Dissociable recruitment of rostral anterior cingulate and inferior frontal cortex in emotional response inhibition

Pearl H. Chiu [a,b,*], Avram J. Holmes [a], Diego A. Pizzagalli [a]

[a] Department of Psychology, Harvard University, Cambridge, MA 02138, USA
[b] Department of Neuroscience and Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX 77030, USA

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ABSTRACT

The integrity of decision-making under emotionally evocative circumstances is critical to navigating complex environments, and dysfunctions in these processes may play an important role in the emergence and maintenance of various psychopathologies. The goal of the present study was to examine the spatial and temporal dynamics of neural responses to emotional stimuli and emotion-modulated response inhibition. High-density event-related brain potentials (ERPs) were measured as participants ($N=25$) performed an emotional Go/NoGo task that required button presses to words of a "target" emotional valence (i.e., positive, negative, neutral) and response inhibition to words of a different "distractor" valence. Using scalp ERP analyses in conjunction with source-localization techniques, we identified distinct neural responses associated with affective salience and affect-modulated response inhibition, respectively. Both earlier (~300 ms) and later (~700 ms) ERP components were enhanced with successful response inhibition to emotional distractors. Only ERPs to target stimuli differentiated affective from neutral cues. Moreover, source localization analyses revealed right ventral lateral prefrontal cortex (VLPFC) activation in affective response inhibition regardless of emotional valence, whereas rostral anterior cingulate activation (rACC) was potentiated by emotional valence but was not modulated by response inhibition. This dissociation was supported by a significant Region×Trial Type×Emotion interaction, confirming that distinct regional dynamics characterize neural responses to affective valence and affective response-inhibition. The results are discussed in the context of an emerging affective neuroscience literature and implications for understanding psychiatric pathologies characterized by a detrimental susceptibility to emotional cues, with an emphasis on major depressive disorder.

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Introduction

Adaptive goal-directed behavior requires responding to relevant environmental cues while disregarding distracting events (for review, see Dillon and Pizzagalli, 2007). In particular, emotionally evocative situations are inevitable in human interaction, and the capacity to inhibit responses to irrelevant affective stimuli is critical to navigating a complex environment. Indeed, increased susceptibility to affective triggers has been implicated in the etiology and maintenance of major psychiatric disorders, including depression (e.g., Beauregard et al., 2006; Chiu and Deldin, 2007; Elliott et al., 2002; Holmes and Pizzagalli, 2007, 2008; Johnstone et al., 2007), post-traumatic stress disorder (e.g., Frewen and Lanius, 2006; Price et al., 2006), and borderline personality disorder

(e.g., Conklin et al., 2006; Johnson et al., 2003). Toward the aim of elucidating how emotional response monitoring may be perturbed in psychopathology, the primary goal of the present work was to examine the timecourse and regional specificity of neural processes involved in response inhibition to emotional cues. To this end, we measured event-related brain potentials (ERPs) as participants performed an affective Go/NoGo task that required the inhibition of responses to emotional distractor stimuli and the accurate identification of emotionally incongruent targets.

The Go/NoGo paradigm is among the most well-characterized assays of response inhibition to perceptual stimuli (Aron, 2007; Dillon and Pizzagalli, 2007). Go/NoGo tasks involve the presentation of a continuous series of "Go" or "target" cues to which subjects are asked to respond as quickly as possible, and "NoGo" or "distractor" cues that require subjects to inhibit motor responses. ERP and functional magnetic resonance imaging (fMRI) studies using Go/NoGo tasks with non-emotional stimuli have yielded a consistent pattern of findings. First, ERP studies reliably identify a negative-going component

occurring 200–400 ms following NoGo stimuli. This component, known as the "NoGo N2," occurs maximally at fronto-central scalp locations and is considered a robust index of response inhibition across a variety of tasks (e.g., Go/NoGo, stop signal, anti-saccade) and stimulus modalities (Eimer, 1993; Falkenstein et al., 1999; Fallgatter and Strik, 1999; Jackson et al., 1999; Jodo and Kayama, 1992; Kirmizi-Alsan et al., 2006; Kok et al., 2004; Pfefferbaum et al., 1985). On NoGo trials, the N2 is followed by a positive-going shift. This positive complex, termed the "NoGo P3", also occurs maximally at fronto-central scalp sites and is typically seen 300–700 ms following the NoGo stimulus (Kiefer et al., 1998; Pfefferbaum et al., 1985; Roberts et al., 1994).

These findings are complemented by ERP source localization and fMRI data that strongly implicate lateral prefrontal cortical regions in response inhibition. Specifically, the right ventral lateral prefrontal cortex (PFC), particularly the inferior frontal gyrus (IFG), is consistently activated with successful motor control on Go/NoGo tasks, and lesions to the IFG impair such inhibitory control (Aron et al., 2003, 2007; Bellgrove et al., 2004; Braver et al., 2001; Bunge et al., 2002; Chikazoe et al., 2007; Durston et al., 2002; Garavan et al., 1999, 2002; Horn et al., 2003; Konishi et al., 1999; Lavric et al., 2004; Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001). Together these data indicate that the right IFG is critical for stopping prepotent responses to perceptual stimuli.

Implications for major depression and treatment

Incorporating emotion-evoking, affectively salient stimuli into paradigms that typically use perceptual cues may provide unique insight about pathologies characterized by abnormal sensitivity to affective triggers (Whalen et al., 1998; Williams et al., 1997). For example, the emotional Go/NoGo task both assesses motor response inhibition and allows the investigation of perturbations in emotional response monitoring. In particular, fMRI data not only support the role of the IFG in response inhibition and cognitive interference involving affective stimuli (Dolcos and McCarthy, 2006; Dolcos et al., 2006; Elliott et al., 2000; Goldstein et al., 2007; Hare et al., 2005; Shafritz et al., 2006), but also describe activation within rostral anterior cingulate cortex (rACC) and ventromedial prefrontal cortex (vmPFC) that is modulated by emotional valence (e.g., greater BOLD response to negative versus neutral target stimuli). These rACC/vmPFC activations overlap with regions implicated in a range of paradigms incorporating affective stimuli or emotional provocation that do not necessarily elicit response competition (Bush et al., 2000; Canli et al., 2004; Damasio et al., 2000; Etkin et al., 2006; Keightley et al., 2003; Maddock et al., 2003; Phan et al., 2003; Whalen et al., 1998). Equally intriguing, these regions overlap with those identified to predict or vary with treatment response in major depressive disorder across a variety of therapeutic protocols including antidepressants, electroconvulsive therapy (ECT), and sleep deprivation (Awata et al., 2002; Brody et al., 2001a,b; Chen et al., 2007; Davidson et al., 2003; Fu et al., 2004; Holthoff et al., 2004; Langenecker et al., 2007; Mayberg et al., 1997, 2000; Pizzagalli et al., 2001; Saxena et al., 2003; Walsh et al., 2007; Wu et al., 1999). Based on these observations, the affective Go/NoGo and related tasks may be useful tools for assessing well-defined neural pathways in major depression and other psychopathologies characterized by impairments in emotion

regulation, offering promising methods for improving psychiatric diagnosis or prognostic assessment (Hyman, 2007; Ressler and Mayberg, 2007).

