Insula and Orbital Frontal Cortex Activity Underlying Emotion Interference Resolution in Working Memory

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Abstract

■ Previous research has shown that emotional information aids conflict resolution in working memory [WM; Levens, S. M., & Phelps, E. A. Emotion processing effects on interference resolution in working memory. *Journal of Emotion, 8,* 267–280, 2008]. Using a recency-probes WM paradigm, it was found that positive and negative emotional stimuli reduced the amount of interference created when information that was once relevant conflicted with currently relevant information. To explore the neural mechanisms behind these facilitation effects, an event-related fMRI version of the recency-probes task was conducted using neutral and arousing positive and negative words as stimuli. Results replicate previous findings showing that the left and right inferior frontal gyrus (IFG) is involved in the interference resolution of neutral information and reveal that the IFG is involved in the interference resolution of emotional information as well. In addition, ROIs in the right and left anterior insula and in the right orbital frontal cortex (OFC) were identified that appear to underlie emotional interference resolution in WM. We conclude that the IFG underlies neutral and emotional interference resolution, and that additional regions of the anterior insula and OFC may contribute to the facilitation of interference resolution for emotional information. These findings clarify the role of the insula and OFC in affective and executive processing, specifically in WM conflict resolution. ■

INTRODUCTION

It is through working memory (WM) that we are able to sift through the plethora of information we encounter in our daily lives to isolate the stimuli that are relevant to a task or situation. To isolate relevant information, the contents of WM must be updated continually so that relevant information is selected and maintained whereas irrelevant information is not (Jonides & Nee, 2006; Shimamura, 2000; Anderson, Reder, & Lebiere, 1996; Baddeley, 1996). As the contents of WM are updated, interference arises amidst the contents of WM as the representations compete for cognitive resources. To cope with interference, interference resolution protects the contents of WM by resolving conflict between competing WM representations (Jonides & Nee, 2006). For example, when trying to remember a new acquaintance's name after being introduced to a group of people, interference resolution prevents the previously learned names from interfering with the recall of the most recent name by selecting one response and inhibiting others. Due to common occurrences of interference between representations in WM, many researchers have proposed that WM as a system evolved to cope with interference (e.g., Engle, 2005).

Despite the importance of interference resolution in WM processing, little is known about how emotional information interacts with conflict resolution between competing representations in WM. Multiple studies have examined emotional interference in the context of attention and response inhibition. Research using emotion Stroop tasks has found that emotional information impairs performance by capturing attention (Whalen, Bush, Shin, & Rauch, 2006), whereas studies using the emotion go/no-go paradigm have found that participants are slower to approach fearful target expressions and have more difficulty avoiding happy nontarget expressions revealing that emotional information selectively affects response inhibition (Hare, Tottenham, Davidson, Glover, & Casey, 2005). To our knowledge, however, only one study, by Levens and Phelps (2008), has examined the effect of emotion on the resolution of interference between *competing WM representations*. Levens and Phelps found that emotional information facilitates the resolution of interference between competing WM representations; specifically, interference was resolved faster for negative and positive emotional information than for neutral information. Our goal in this article was to enhance the understanding of interference resolution within WM by determining what brain regions underlie emotion's impact on interference resolution.

A common way to measure the effect of interference on WM performance is to use the recency-probes paradigm. On the basis of the research by Monsell (1978), the recency-probes task examines interference resolution

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in WM by inducing interference between current and prior representations of a stimulus in WM. On select trials, source recognition and familiarity are placed in conflict that induces interference that must be resolved to respond to the trial. The interference lengthens RT, an increase that is then operationally measured as the RT difference between trials with interference and those without. Recent imaging studies conducted with neutral stimuli in this task have suggested that the inferior frontal gyrus (IFG) underlies interference resolution within WM (e.g., Nee, Wager, & Jonides, 2007; Badre & Wagner, 2005; Thompson-Schill et al., 2002; D'Esposito, Postle, Jonides, & Smith, 1999; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998). The original imaging recency-probes study conducted by Jonides et al. (1998) using verbal stimuli (letters) with PET found a region of activation within the left IFG which corresponded to the increase in RT present in interference versus noninterference trials. As follow-up, to determine if the IFG region showed greater activity at the point at which interference occurred within a trial, D'Esposito et al. (1999) conducted an event-related fMRI study of the recency-probes task. Their findings supported the findings of Jonides et al. (1998) and further revealed that only at the point of interference, when subjects were required to respond, was there an increase in activation in the left IFG region. Finally, Badre and Wagner (2005) conducted the task with words instead of letters and found bilateral increases in activation in the IFG region for interference versus noninterference trials, suggesting that the right IFG may be involved in interference resolution as well.

