesting relative constancy of emotional arousal across conditions (Kensinger and Schachter, 2006; Phelps and LeDoux, 2005). It is also possible that cognitive task demands generated a reciprocal inhibitory effect on limbic sites, including amygdala (e.g., Hariri et al., 2003).

However, significantly greater L amygdala activity was revealed by the [(*Neg* vs. *Neu*)×(*NoGo* vs. *Go*)] and [(*Pos* vs. *Neu*)×(*NoGo*

vs. *Go*)] interaction contrasts. The latter contrast also revealed greater R amygdala activity (though less prominent). That the only significant amygdala activity differences were restricted to these interaction contrasts highlighting emotional (both negative and positive) stimulus effects suggests that there existed a unique amygdala-influencing feature associated with the interaction of behavioral inhibition and emotional stimulus processing (independent of valence). Clarification of the precise nature of this feature requires further study. Relative predominance of L lateralization may of course be related to the linguistic nature of the task.

*Hippocampus/parahippocampus*. Hippocampal activation has been previously associated with *go/no-go* task performance (Rubia et al., 2001), and recent work (e.g., Laurens et al., 2005) found activation associated with "go" responses to target stimuli. Extensively greater bilateral hippocampal/parahippocampal activation associated with *NegativeNoGo* extends prior findings to suggest these regions are modulated by the interaction of inhibitory task demand and negative stimulus processing.

*Lateral and inferior temporal (neocortical)*. Although other studies of *go/no-go* tasks have reported neocortical temporal activations associated with response inhibition (Rubia et al., 2001), extensively greater activity of lateral and inferior (especially fusiform) temporal regions associated with *NegativeNoGo*, demonstrated across multiple contrast perspectives, implicates these regions as additional neural mediators of the interaction of inhibitory control and negative stimulus processing.

### *Parietal*

Prior imaging studies of *go/no-go* tasks have also reported parietal activations associated with response suppression (e.g., Rubia et al., 2001). Increased parietal activation in *NegativeNoGo* may be reflecting important interface of established parietal attentional functions (Fan et al., 2005; Posner et al., 1987) with the conjunction of behavioral inhibition and negative stimulus processing.

### *Pre-motor cortex: emotional influence on motor outflow*

Emerging data are elucidating the neural relationship of cognitive and motor regulation (Georgopolous, 2000), including the role of pre-/primary motor cortex in complex motor control. Although only reaching significance as revealed by the interaction contrast [(*Neg* vs. *Neu*)×(*NoGo* vs. *Go*)], *greater* pre-motor cortical activity associated with *NegativeNoGo* suggests potentially profound implications for understanding behavioral control within negative emotional contexts. For example, does this represent relatively reduced efficacy of neural inhibitory control over motor cortical outflow within the context of negative emotional processing? If so, does this finding suggest that human capacity to inhibit motor behavior is reduced within negative as compared to neutral emotional processing? This would have implications for understanding behavioral inhibitory failure within negative emotional situations sometimes observed in normal individuals (e.g., "crime of passion"), and certain psychiatric disease states (e.g., borderline personality disorder). Alternatively conceptualizing this finding as a greater tendency toward motor response expression than inhibition within negative emotion, consideration within an evolutionary perspective would suggest that humans are more prone to action than inaction within certain negative emotional contexts, consistent with known physiologic responses to at least certain negative situations (e.g., fight/flight response to threat).

### *Paradigm design and limitations*

Contrasting response inhibition vs. expression within neutral valence (*NeuNoGo* vs. *NeuGo*) revealed *deactivation* of bilateral mOFC and absence of any other statistically significant neural changes. Therefore valence-neutral inhibitory task demand as operationalized by this paradigm failed to demonstrate activation patterns typically associated with response inhibition (Rubia et al., 2001). It is possible that the embedding of valence-neutral inhibitory task demand within an emotional block design creates a supra-block neural state which influences within-block neural responsivity. If so, this may in fact be closer to real-world contexts which can be marked by continuous internally- or externally-prompted shifts of emotional valence (as opposed to laboratory paradigms designed to maintain emotional sterility).

Despite limitations, advantages of block design are compelling when studying emotional modulation of motor behavioral control.

*From a neuro-psychologic/physiologic perspective*

Response *inhibition*, distinct from mere non-response, requires existence of a pre-potent response *tone* needing to be inhibited. Further, time course of emotional processing may be valence-dependent (e.g., Esslen et al., 2004; Garrett and Maddock, 2001). Emotional valences may psychologically differ in their relative tonic vs. phasic nature (e.g., positive and non-threat related negative emotion (e.g., sadness, anger) may be more tonic than phasic). Therefore, we chose block-design to optimize operationalization of sustained inhibitory tone; build and sustain emotional *tone* (Horn et al., 2003); and thereby optimize interaction of the latter with independent manipulation of the former.