Toward this end, our primary goals were, first, to examine whether emotional valence is sufficient to establish a prepotent response tendency; and second, to assess the utility of source localization techniques coupled with the emotional Go/NoGo task as a functional assay of right IFG and rACC/vmPFC regions. We hypothesized that enhanced NoGo ERPs and IFG activation should characterize the spatiotemporal dynamics of successful response inhibition to affective stimuli, whereas rACC/vmPFC activation should be specifically modulated by emotional salience.

Methods

Participants

Twenty-five participants recruited from the Harvard University Study Pool took part in the study. Inclusion criteria included males and females of any ethnic background, aged 18–55. Exclusion criteria included left-handedness, current psychiatric treatment, and history of major medical illness or head trauma. The demographic composition of the total group ($N=25$) was: 14 Caucasian individuals, 14 females, 19.5 ± 0.9 years of age, and 13.4 ± 0.8 years of education. In accord with Institutional Review Board guidelines, written informed consent was obtained prior to beginning the study. All subjects received course credit for their participation and were fully debriefed upon completion of the study.

Stimuli and task

The primary task, illustrated in Fig. 1, used affective words as "Go" (target) and "NoGo" (distractor) stimuli in an emotional Go/NoGo task adapted from previous fMRI reports (Elliott et al., 2000; Elliott et al., 2002). Participants viewed a series of individually presented words taken from the Affective Norms for Emotional Words list (ANEW; Bradley and Lang, 1999) and from the Standard Corpus of Present-Day American English (Francis and Kučera, 1979; Francis et al., 1982). Within each of 6 blocks, subjects were asked to respond with a key press to each word that belonged to a target valence category (i.e., positive, negative, or neutral), and to withhold responses to all other words. Each block consisted of 90 words, half of which were taken from one valence category and half from a different valence category. Words across valence categories were matched for length and frequency ($p > 0.1$ for all pairwise comparisons) and differed significantly in valence ratings ($p < 0.05$ for all pairwise comparisons). In addition, positive and negative words were matched on ANEW arousal ratings (positive vs. negative, $p > 0.1$; positive and negative vs. neutral, both $p < 0.05$).

Within each block, words were presented for 280 ms, followed by an 1100 ms jittered inter-trial interval (ITI; range 1000 to 1200 ms). Words were presented in pseudo-random order, such that a maximum of three words in any category occurred in sequence. Block order was randomized across subjects. To reduce confounding effects of motor-induced laterality, participants were asked to respond to Go stimuli by simultaneously pressing the two lateral keys of the response box with the index fingers of each hand. Irrespective of participants' responses, trials advanced upon reaching the pre-determined ITI.
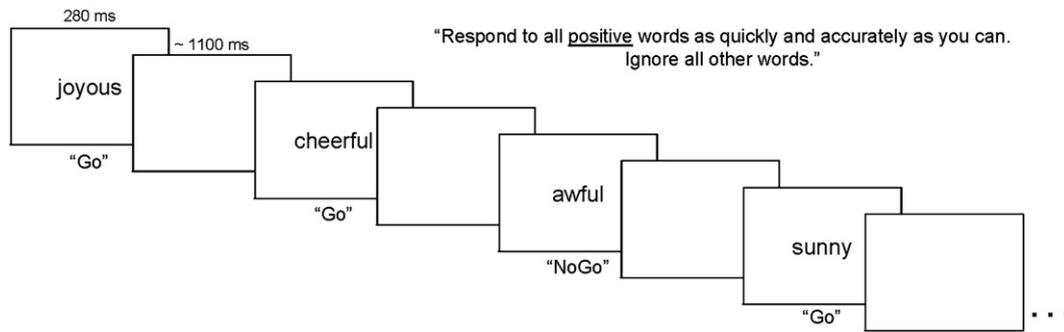
Fig. 1. Schematic depiction of the affective Go/NoGo task. Participants viewed a series of individually presented words, half of which belonged to a "target" or "Go" valence category and half of which belonged to a "distractor" or "NoGo" valence category. Participants were asked to respond with a key press to words of the target valence and to withhold responses to all other words. The following six experimental blocks were presented: (1) positive targets, negative distractors; (2) positive targets, neutral distractors; (3) negative targets, positive distractors; (4) negative targets, neutral distractors; (5) neutral targets, positive distractors; (6) neutral targets, negative distractors.

Prior to physiological recording, all participants completed the Affective Intensity Measure (AIM; Larsen and Diener, 1987) and Beck Depression Inventory, Second Edition (BDI-II; Beck et al., 1996) to assess the trait intensity with which an individual experiences emotions and the current level of depression symptoms, respectively. Participants also completed two short practice blocks (10 trials each) of the affective Go/NoGo task to ensure understanding of task instructions.

Apparatus

Electroencephalogram data were collected using the Geodesic Sensor Net system (Electrical Geodesics, Inc., OR). Data were sampled at 500 Hz (16 bit precision; bandwidth: 0.01–100 Hz), with the vertex electrode (Cz) as recording reference. Amplifier gains and zeros were measured prior to each recording session, and electrode impedances were kept below 50 kΩ. Stimuli were presented with E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA). Behavioral responses were collected with the Response Pad 200 (Electrical Geodesics, Inc., OR).

Data reduction

Behavioral data

Correct "Go" trials were defined as Go trials in which participants pressed the response keys (i.e., "hits"); incorrect Go trials were those in which a response was not lodged by the subject (i.e., "misses"). Similarly, correct response inhibition trials were defined as "NoGo" trials in which no response occurred, and incorrect NoGo trials are those in which a response was lodged by the subject (i.e., "false alarms"). The primary analyses of interest focused on reaction time and accuracy to emotional targets, and accuracy of emotion-modulated response inhibition. As an additional measure of accuracy, a signal detection sensitivity measure (d') was computed (Macmillan and Creelman, 2005; $d' = z(hits) - z(false\ alarms)$).