Imaging findings, therefore, seemed to point primarily to the left and right IFG as the region of the brain that mediates verbal interference resolution in WM. To test this hypothesis and to explore the regions critical to interference resolution, Thompson-Schill et al. (2002) conducted a pFC lesion study using the same recency-probes paradigm. They identified patient R.C., who had a lesion in the left IFG that extended medially into the insula, the same region identified by Jonides et al. (1998). No patients with right IFG damage performed the task. Patient R.C. showed a selective increased susceptibility to interference, indicating that the left IFG region found by D'Esposito et al. (1999) and Jonides et al. may be critical to interference resolution.

Interestingly, alternate tasks that the measure the effects of interference on performance have found that it is not the IFG region that mediates interference but rather an adjacent region, the insula. In a related fMRI study, Wager et al. (2005) measured interference across three tasks: a go/no-go task, a stimulus-response compatibility task, and a flanker task. Wager et al. found that the bilateral insula was the region that correlated significantly with behavioral measures of interference across all three tasks, suggesting that the insula may mediate interference resolution more generally. Although at first glance the IFG and the insula results appear incompatible, the regions are adjacent, and different peak voxels of overlapping activation maps may account for the differences across studies. In support of this, the individual subject data presented in the examination of the recency-probes paradigm by D'Esposito et al. (1999), one of the first studies to isolate the IFG region, also shows consistent increases in insula activation for interference versus noninterference trials across subjects. Furthermore, recent investigations have found that the insula, particularly the anterior insula, may be critical to cognitive control. For example, a meta-analysis by Wager and Feldman Barrett (2004) found that the anterior insula is commonly activated in tasks that require executive control and attention, including WM manipulation tasks (Wager & Smith, 2003), response inhibition tasks (Nee et al., 2007), and attention shifting tasks (Wager, Jonides, & Reading, 2004).

Although prior research has explored interference resolution for neutral information and identified the IFG and insula as critical regions in this process, little research has been conducted to examine what regions of the brain may be involved in the resolution of interference between conflicting representations of emotional information in WM. Prior research has, however, examined what brain regions mediate the effect of emotional information on response inhibition and attention. An emotion go/no-go task conducted by Hare et al. (2005) revealed that increased activity in the amygdala was associated with detecting negative emotional information, whereas activity in the right caudate was observed when avoiding positive emotional information. In addition, emotional Stroop tasks modified for fMRI reveal consistent activation in the rostral and ventral ACC for avoiding interference associated with emotional stimuli (Shin et al., 2001; Whalen et al., 1998). However, as the emotion go/no-go task measures interference as a function of response inhibition and the Stroop task measures attentional interference, the results of those studies do not clarify what regions of the brain are mediating interference resolution between conflicting emotional information in WM.

To examine emotional interference resolution within WM, we adapted the behavioral emotion recency-probes task conducted by Levens and Phelps (2008) for fMRI. Levens and Phelps compared interference resolution RTs for neutral, positive, and negative stimuli and found that interference was resolved faster for both positive and negative arousing stimuli than for neutral stimuli, indicating that arousal, regardless of valence, reduces interference compared with neutral stimuli. On the basis of these findings, they concluded that highly arousing emotional stimuli facilitates interference resolution within WM, specifically the valence and arousal components of emotional information provide an additional context at encoding that helps resolve any subsequent interference to aid responding to the trail. In the context of previous interference resolution imaging and patient research, the above behavioral findings indicate that interference resolution may be facilitated by emotion in three ways: (1) different neural mechanisms may mediate interference resolution for emotional versus neutral

information, (2) additional neural mechanisms to those that mediate interference resolution for neutral information may be involved, or (3) the same neural mechanisms that mediate neutral interference may respond differently to emotional stimuli.

As the anterior insula has been implicated in both interference resolution and tasks that require executive control (Nee et al., 2007; Badre & Wagner, 2005; Wager et al., 2005; Fan, Flombaum, McCandliss, Thomas, & Posner, 2003) and emotion processing, specifically the processing of emotional information and the experience of emotion (Blood & Zatorre, 2001; Damasio et al., 2000; Mayberg et al., 1999; Phillips et al., 1997; Reiman et al., 1997), we hypothesize that this region in particular may be integral to the emotion facilitation effect isolated by Levens and Phelps (2008). As the insula is a relay station, receiving input from and sending signals to other subcortical and cortical regions that process emotional information (Wager & Feldman Barrett, 2004; Craig, 2002), other regions of the brain may also be involved in the emotional facilitation of interference resolution in WM. The orbital frontal cortex (OFC), for example, is integral to the temporal monitoring of emotional information for reward and contingency changes. The OFC has also been implicated as a region that gates the influence of emotion on other cortical regions (Rule, Simammura, & Knight, 2002), with strong reciprocal connections to the anterior insula. Given this, this region may also play a role the facilitation of interference resolution for emotion in WM (Hikosaka, Nakamura, & Nakahara, 2006; Rolls, 1996, 2004). Additionally, the rostral ACC, which is thought to be an affect attention monitoring region (Whalen et al., 1998), and the ventral ACC, which is thought to be an affective "regulatory" region (Mayberg, 2007), may be involved in emotional interference resolution within WM as well.