*From a functional imaging methodology perspective*

We chose block-design because (a) by considering the block (containing both *go* and *no-go* trials) rather than individual *go*/*no-go* trials as the functional unit of observation, we hoped to sample neural activity across a behavioral response *set* rather than individual phasic motor *responses* (*go* or *no-go*), thereby presumably minimizing potentially confounding extraneous cognitive/motor functions (e.g., set-shifting, response selection, intrinsic neural apparatuses mediating motor action unequally engaged by *go* and *no-go* performance); and (b) we hoped to leverage greater imaging sensitivity bestowed by block design.

*From an imaging analysis perspective*

We chose block-design: (a) to facilitate functional imaging analysis of pre-potent response set and emotional tone while avoiding complications related to rapid trial BOLD analyses (e.g., assumptions associated with deconvolution of BOLD responses), and (b) to enable factorial comparison of different permutations of emotional valence and response conditions. (Although event-related design can be structured to enable factorial comparison, the neuro-psychologic/physiologic characteristics intrinsic to the present targets of study are particularly suited for block-design.)

Because *no-go* and *go* condition blocks contain different numbers of *go* trials, it may be that when contrasting *no-go* with *go* conditions, consequent inferences regarding neural processes underlying response inhibition could be confounded by differences in neural activation attributable to comparing conditions containing unmatched response trial compositions. But evidence suggests that response number differences between *go* and *no-go* blocks in block design *go/no-go* studies do not significantly alter analyses

contrasting *go* vs. *no-go* neural activation patterns. For example, Casey et al. (1997) determined that differences in fMRI data between *no-go* blocks matched for stimuli and *no-go* blocks matched for responses did not significantly alter findings in a *go/no-go* block design study (Casey et al., 1997). Though the precise nature of BOLD changes associated with motor inhibition remains under investigation (Logothetis, 2002; Waldvogel et al., 2000), that we observed BOLD differences, including *increases*, associated with conditions containing *fewer* motor responses, would appear to support inferences implicating regions demonstrating these changes with neurobehavioral inhibitory processes. Further, in the present study, between-valence (e.g., negative vs. neutral) within-motor response condition (e.g., *no-go*) comparisons (e.g., *NegativeNoGo* vs. *NeutralNoGo*) involve conditions matched for number of *go* and *no-go* response trials. Such comparisons should therefore provide valence-dependent but motor response difference-independent contrasts of neural function underlying behavioral inhibition.

A more difficult problem involves the issue that response inhibition in a *no-go* task might involve not only motor inhibition per se, but also selection of a less frequent response (e.g., Miller et al., 2001); as such, this might implicate more general selection/monitoring processes. However, the latter is likely a component process of many real-world behavioral inhibitory tasks, and therefore may not necessarily constitute a confounding process.

The valence and magnitude of *actual* emotion induction associated with each trial of implicit emotional stimulus processing remains unclear and this uncertainty constitutes a significant limitation; subsequent studies should add physiologic indices of emotional responsivity to inform these parameters and thereby improve specificity of result interpretation.

We included two left-handed subjects among the total *N* of 14 (approximately 14%) to demonstrate (a) handedness/hemispheric lateralization-independent robustness of these findings, and (b) enable applicability of this paradigm to future studies of target patient populations for whom relative hemispheric dominance is less certain (Crow, 1997; Niederhofer, 2004). Evidence supporting the suitability of including a minority of left-handers in a linguistic paradigm includes data suggesting that handedness is not as reliable an indicator of hemispheric dominance for language as conventionally thought (Knecht et al., 2000; Springer et al., 1999). For example, Pujol et al. (1999) demonstrated in a fMRI study that silent word generation (thus similar to the linguistic component of this paradigm) lateralizes to the left cerebral hemisphere in both handedness groups (i.e., the majority of LHs are left hemisphere dominant for language).

Although menses phase can influence neural processing of emotional stimuli, including as operationalized by a paradigm like the present one (Protopopescu et al., 2005), this variable was not controlled among female subjects.

Sample size provided sufficiently robust activations to permit key contrasts for hypothesis testing. A mixed-effects model was used, and while this can decrease result significance, it takes inter-subject variability into account, allowing greater population inference. Future studies, with additional subjects, will be important to substantiate and extend these findings.

## Conclusion

Building on emerging functional neuroanatomic understanding of response inhibition, and complementing recent studies of emotional–cognitive interaction using explicit emotion, this study aimed to elucidate neural mechanisms by which incidental emotional stimulus processing modulates response inhibition. It is thought that such interaction better approximates that operating in many real-world socio-behavioral contexts. The conjunction of emotional stimulus processing with behavioral inhibitory task demand, as operationalized by this paradigm, consistently activated predicted fronto-limbic regions including mOFC and amygdala, and was associated with valence-dependent activity variations in distributed cortico-limbic regions. A distinct neural network including prefrontal (mOFC, DLPFC, ACC), limbic (amygdala), paralimbic, and parietal regions was engaged by the conjunction of negative stimulus processing and inhibitory task demand (*NegativeNoGo*). Present findings can be interpreted within evolving neurocognitive models of behavioral control, and have implications for elucidating the neuropsychological dynamics of approach/withdrawal behavior. Future studies will be needed to clarify the potential role of these circuits in pathophysiologic mechanisms of socio-emotional dyscontrol typifying many sociopathic behaviors and psychiatric disorders.

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