Scalp ERP data

Analysis of EEG and ERP data was conducted using BrainAnalyzer software (Brain Vision, Gmbh). Correction of eye-blink artifact was performed using the Gratton, Coles, and Donchin (1983) regression algorithm, and channels with corrupted signal were replaced using spatially weighted linear interpolations (Hjorth nearest neighbors algorithm). Data were then re-derived to an average reference. EEG exceeding ± 100 μV were automatically rejected; remaining EEG segments were subjected to manual scoring to remove residual eye-movement and electromyogram artifacts. Two subjects were excluded from subsequent analyses due to excessive artifacts.

Stimulus-locked ERPs were computed −200 to 1200 ms from stimulus onset. Individual ERP averages were derived for correct trials of each stimulus type (Go, NoGo) and emotional valence (Positive, Negative, Neutral), and band-pass filtered (0.01–30 Hz; 12dB/octave roll-off). The N2 component was quantified as the most negative amplitude within a 200 to 420 ms window following stimulus onset, relative to a −200 ms baseline. The P3 component was quantified as the most positive amplitude within 350 ms following the N2 peak, relative to the same −200 ms baseline.

Source localization

Source localization analyses of ERP peak amplitudes were conducted using Low Resolution Electromagnetic Tomography (LORETA) with a solution space of 2394 voxels and 7 mm^3 voxel resolution within cortical gray matter (Pascual-Marqui et al., 1994). LORETA computes the three-dimensional intracerebral current density within specified time windows and uses the smoothest of all possible activity distributions to identify potential cortical generators underlying given ERP components. The algorithm relies on the assumption that neighboring voxels have similar orientation and strength of neuronal activity but does not assume an a priori number of neural sources (Pascual-Marqui et al., 1994). Studies combining LORETA with traditional tomographic methods, including fMRI and PET, have described good correspondence between cortical regions identified with the various neuroimaging techniques (Mulert et al., 2004; Pascual-Marqui et al., 2002; Pizzagalli et al., 2004; Vitacco et al., 2002). Here, LORETA was implemented to identify brain regions engaged by affective cues and emotion-modulated response inhibition, respectively.

Statistical analyses

Behavioral data

Reaction time. To assess the effects of emotion on reaction time (RT) to correct Go stimuli, a univariate repeated-measures ANOVA was performed using *Emotion* (Positive,

Negative, Neutral) as a factor. As no button press responses are obtained on NoGo stimuli, RTs are not available for these trials.

Accuracy.   To assess the effects of emotion and trial type on response accuracy, an *Emotion* (Positive, Negative, Neutral) × *Trial Type* (Go, NoGo) repeated measures ANOVA was performed on accuracy rates. In addition, a univariate repeated-measures ANOVA was performed on target sensitivity (d') using *Emotion* (Positive, Negative, Neutral) as a factor.

Emotion effects on subsequent responses.   To assess effects of emotion and trial type on post-trial RT adjustment, an *Emotion* (Positive, Negative, Neutral) × *Trial Type* (Go, NoGo) repeated measures ANOVA was performed on RTs on correct "Go" trials following Positive, Negative, and Neutral Go and NoGo trials. Given the high accuracy rates in all blocks (overall mean 88.5%, S.D. = 1.1%) and corresponding limited variability in post-response accuracy, emotion effects on subsequent accuracy were not computed.

Physiological data

Scalp ERP data.   To assess the effects of response inhibition and emotion on brain activity, a *Trial Type* (Go, NoGo) × *Emotion* (Positive, Negative, Neutral) × *Site* (8 fronto-central sites; EGI sites 4, 5, 6, 11, 12, 13, 20, and 113; see Fig. 3A) ANOVA was performed for peak N2 and P3 amplitudes, respectively. For the sake of brevity, interactions involving the *Site* factor are not discussed; the data may be requested from the authors.

LORETA.   For each identified peak in the N2 time window, voxel-wise *Trial Type* (Go, NoGo) × *Emotion* (Positive, Negative, Neutral) ANOVAs were performed to assess differences in current density among conditions. Given our a priori hypotheses involving the right IFG and rACC, the output was thresholded at $p < 0.01$, uncorrected (Pizzagalli et al., 2001).

For all analyses, two-tailed tests were used, and higher-order interactions were required to reach statistical significance prior to parsing. In the case of significant main effects with more than two levels, post-hoc pairwise comparisons were performed. Standard deviations (S.D.) are reported throughout the text.

Results

Behavioral data

Reaction time

Subjects were quicker to respond to both Positive and Negative relative to Neutral Go words (*Emotion*: $F(2,44) = 52.9$, $p < 0.0001$; Positive vs. Neutral, $p < 0.001$; Negative vs. Neutral, $p < 0.001$; Table 1). Reaction times to Positive and Negative words did not differ ($F(1,22) = 2.9$, $p > 0.1$).

Accuracy

Subjects exhibited high levels of accuracy across both Go and NoGo trials (.87 ± .05 and .90 ± .05, respectively) and greater accuracy for NoGo trials (*Trial Type*: $F(1,22) = 4.3$, $p = 0.05$). A main effect of *Emotion* emerged, due to higher overall accuracy on Negative trials relative to both Positive and Neutral trials ($F(2,44) = 29.4$, $p < 0.001$; Negative vs. Positive, $p < 0.001$; Negative vs. Neutral, $p < 0.001$). Accuracy on Positive and Neutral trials did not differ ($F(1,22) = 1.6$, $p > 0.22$). The main effect of *Emotion* was qualified by a significant *Emotion* × *Trial Type* interaction, $F(2,44) = 18.1$, $p < 0.0001$. Parsing of this interaction revealed that within Go trials, responses to Negative words were more accurate than to Positive words, which in turn were more accurate than Neutral trials (*Emotion*: $F(2,44) = 39.0$, $p < 0.0001$; Positive vs. Negative, $p < 0.001$; Positive vs. Neutral, $p < 0.002$; Negative vs. Neutral, $p < 0.001$; Table 1). Among NoGo trials, response inhibition was most accurate to Negative words, relative to both Positive and Neutral words (*Emotion*: $F(2,44) = 15.0$, $p < 0.0001$; Negative vs. Positive, $p < 0.001$; Negative vs. Neutral, $p < 0.003$; Table 1). Response inhibition accuracy to Positive and Neutral words did not differ ($F(1,22) = 2.8$, $p > 0.1$).