On the basis of previous interference resolution and emotion imaging and lesions studies therefore, we hypothesize (1) that the IFG will function as a generalized interference resolution region, mediating both neutral and emotional interference, (2) that regions of the insula may specifically mediate emotional interference, and (3) that additional regions such as the OFC and the ACC may play a role in the emotional facilitation of interference resolution in WM.

METHODS

Subjects

Twenty-seven participants (10 men, 17 women) aged 18 years and older gave informed consent and were compensated $25 per hour.

Stimuli

A total of 590 emotional and neutral words (260 emotional, 330 neutral) from the Affective Norms for English Words battery developed by Bradley and Lang (1999) were selected as stimuli. Each word was selected on the basis of valence and arousal ratings provided by Bradley and Lang to form three groups of words: neutral words (e.g., chair, bread), negative valence, high arousal words (e.g., mutilation, terror, murder), and positive valence, high arousal words (e.g., desire, treasure, erotic). The mean, range, and standard deviation for each of the three word groups are presented in Table 1.

Behavioral Task Design

The experiment was divided into two sessions, distinguished by the stimulus set used. The two sessions were performed over two consecutive days to avoid fatigue. One session, the positive valence session, used positive and neutral words as stimuli, whereas the other session, the negative valence session, used negative and neutral words for stimuli. The presentation order of the two sessions was counterbalanced across subjects.

The experimental procedure was the same for each session. Instructions about the experiment were given to participants in both oral and written form. The design was a within-subjects recency-probes proactive interference task modified from D'Esposito et al. (1999) and Jonides et al. (1998). The experiment consisted of 360 trials separated into 12 blocks of 30 trials as well as an additional 16 practice trials that were not scored in data analysis. For each session, participants completed eight practice trials followed by 180 experimental trials separated into 6 blocks of 30 trials. For each trial, participants saw a target

Table 1. Interference and Noninterference Trial Reaction Times for Each Condition in Each Valence Session

Trial Types	*M (SD)*	*Accuracy (%)*	*RT Difference Score*
Positive Valence Session			
Neutral condition			
Noninterference	800 (125)	94	109
Interference	909 (166)	95	
Emotion condition			
Noninterference	834 (135)	95	43
Interference	877 (149)	96	
Negative Valence Session			
Neutral condition			
Noninterference	814 (139)	89	101
Interference	915 (182)	90	
Emotion condition			
Noninterference	831 (142)	89	50
Interference	881 (161)	92	

set of three words displayed on the computer screen for 2000 msec, followed by a variable delay of either 4000, 6000, or 8000 msec during which a fixation cross was presented, followed by the presentation of a single probe word for 2000 msec. A variable intertrial interval (ITI) with a range of 4,000 to 16,000 msec separated each trial. Participants were instructed to indicate as quickly and accurately as possible whether or not the probe word matched a word in the current target set by pressing buttons corresponding to "Yes" or "No" on a button box.

The positive valence session consisted of blocks that had both positive and neutral word trials and blocks that had only neutral word trials. Similarly, the negative valence session consisted of blocks with both negative and neutral word trials and blocks with only neutral word trials. Emotional words for both sessions were placed strategically to permit an examination of the effects of emotion on interference resolution in WM. Trial target sets had a minimum of one emotional word and a maximum of three emotional words; most trials had two emotional words. The presentation order of neutral and emotion blocks was counterbalanced to control for any order effects, such as the induction of an emotional state. Individual trials within a block were also counterbalanced so that "No" and "Yes" responses were equally likely to precede/follow each other. Finally, within each block, between-trial repetitions of target items were equally likely to precede "No" and "Yes" responses and recent and nonrecent trials.

For purposes of subsequent data analysis, two conditions were defined in each valence session: a neutral condition, which included trials with all neutral words, and an emotion condition, which consisted of trials in which the probe words were emotional (see Figure 1 for trial examples). For each valence session, the emotion condition is referred to by its specific valence (i.e., negative and positive). Trials were separated into four trial types: (1) recent no-response trials, in which the probe does not match any items in the target set of the present trial but does match an item from the target set of the past two trials; (2) nonrecent no-response trials, in which the probe does not match items from the current or the past two target sets; (3) recent yes-response trials, in which the probe matches an item from the current target set as well as an item from each of the two preceding target sets; and (4) nonrecent yes-response trials, in which the probe matches an item from the current target set but not from the preceding two target sets.

Proactive interference was introduced in the recent no-response trials because a decision that was based on what was coded into short-term memory during the current trial was put into competition with the probe's encoding into WM during the previous two trials. Because the probe of a recent no-response trial was not in the current target set, source recognition dictated a correct negative response of "No." However, the probe of a recent no-response trial was in the two previous target sets, inducing familiarity. Familiarity and source recognition were thus placed in conflict: source recognition supported a correct "No" response, whereas familiarity supported an incorrect "Yes" response. This source recognition/familiarity conflict

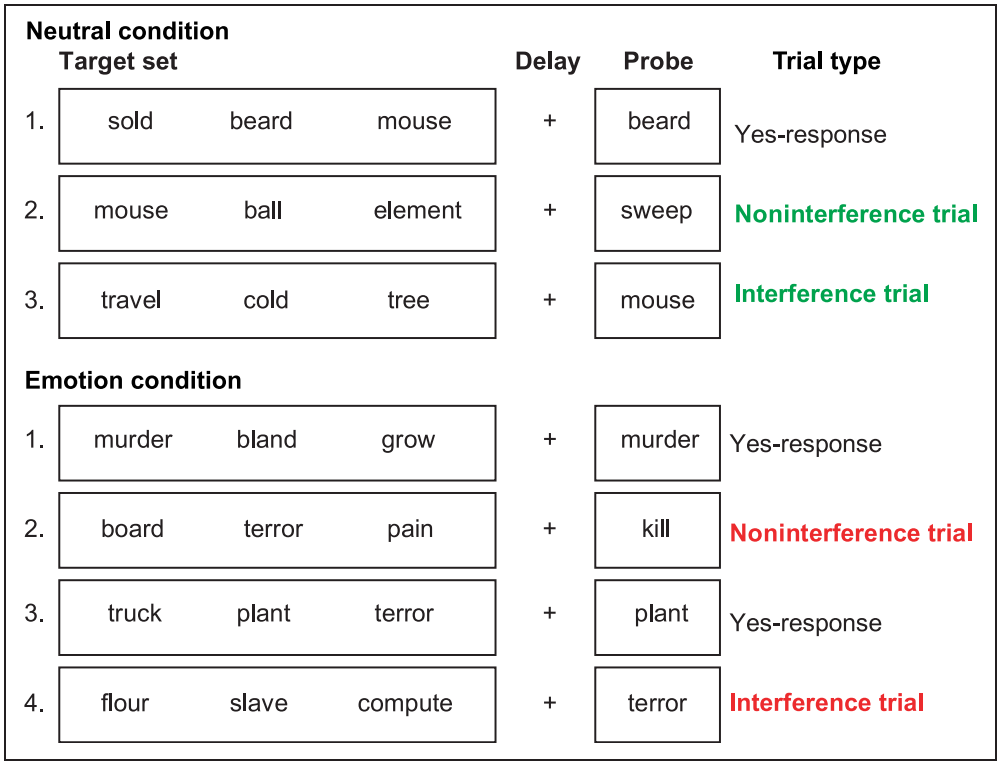

Figure 1. Sample trials and trial types from the neutral condition (all neutral words) and emotion condition (neutral and emotional words). The emotion condition trials above are examples of negative valence session trials. Positive valence session trials would show the same type of emotion word distribution throughout the trials, yet positive and neutral words would be used as stimuli. The trial types necessary for determining neutral condition interference levels are shown in bold green font (interference and noninterference trials), whereas the trial types used for emotion condition interference levels are shown in bold red font.

induced interference in WM. Because the interference must be resolved before the individual can respond, RTs in recent no-response trials or interference trials are longer than that in nonrecent no-response trials or noninterference trials (D'Esposito et al., 1999). The difference between recent no-response and nonrecent no-response trials, therefore, represents the amount of interference that must be resolved in recent no-response trials prior to response. In accordance with prior recency-probes paradigms (Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003; D'Esposito et al., 1999), data analysis focused on no-response trials as yes-response trials did not include any interference manipulations.[1] To simplify further discussion, we will refer to recent no-response trials as interference trials and nonrecent no-response trials as noninterference trials. The distinction between the neutral and the emotion conditions resulted in a total of four trial types for each positive and negative valence session: neutral interference trials, neutral noninterference trials, emotion interference trials, and emotion noninterference trials.