Subjects also exhibited high sensitivity (d') to all target words, with greatest d' values for Negative target words (3.3 ± .59), followed by Positive (2.9 ± .56) then Neutral (2.2 ± .64) words (*Emotion*: $F(2,44) = 66.1$, $p < 0.001$; Negative vs. Positive, $p < 0.002$; Positive vs. Neutral, $p < 0.001$; Negative vs. Neutral, $p < 0.001$).

Post-emotion behavioral adjustment

Mean reaction times following Go and NoGo trials did not differ (*Trial Type:* $F(1,22) = 2.2$, $p > 0.15$). In contrast, affective arousal modulated subsequent RTs such that responses following both Positive and Negative words were faster than those

Table 1
Means and S.D. of ERP amplitude, current density, behavioral accuracy, and reaction time to emotional Go and NoGo words

Variable	N2	P3	IFG	rACC	Accuracy	Reaction time
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
Target ("Go") valence						
Positive	−2.60 ± 1.39	1.97 ± 1.68	−3.59 ± 0.90	−3.42 ± 1.11	0.86 ± 0.08	580.38 ± 66.85
Negative	−2.79 ± 1.77	1.71 ± 1.77	−3.54 ± 1.03	−3.29 ± 0.82	0.94 ± 0.04	570.28 ± 58.77
Neutral	−3.31 ± 1.68	1.06 ± 1.82	−3.56 ± 0.82	−3.47 ± 1.20	0.80 ± 0.11	646.06 ± 72.95
Distractor ("NoGo") valence						
Positive	−3.18 ± 1.68	2.29 ± 1.97	−3.46 ± 0.88	−3.34 ± 0.68	0.86 ± 0.09	–
Negative	−3.04 ± 1.53	2.56 ± 1.87	−3.41 ± 0.75	−3.33 ± 0.75	0.95 ± 0.04	–
Neutral	−3.13 ± 1.29	2.57 ± 2.16	−3.52 ± 1.10	−3.40 ± 0.82	0.89 ± 0.10	–

N2 and P3 are peak amplitudes in microvolts averaged across 8 recorded scalp sites (EGI sites 4, 5, 6, 11, 12, 13, 20, and 113).
IFG and rACC are average current density in the N2 time window in the identified inferior frontal gyrus and rostral anterior cingulate clusters, respectively.
Accuracy is proportion accurate (number correct/total trials).
Reaction time is milliseconds from stimulus onset.
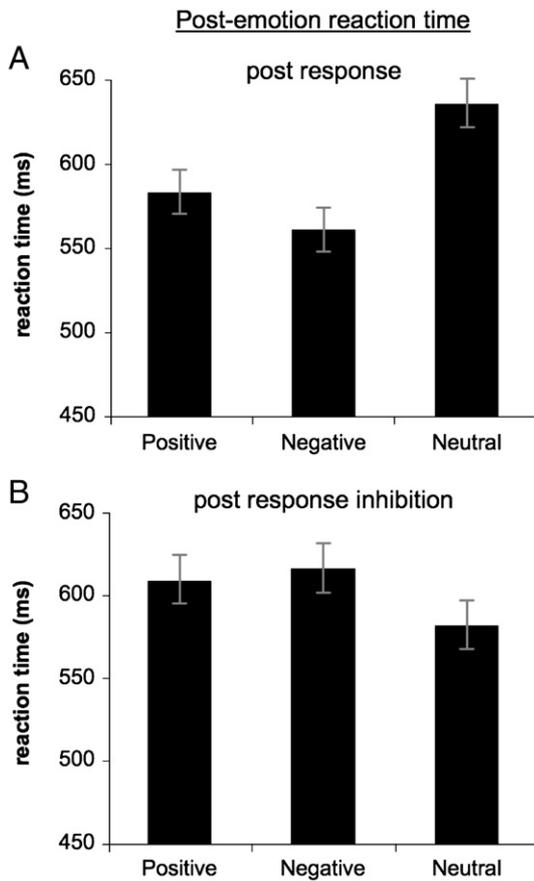All significant comparisons are described in the Results text.

Post-emotion reaction time

A

post response

B

post response inhibition

Fig. 2. Post-emotion adjustment of reaction time following affective Go and NoGo words. (A) Emotional stimuli facilitated reaction times in immediately following trials. Responses following Negative targets were faster than those following Positive targets, which were in turn faster than those following Neutral targets (all pairwise comparisons, $p < 0.002$). (B) Affective arousal modulated reaction times following successful response inhibition. Responses were slower following successful response inhibition to emotional words than following response inhibition to Neutral words; reaction times following response inhibition to Positive and Negative words did not differ (Positive vs. Neutral, $p < 0.009$; Negative vs. Neutral, $p < 0.003$; Negative vs. Positive, $p > 0.35$).

A

B

C

Fig. 3. Event-related brain potentials differentiate response inhibition and affective salience, respectively. (A) Schematic depiction of scalp sites used in the ERP analyses. Scalp ERP analyses focused on fronto-central cortical sites commonly shown to yield maximal N2 and P3 amplitudes on response inhibition tasks. These sites are highlighted in black (EGI sites 4, 5, 6, 11, 12, 13, 20, and 113). (B) Both earlier (N2) and later (P3) components of the ERP are modulated by response inhibition in the affective Go/NoGo task. Specifically, greater amplitude in both components is observed to words that engage successful response inhibition, relative to successful responses. Stimulus-locked grand average waveforms averaged across the 8 indicated scalp sites are presented. The dark line represents ERP responses to NoGo stimuli; the light line represents ERP responses to Go stimuli. (C) ERPs to "Go," and not "NoGo," stimuli were modulated by emotional versus neutral words. Specifically, enhanced Go N2 magnitude is observed to Neutral relative to both Positive and Negative stimuli whereas greater Go P3 is observed to emotional relative to Neutral stimuli. Stimulus-locked grand average waveforms averaged across the 8 indicated scalp sites are presented. The dark line shows ERP responses to Positive target words, the thin line shows ERP responses to Negative target words, and the dotted line shows ERP responses to Neutral target words.

following Neutral words (*Emotion*: $F(2,44) = 6.9$, $p < 0.005$; Negative vs. Neutral, $p < 0.002$; Positive vs. Neutral, $p < 0.06$). *Emotion* also interacted with *Trial Type* to modulate RTs on subsequent trials (*Type × Emotion*: $F(2,44) = 36.9$; $p < 0.001$). Specifically, emotional targets facilitated subsequent RTs such that latencies following Negative targets were faster than those following Positive targets which, in turn, were faster than those following Neutral targets (*Emotion*: $F(2,44) = 44.0$, $p < 0.0001$; Negative vs. Positive, $p < 0.002$; Positive vs. Neutral, $p < 0.001$; Negative vs. Neutral, $p < 0.001$; Fig. 2A).