fMRI Data Acquisition

A 3-T Siemens Allegra scanner collected structural (T1-weighted MPRAGE: 256 × 256 matrix; field of view = 256 mm; 176 1-mm sagittal slices) and functional images (repetition time =2000 msec; echo time = 25 msec; field of view = 192 cm; flip angle = 80°; matrix = 64 × 64; slice thickness = 3 mm). Forty contiguous oblique-axial slices (3 mm^3 voxels) parallel to the AC–PC line were obtained. fMRI data were analyzed using Brain Voyager software. Preprocessing included motion correction (six-parameter, three-dimensional motion correction), spatial smoothing (4-mm FWHM), voxel-wise linear detrending, high-pass filtering, and normalization to Talairach stereotaxic space. Of the 27 participants in the study who completed both the positive and the negative valence sessions, two participants from the negative valence session were eliminated because of scanner malfunction, excessive movement, or corrupted data. No participants were eliminated from the positive valence session.

Behavioral Data Analysis

RT analyses were performed separately for the negative and positive valence sessions. For each valence session, RT means for all four trial types were analyzed in a 2 × 2 ANOVA comparing condition (neutral and emotion) and recency (interference and noninterference). Follow-up *t* tests were conducted to isolate any behavioral interference effects. Interference was measured as the RT difference between interference trials and noninterference trials (see Figure 1). Incorrect and outlier trials were excluded from the analysis. Outlier trials were identified as trials with RTs greater than 2.5 standard deviations from the mean.

fMRI Data Analysis

A random-effects analyses was performed for the negative and positive valence session data combined as well as each valence session separately. For the combined valence session random-effects analysis, a general linear model (GLM) was run that defined 30 regressors including target set, delay, ITI, and trials types for each neutral and emotion condition from each valence session. For the individual valence session random-effects analysis, a GLM was run that defined 16 regressors, including target set, delay, ITI, errors, and trials types for each neutral and emotion condition. All functional ROIs were defined via contrasts between interference and noninterference trials in the neutral and emotion conditions for the negative and positive valence sessions using a threshold of $p < .005$ with a cluster threshold of 10 voxels.

The following series of contrasts were conducted. First, a combined session conjunction analysis of interference and noninterference trials to identify regions that show a greater BOLD response to interference than to noninterference trials across all stimulus types (neutral, positive, and negative stimuli). Second, a combined session conjunction analysis of emotion interference and noninterference trials to identify regions that show a greater BOLD response to interference than to noninterference trials for emotional stimuli only (negative and positive stimuli combined). Third, a combined session conjunction analysis of neutral interference and noninterference trials was conducted to identify regions that show a greater BOLD response to interference than to noninterference trials for neutral stimuli only. Fourth, a combined session emotion interference trial contrast was conducted to identify regions that show a greater BOLD response to negative than to positive interference trials or vice versa. Fifth, to examine regions that process emotional information, irrespective of interference, we conducted a combined session emotion versus neutral noninterference trial contrast to identify regions that show a greater BOLD response to emotional than to neutral stimuli. Emotional versus neutral noninterference trials were used in this contrast because BOLD activity at probe in noninterference trials is the only way to directly compare emotional and neutral information encountered for the first time. The resulting functional ROIs are presented in Table 2.

For select functional ROIs (in bold in Table 2), we calculated the percent signal change for each no-response trial type; for further analysis, we selected the highest signal change value at either 4 or 6 sec following stimulus onset. These values were then used in repeated measures ANOVAs to examine interference differences across the neutral and emotion conditions of each valence session. For each ROI, an Interference (interference and

Table 2. GLM Interference versus Noninterference Trials

Area	*Hem*	*Session*	*Predictor*	*x*	*y*	*z*	*Size*
Combined Valence Sessions: Differentiates Neutral and Emotion Interference and Noninterference Trials							
IFG	**R**	**Comb**	**Int**	**45**	**15**	**2**	**987**
IFG	**L**	**Comb**	**Int**	**−46**	**14**	**2**	**940**
Caudate	R	Comb	Int	10	13	11	366
Lateral temporal lobe	R	Comb	Int	64	−25	−6	223
Lateral temporal lobe	L	Comb	Int	−60	−22	−7	258
Rostral prefrontal cortex	R	Comb	Int	27	48	28	305
Rostral prefrontal cortex	L	Comb	Int	−26	49	27	642
Cerebellum	R	Comb	Int	6	−62	−29	352
Combined Valence Sessions: Differentiates Emotion Interference and Noninterference Trials							
IFG	**R**	**Comb**	**Int**	**44**	**14**	**−1**	**383**
IFG	**L**	**Comb**	**Int**	**−44**	**16**	**0**	**102**
IFG	R	Comb	Int	49	−3	2	109
Anterior insula	**L**	**Comb**	**Int**	**−32**	**21**	**2**	**53**
OFC	**R**	**Comb**	**Int**	**33**	**24**	**−8**	**161**
Combined Valence Sessions: Differentiates Neutral Interference and Noninterference Trials							
IFG	R	Comb	Int	43	21	3	808
IFG	L	Comb	Int	−45	16	8	666
Caudate	R	Comb	Int	10	15	13	167
Caudate	L	Comb	Int	−10	14	14	76
Rostral prefrontal cortex	R	Comb	Int	27	52	29	683
Rostral prefrontal cortex	L	Comb	Int	−25	56	23	417
Lateral MFG	**L**	**Comb**	**Int**	**−44**	**34**	**10**	**409**
Cerebellum	R	Comb	Int	6	−62	−29	352
Combined Valence Sessions: Differentiates Negative and Positive Interference Trials							
Anterior insula	**R**	**Comb**	**Int**	**40**	**15**	**1**	**234**
Ventral OFC	**R**	**Comb**	**Int**	**21**	**12**	**−12**	**66**
Ventral anterior cingulate cortex	**R**	**Comb**	**Int**	**8**	**27**	**−4**	**57**
Combined Valence Sessions: Differentiates Emotional and Neutral Noninterference Trials							
Amygdala	**L**	**Comb**	**Non**	**−29**	**−5**	**−15**	**42**
Frontal gyrus	L	Comb	Non	−44	14	14	92
Individual Valence Sessions: Differentiates Neutral and Emotion Interference and Noninterference Trials							
IFG	R	Neg	Int	44	9	1	491
IFG	L	Neg	Int	−46	12	1	305

Table 2. (*continued*)

Area	*Hem*	*Session*	*Predictor*	*x*	*y*	*z*	*Size*
IFG	R	Pos	Int	45	13	0	725
IFG	R	Pos	Int	56	1	2	589
IFG	L	Pos	Int	−49	18	2	410
IFG	L	Pos	Int	−56	0	2	592
Mid insula	R	Neg	Int	37	7	9	434
Lateral prefrontal cortex	L	Neg	Int	−48	31	17	305
Doral prefrontal cortex	R	Pos	Int	23	50	25	417
Doral prefrontal cortex	L	Pos	Int	−18	50	29	333
Individual Valence Sessions: Differentiates Emotion Interference and Noninterference Trials							
IFG	R	Neg	Int	44	5	2	519
IFG	R	Pos	Int	49	15	0	242
IFG	L	Pos	Int	−43	16	12	66
Mid insula	R	Neg	Int	29	7	14	436
Mid insula	L	Neg	Int	−35	3	5	372
Mid insula	L	Neg	Int	−30	5	17	216
Anterior insula	R	Neg	Int	33	11	5	121
Anterior insula	L	Pos	Int	−33	24	2	57
OFC	R	Neg	Int	22	10	−13	119
OFC	R	Pos	Int	31	26	−8	171
Caudate	R	Pos	Int	13	9	20	74
Caudate	L	Pos	Int	−13	3	21	129
Thalamus	R	Pos	Int	13	−18	4	79
Thalamus	L	Pos	Int	−23	−19	6	147
Lateral temporal lobe	R	Pos	Int	64	−27	−4	425
Lateral temporal lobe	L	Pos	Int	−58	−29	−4	448
Individual Valence Sessions: Differentiates Neutral Interference and Noninterference Trials							
IFG	R	Neg	Int	42	7	6	171
IFG	R	Pos	Int	44	14	0	179
IFG	L	Neg	Int	−46	15	6	201
IFG	L	Pos	Int	−50	17	3	635
IFG	L	Pos	Int	−47	−3	4	520
Mid insula	L	Neg	Int	−33	5	15	175
Cerebellum	R	Neg	Int	40	−47	−26	90
Cerebellum	L	Pos	Int	−13	−46	−18	213

Centers of mass of significant contrasts between interference and noninterference trials. Areas in bold are discussed in the Results section. Hem = hemisphere (L = left; R = right); Session (Comb = combined sessions; Pos = positive session; Neg = negative session); Predictor, condition with the stronger BOLD response (Int = interference trials; Non = noninterference trials); *x*,*y*,*z* = Talairach coordinates; cluster size is provided in mm^3.

noninterference) × Condition (neutral and emotion) × Valence Session (negative and positive) ANOVA was conducted.