Affective arousal also modulated RTs following successful response inhibition. Specifically, response inhibition to both Negative and Positive vs. Neutral words led to significantly slower RTs on immediately following trials (*Emotion*: $F(2,44) = 8.3$, $p < 0.002$; Positive vs. Neutral, $p < 0.009$; Negative vs. Neutral, $p < 0.003$; Negative vs. Positive, $p > 0.35$; Fig. 2B).

Collectively, these behavioral data suggest that the present emotional Go/NoGo task elicited behavioral effects consistent with those observed in non-emotional Go/NoGo tasks and supports the use of the task to assess emotion-modulated response-inhibition (Schulz et al., 2007).
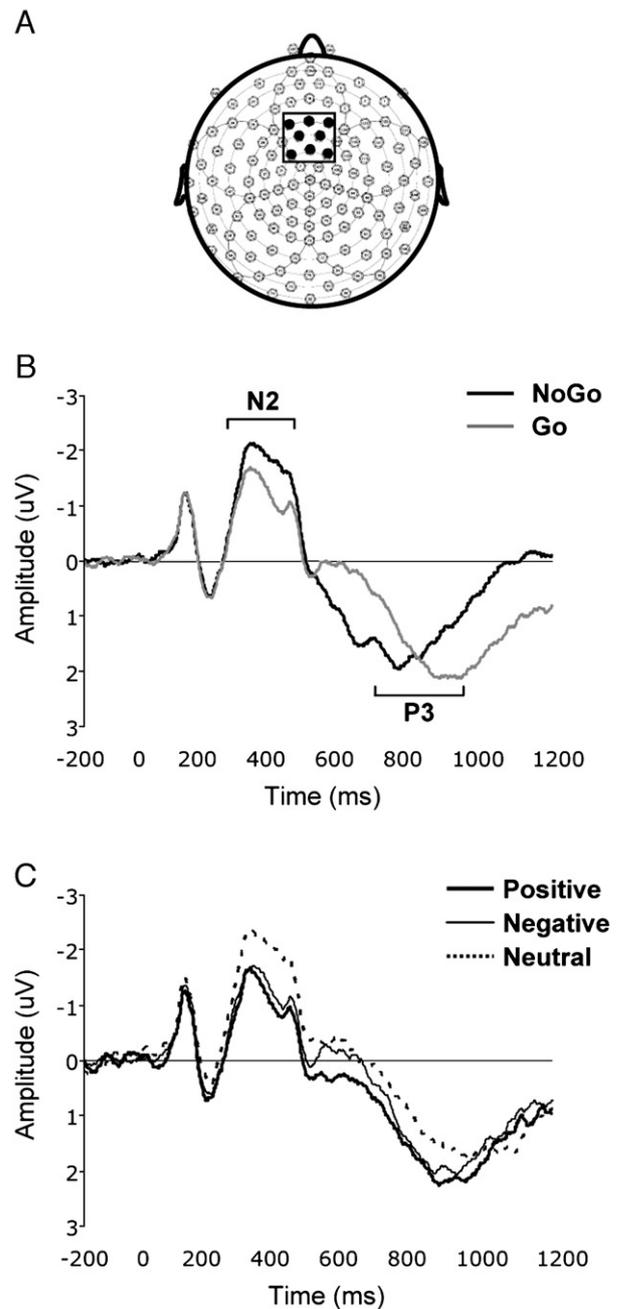
That is, subjects exhibited high levels of accuracy and target sensitivity across all conditions, response facilitation by affective cues (indicated by quicker responses to emotional versus neutral targets and increased response time following emotional stimuli versus neutral stimuli), and attentional engagement by affective stimuli (indicated by slower responses on trials following response inhibition to emotional versus neutral words).

Scalp ERP data

N2 amplitude

As hypothesized, NoGo stimuli elicited larger N2 amplitudes than Go stimuli across all sites (*Trial Type*: $F(1,22)=3.9$, $p=0.05$; Fig. 3B). This effect was qualified by a significant *Trial Type×Emotion* interaction, $F(2,44)=4.9$, $p<0.02$. Parsing of this interaction revealed that among Go trials, Neutral words elicited enhanced N2 magnitude relative to Positive and Negative words (*Emotion*: $F(2, 44)=6.8$, $p<0.004$; Neutral vs. Positive, $p<0.005$; Neutral vs. Negative, $p<0.02$; Table 1 and Fig. 3C). N2 amplitude did not differ between Positive and Negative Go words ($F(1,22)=1.3$, $p>0.26$). Among NoGo stimuli, no main effects of *Emotion* on N2 amplitude were observed, $F(2, 44)=.32$, $p>0.72$; Table 1.

P3 amplitude

Consistent with our hypotheses, NoGo stimuli evoked greater P3 amplitudes than Go stimuli across all sites (*Trial Type*: $F(1,22)=9.8$, $p<0.005$). The *Trial Type×Emotion* interaction was also significant, $F(2,44)=4.6$, $p<0.025$. Specifically, Positive and Negative Go words elicited enhanced P3 relative to Neutral words (*Emotion*: $F(2,44)$ 6.1, $p<0.005$; Neutral vs. Positive, $p<0.007$; Neutral vs. Negative, $p<0.04$; Table 1 and Fig. 3C). P3 amplitude did not differ between Positive and Negative Go words ($F(1,22)=1.5$, $p>0.23$). For NoGo stimuli, the main effect of *Emotion* was not significant ($F(2,44)=0.64$, $p>0.53$).