RESULTS

Behavioral Data

An Interference (interference and noninterference) × Condition (neutral and emotion) ANOVA was conducted on trial RTs from each valence session. The negative valence session ANOVA revealed a main effect of Interference, $F(1, 24) = 42.09, p < .001$, and a significant Interference × Condition interaction, $F(1, 24) = 8.13, p < .01$. Similarly, the positive valence session ANOVA revealed a main effect of Interference, $F(1, 26) = 44.64, p < .001$, and a significant Interference × Condition interaction, $F(1, 26) = 8.07, p < .01$. Follow-up t test comparisons revealed that the data replicate the basic proactive interference effect (D'Esposito et al., 1999; Jonides et al., 1998) as well as the emotion facilitation effect (Levens & Phelps, 2008). Interference trial RTs were significantly longer than noninterference trials in the neutral condition in both the negative, $t(24) = 6.3, p < .001$, and the positive, $t(26) = 6.2, p < .001$, valence sessions. In the emotion conditions of each valence session, however, the data pattern changed—the difference between interference and noninterference trials significantly decreased (see Table 1). Interference trial RTs were significantly shorter in the negative emotion condition, $t(24) = 2.45$, $p < .05$, and positive emotion condition, $t(26) = 2.09$, $p < .05$, than that in interference trials in the corresponding neutral conditions. This reduction of interference for emotional information underlies the Condition × Interference interaction and is consistent with previous data suggesting that both positive and negative emotional information aids interference resolution in WM (Levens & Phelps, 2008).

fMRI Data

The imaging data are presented in five sections. The first section describes regions that differentiate between interference and noninterference trials across all stimulus types (neutral, negative, and positive stimuli). The second describes regions that differentiate between interference and noninterference trials for neutral stimuli only. The third section describes regions that differentiate between interference and noninterference trials for only emotional stimuli, combining positive and negative valence. The fourth section describes regions that are valence sensitive, showing increased BOLD activation to either negative or positive interference trials. The final section describes regions that show increased BOLD response to emotional than to neutral stimuli, irrespective of interference.

Regions That Differentiate between Interference and Noninterference Trails across Stimulus Types

The combined session interference and noninterference trail contrast revealed two regions that showed greater bold activation for interference than for noninterference trials across all stimulus types (neutral, positive, and negative stimuli): the left and the right IFG (Figure 2). We extracted the BOLD responses of this region for negative and positive valence session, neutral and emotional interference, and noninterference trials. An Interference × Condition × Valence Session ANOVA of the left and right IFG, respectively, resulted in a main effect of Interference, $F(1, 25) = 24.39, p < .001, \eta^2 = .5$; $F(1, 25) = 19.54, p < .001, \eta^2 = .46$. There were no other significant main effects or interactions. This finding shows that the IFG responds to neutral and emotion condition interference trials, regardless of affective valence.

Regions That Differentiate Neutral Interference and Noninterference Trials

The combined session interference and noninterference trail contrast to identify regions that show a differential response to interference versus noninterference trials revealed one region that responded solely to neutral stimuli: the left middle frontal gyrus (MFG). An Interference × Condition × Valence Session ANOVA of the left lateral pFC showed a main effect of Interference, $F(1, 25) = 7.75, p < .01, \eta^2 = .24$, qualified by an Interference × Condition interaction, $F(1, 25) = 11.46, p < .01, \eta^2 = .32$. Follow-up paired t tests indicate that the interaction is due to significantly greater neutral interference than emotion interference BOLD responses, $t(52) = 2.631, p < .01$.

Regions That Differentiate Emotion Interference and Noninterference Trials

The combined session interference and noninterference trail contrast to identify regions that show a differential response to interference versus noninterference trials revealed two regions—the left anterior insula and the right OFC (Figure 3)—that showed greater BOLD activation for interference than for noninterference trails for both negative and positive stimuli. An Interference × Condition × Valence Session ANOVA of the left anterior insula showed a main effect of Interference, $F(1, 25) = 11.46, p < .01, \eta^2 = .31$, qualified by an Interference × Condition interaction, $F(1, 25) = 4.13, p < .05, \eta^2 = .15$. Follow-up paired t tests indicate that the interaction is due to significantly greater emotion interference than neutral interference BOLD responses, $t(52) = 2.487, p < .05$.