Source localization data

As hypothesized, response inhibition identified a cluster in the right lateral PFC (inferior frontal gyrus, Brodmann area 44) in which current density to NoGo trials was significantly greater than to Go trials (*Trial Type*: peak voxel; $t(23)=2.3$; $p<0.01$; 3 voxels; see Table 1 for current density values). As illustrated in Fig. 4A, the identified IFG cluster in the current affective Go/NoGo task lies at the center of activation loci identified in fMRI studies of response inhibition across a variety of stimulus types and response modalities.
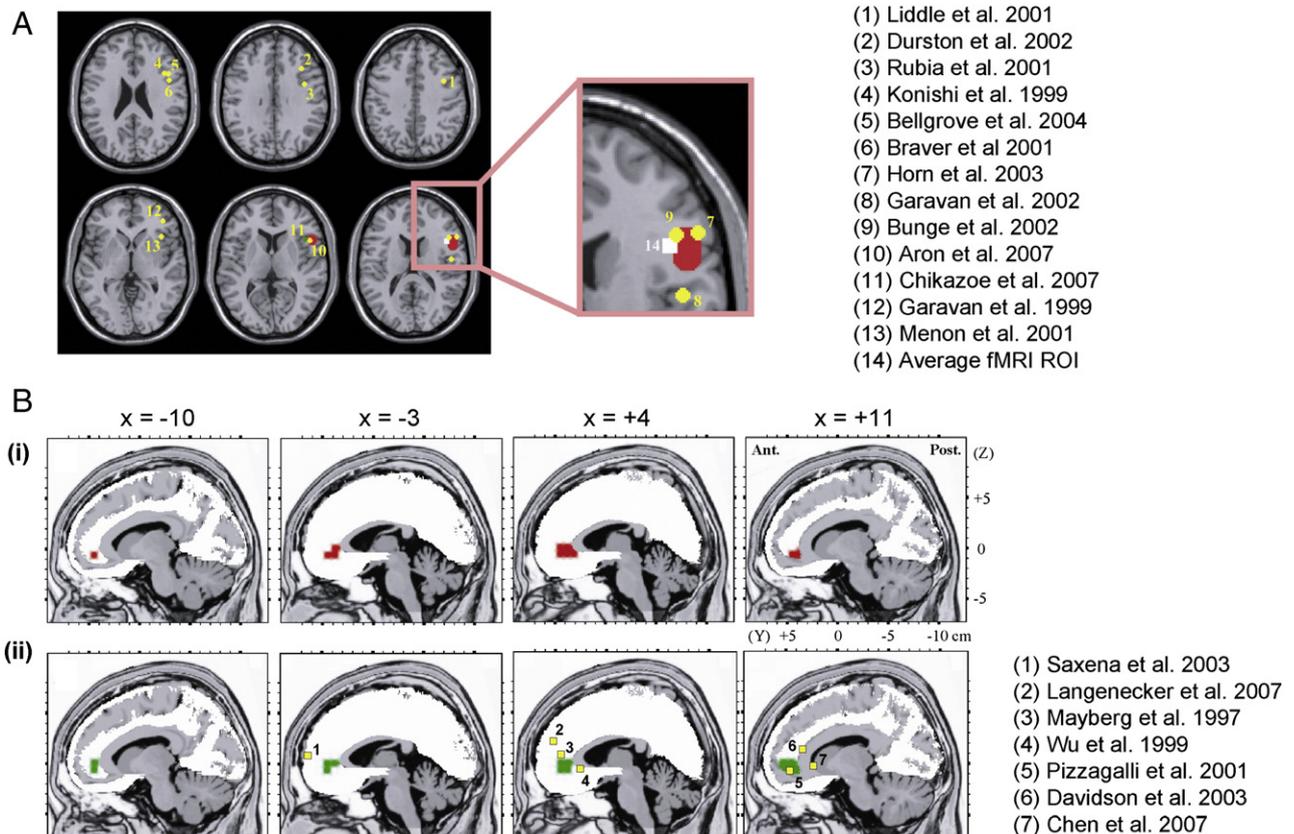

(1) Liddle et al. 2001
(2) Durston et al. 2002
(3) Rubia et al. 2001
(4) Konishi et al. 1999
(5) Bellgrove et al. 2004
(6) Braver et al 2001
(7) Horn et al. 2003
(8) Garavan et al. 2002
(9) Bunge et al. 2002
(10) Aron et al. 2007
(11) Chikazoe et al. 2007
(12) Garavan et al. 1999
(13) Menon et al. 2001
(14) Average fMRI ROI

(1) Saxena et al. 2003
(2) Langenecker et al. 2007
(3) Mayberg et al. 1997
(4) Wu et al. 1999
(5) Pizzagalli et al. 2001
(6) Davidson et al. 2003
(7) Chen et al. 2007

Fig. 4. Source localization analyses reveal inferior frontal gyrus activation to response inhibition and rostral anterior cingulate cortex activation modulated by affective valence. (A) Response inhibition on the emotional Go/NoGo task activated a cluster in the ventral lateral prefrontal cortex (VLPFC; inferior frontal gyrus; Brodmann area 44). This region of inferior frontal gyrus lies at the center of activations elicited in fMRI studies of response inhibition across a variety of stimulus types and response modalities. Red voxels indicate regions in the present task where current density to NoGo trials was significantly greater than to Go trials at the time of the average peak amplitude N2 NoGo ERP component (i.e., ~330 ms following stimulus presentation). Yellow circles indicate peak BOLD activations identified to response inhibition in the indicated fMRI papers. The white square denotes the mean fMRI coordinates of peak VLPFC activations across the listed studies. (B) Affective valence modulated activation within the rACC/vmPFC (Brodmann area 10/32). Activations are plotted in MNI space, origin at the anterior commissure. (i) In the cluster highlighted in red, current density was significantly higher in response to Negative words than either Neutral or Positive words. (ii) The cluster emerging from the present analyses overlaps with rACC/vmPFC regions whose pre-treatment hyperactivation has been found to predict eventual symptom improvement across a variety of treatment modalities in major depression (yellow voxels; studies listed at right). This region also overlaps with voxels in bilateral rACC (BA 24/32) previously identified by our group to predict degree of treatment response in major depressive disorder (Pizzagalli et al., 2001; voxels highlighted in green).

Emotional valence further identified a significant activation in rACC/vmPFC (Brodmann area 10/32; *Emotion*: peak voxel *F* (2,44)=6.4; *p*<0.006; cluster size 11 voxels). Post-hoc pairwise comparisons indicated that current density on Go trials was enhanced for Negative trials compared with both Neutral and Positive trials (Negative vs. Neutral, *p*<0.007; Negative vs. Positive, *p*<0.04; Neutral vs. Positive, *p*>0.1; see Table 1 for current density values). As illustrated in Fig. 4B, the identified region of rACC/vmPFC overlaps both with activations identified in fMRI affective Go/NoGo studies in controls (Elliott et al., 2000; Shafritz et al., 2006) and also with rACC regions predictive of therapeutic response in major depression (Chen et al., 2007; Davidson et al., 2003; Langenecker et al., 2007; Mayberg et al., 1997; Pizzagalli et al., 2001; Saxena et al., 2003; Wu et al., 1999).

To assess for differences in the recruitment of IFG and rACC in emotion-modulated response inhibition, we subjected the average current density in the N2 time window in these regions-of-interest (ROIs) to a *Region* (IFG, rACC)×*Trial Type* (Go, NoGo)×*Emotion* (Positive, Negative, Neutral) repeated measures ANOVA. All current density values and standard deviations are reported in Table 1. This analysis revealed main effects of *Region, Trial Type* and *Emotion*, such that current density: a) in the rACC was greater than that in the IFG (*Region: F*(1,22)=14.2, *p*<0.002); b) to NoGo trials was greater than to Go trials (*Trial Type: F*(1,22)=9.2, *p*<0.007); and c) was enhanced for Negative trials compared with both Positive and Neutral trials (*Emotion: F* (2,21)=7.1, *p*<0.005; Negative vs. Positive, *p*<0.009; Negative vs. Neutral, *p*<0.002; Positive vs. Neutral, *p*>0.1). Of particular importance, the ANOVA further revealed that IFG and rACC were differentially recruited by Trial Type and Emotion (*Region×Trial Type×Emotion*: *F*(2,21)=3.9, *p*<0.04). Parsing of this interaction demonstrated that in IFG, significant differences in current density were observed only to *Trial Type* and not *Emotion* (*Trial Type*: *F*(1,22)=22.3, *p*<0.0001; *Emotion*: *F*(2,44)= 2.6, *p*>0.1; *Emotion×Trial Type*: *F*(2,44)=93, *p*>0.4). In contrast, in the rACC/vmPFC, current density differences were observed only to *Emotion* and not *Trial Type* (*Emotion*: *F*(2,44)= 6.4, *p*<0.005; *Trial Type*: *F*(1,22)=1.8, *p*>0.1; *Emotion×Trial Type*: *F*(2,44)=2.3, *p*>0.1). Thus, these data support the hypothesis that rACC and IFG play differential and dissociable roles in emotion-modulated response inhibition.

Discussion

In the present study, we characterize spatial and temporal aspects of neural responses to emotion-modulated response inhibition. Specifically, we show enhanced magnitude of early and late ERP NoGo components and right IFG activity to affective response inhibition. Second, we show that activation of the rACC/vmPFC and ERP Go components differentiates emotional from neutral cues. The implications of these data for understanding emotional response inhibition and major depression are discussed below.

First, these data show that response inhibition to affective stimuli engages a timecourse of neural responses similar to those seen in tasks that require only perceptual distinction of stimuli (e.g., differentiating sounds, letters, or symbols). Specifically, subjects showed enhanced NoGo N2 and P3 components to emotional NoGo stimuli (Fig. 3B). As noted earlier, the NoGo N2 and P3 are highly sensitive to the degree to which "Go" stimuli establish a tendency to make a prepotent (but incorrect) response and likely reflect cognitive control

elicited by task demands (Eimer, 1993; Falkenstein et al., 1999; Fallgatter and Strik, 1999; Jackson et al., 1999; Jodo and Kayama, 1992; Kirmizi-Alsan et al., 2006; Kok et al., 2004; Nieuwenhuis et al., 2003; Nieuwenhuis et al., 2004; Pfefferbaum et al., 1985). The robust NoGo N2 and P3 highlight that identifying emotional valence, while a more abstract task demand than the perceptual discrimination of letters or sounds, is sufficient for establishing a prepotent response tendency. Moreover, the absence of NoGo ERP differentiation to emotional valence suggests that positive and negative stimuli established similar prepotent tendencies.

While the NoGo N2 and P3 components did not vary as a function of affective valence, the ERPs to Go stimuli varied according to affective intensity (Fig. 3C). That is, the enhanced N2 to neutral words and enhanced P3 to both positive and negative target words identify a clear effect of arousal (affective intensity) and do not show an effect of affective valence (pleasantness versus unpleasantness; for discussion of arousal and valence, see Bradley and Lang, 2007). While many studies have identified modulation of early ERP components by emotional pictures (for review see, Olofsson et al., 2008), these differences have not been well-characterized when using affective words. Nonetheless, substantial evidence indicates that early ERP components reflect attentional processes triggered by task demands (for review, see Fabiani et al., 2007), and the enhanced N2 to neutral Go stimuli may reflect enhanced cognitive resources allocated to this stimulus category. In support of this idea, subjects exhibited diminished accuracy, increased response time, and decreased discriminability to neutral target words, suggesting that identifying neutral targets among emotional distractors required enhanced attentional resources. In comparison, in later ERP components, arousal effects tend to be more common than valence effects (for reviews, see Bradley and Lang, 2007 and Olofsson et al., 2008), and the enhanced P3 to emotional target words is consistent with reports of greater late positive potentials to emotional relative to neutral cues, likely reflecting cognitive engagement by motivationally salient stimuli (Bradley et al., 1992; Cuthbert et al., 2000; Diedrich et al., 1997; Dolcos and Cabeza, 2002; Naumann et al., 1992; Schupp et al., 2000; Schupp et al., 2004).

The differentiation of both the N2 and P3 to affective arousal is reflected in the behavioral reaction time differences observed in the current study. In particular, subjects were quicker to respond to both positive and negative relative to neutral words; responses following both positive and negative words were faster than those following neutral words; and response inhibition to both positive and negative words led to slower RTs on immediately following trials than those following response inhibition to neutral words. Together, the data suggest the utility of ERP methods in conjunction with the affective Go/NoGo task for precisely delineating both the neural dynamics of emotion-modulated response inhibition and potential anomalies in psychiatric pathologies characterized by difficulty disengaging from affective triggers (e.g., Casey et al., 2007; Elliott et al., 2004; Siegle et al., 2002).

Source localization analyses of the current ERP data identified activations that mirror those previously reported in fMRI studies across a variety of response inhibition paradigms. First, we observed reliable neural responses in the same IFG areas seen with fMRI in successful inhibitory control to perceptual and affective stimuli (Aron et al., 2003, 2007; Bellgrove et al., 2004; Braver et al., 2001; Bunge et al., 2002; Chikazoe et al.,

2007; Durston et al., 2002; Garavan et al., 1999, 2002; Horn et al., 2003; Konishi et al., 1999; Lavric et al., 2004; Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001). We further show that IFG activation only differentiates response inhibition from response trials, and does not distinguish specific emotional valence categories.

Equally important, we observed robust neural responses in the rACC/vmPFC to emotional words; response inhibition did not differentially elicit rACC activation. This identified cluster overlaps with fMRI activation loci emerging from affective Go/NoGo paradigms incorporating facial and word stimuli (Elliott et al., 2000; Shafritz et al., 2006). These studies also report greatest rACC activation to negative stimuli and no effects of response inhibition. Increasing evidence suggests that rACC is generally activated by affective cues, regardless of whether response inhibition is evoked, and that these neural responses may be particularly sensitive to negative stimuli. In line with this hypothesis, robust rACC activation has been identified in studies of emotion incorporating a diverse range of stimulus modalities and tasks, including emotional Stroop tasks, passive-viewing or decision-making about emotional words, pictures or faces, resolution of emotional conflict, and self-generated emotion (Bush et al., 2000; Canli et al., 2004; Damasio et al., 2000; Dolcos and McCarthy, 2006; Etkin et al., 2006; Keightley et al., 2003; Maddock et al., 2003; Phan et al., 2003; Whalen et al., 1998). In the current study, the functional dissociation between right IFG and rACC/vmPFC regions was supported by a significant *Region×Trial Type×Emotion* interaction.

Implications for major depression and treatment

The above-mentioned rACC regions also overlap with brain areas implicated in treatment response in major depressive disorder. Specifically, activation in the rACC *before* treatment has been found to predict eventual symptom improvement across a variety of therapies of major depression (Chen et al., 2007; Davidson et al., 2003; Langenecker et al., 2007; Mayberg et al., 1997; Pizzagalli et al., 2001; Saxena et al., 2003; Wu et al., 1999); Fig. 4B). Rostral ACC anomalies also normalize following successful treatment (Awata et al., 2002; Brody et al., 2001a,b; Fu et al., 2004; Holthoff et al., 2004; Mayberg et al., 2000; Walsh et al., 2007). The affective Go/NoGo paradigm has begun to be implemented with clinical populations (Alexopoulos et al., 2007; Elliott et al., 2002; Elliott et al., 2004; Wessa et al., 2007), and this and similar tasks may be used as functional assays targeting discrete brain regions that have been associated with favorable treatment outcome, providing an easy-to-implement and cost-effective assessment with prognostic utility for individuals with major depressive disorder (Mayberg, 2007).

Given the hypothesized role of the ACC in depression, we performed post-hoc exploratory analyses on depression symptoms in our subjects (assessed with the Beck Depression Inventory-II) and neural activation in the rACC. Subjects were divided via median split into "high" (≥8; $N=11$; mean 13.8±4.7) and "low" BDI (≤7; $N=12$; mean 4.1±2.1) groups. A *Group* (high BDI, low BDI)×*Trial Type* (Go, NoGo)×*Emotion* (Positive, Negative, Neutral) on current density in the rACC revealed a significant interaction involving BDI group (*Group×Trial Type×Emotion*: $F(2,42)$ 5.7; $p<0.008$). Parsing of this interaction indicated that the high BDI group showed modulation of rACC activation by Trial Type (*Emotion×Trial Type*: $F(2,20)=9.1$, $p<0.003$) such that Negative targets elicited enhanced rACC activation relative to both Positive and Neutral targets (*Emotion*: $F(2,20)=3.7$, $p<0.05$;

Negative vs. Positive $p<0.03$; Negative vs. Neutral, $p<0.04$). The low BDI group showed no such differentiation (*Emotion×Trial Type*: $F(2,20)=0.18$, $p>0.8$). Moreover, parallel analyses examining subjects "high" (≥155; $N=11$; mean 168.5±7.6) and "low" (≤154; $N=12$; mean 141.6±10.0) on the Affective Intensity Measure revealed no *Group×Trial Type×Emotion* effects ($F(2,42)=0.08$; $p>0.9$). While these are exploratory analyses conducted in a small non-clinical sample, the data provide preliminary evidence for the specificity of the identified rACC activation to depression-related symptoms.

Limitations and future directions

The limitations of the current work suggest directions for future research. First, the use of words instead of pictorial stimuli may have attenuated neural responses on affective NoGo trials. Although we observed robust ERP and rACC differences to emotional target words, images are considered more salient than words (Dolcos and Cabeza, 2002), and it is possible that with more salient stimuli, differentiation of NoGo ERPs by affective valence may also be observed. Second, subjective stimulus ratings were not obtained in the current study (our subjects are likely similar to those in whom the word stimuli were validated; Bradley and Lang, 1999); however, subjective experience may modulate neurobehavioral responses to affective cues. As a preliminary examination of this issue, we performed correlation analyses between Affective Intensity Measure scores (Larsen and Diener, 1987) and behavioral performance on the emotional Go/NoGo task. These analyses revealed modest associations between AIM scores and behavioral accuracy ($r=0.42$, $p=0.05$; $r=0.324$, $p=0.13$, two-tailed, for distractors and targets, respectively) and suggests individual differences in affective response inhibition as an area of future investigation. Finally, the limited spatial resolution of our chosen source localization technique (Pizzagalli, 2007) hinders the examination of functional connectivity of cortical with subcortical regions (e.g., amygdala) that have also recently been implicated in emotion regulation and depression (Etkin et al., 2006; Pezawas et al., 2005; Ressler and Mayberg, 2007). Nonetheless, the present data identify right IFG and rACC/vmPFC regions that overlap with fMRI activation loci from prior studies using Go/NoGo tasks (Fig. 4). This cross-modal validity suggests that ERP techniques in conjunction with the present emotional Go/NoGo task can be used as an economical and reliable assessment tool for probing IFG and rACC regions.

In summary, we show that emotional valence is sufficient to evoke prepotent response tendencies, and we identify the timecourse and regional specificity of neural responses that a) are enhanced to affective NoGo response inhibition (NoGo N2, P3, and IFG), and b) differentiate emotional valence (Go N2, P3, and rACC). Ultimately, the quantification of neural and behavioral endophenotypes using standardized neural responses elicited in the context of this or other well-characterized paradigms may aid in the objective characterization of psychiatric symptom severity and therapeutic response.

Disclosure

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