In addition to the insula, the right OFC also showed greater activation for emotional interference than noninterference trials. An Interference × Condition × Valence Session ANOVA of the right OFC ROI yielded a main effect of Interference, $F(1, 25) = 30.97, p < .01, \eta^2 = .58$,

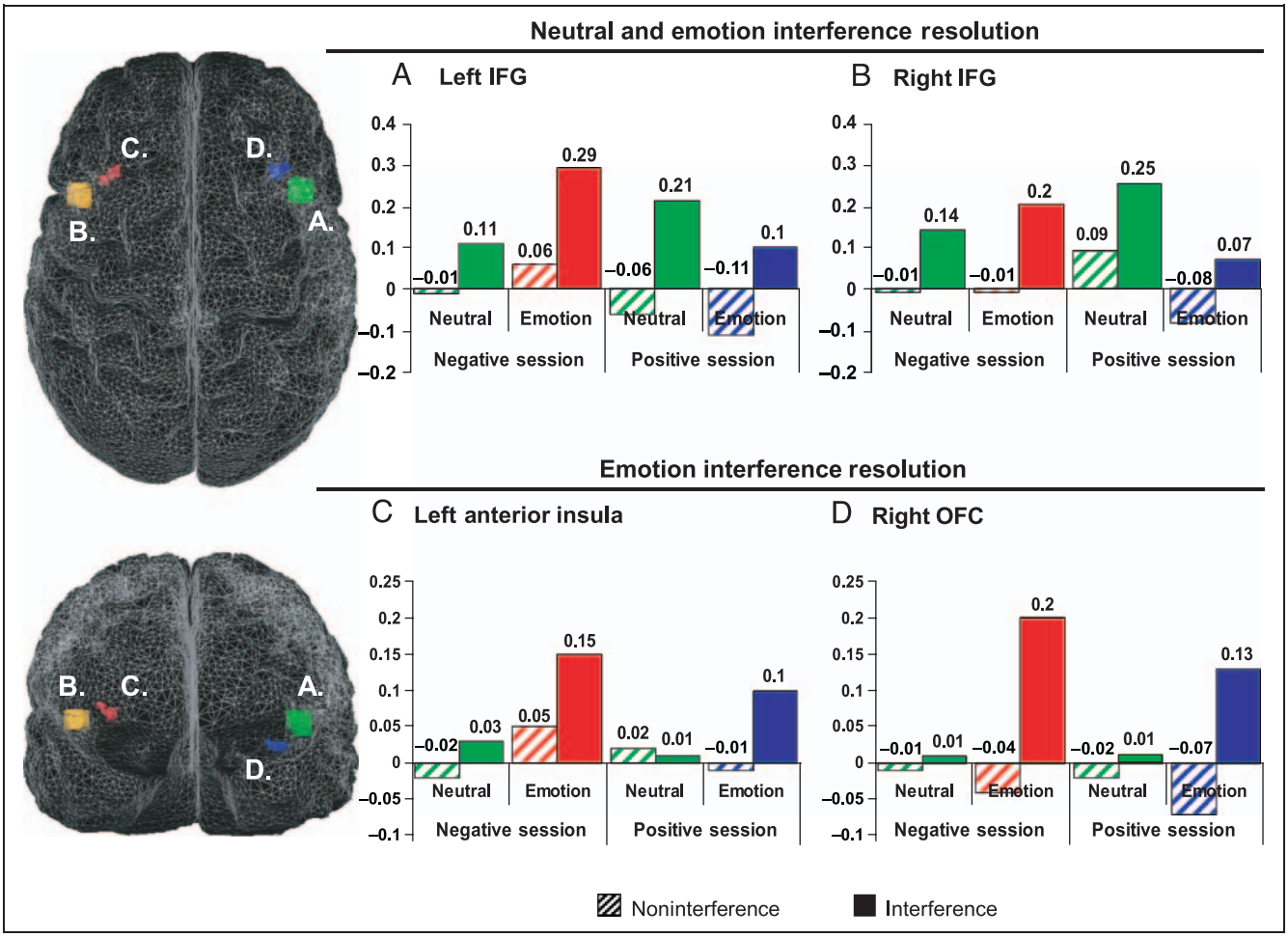

Figure 2. IFG, insula, and OFC ROIs and corresponding graphs are identified by letters A through D. Graphs are percent signal change for interference and noninterference trials in neutral and emotion condition in each valence session, for each of the labeled ROIs.

qualified by a Condition × Interference interaction, $F(1, 25) = 4.427$, $p < .01$, $\eta^2 = .152$. Follow-up paired t tests indicate that the interaction is due to significantly greater emotion interference than neutral interference BOLD responses, $t(52) = 2.149$, $p < .05$. This pattern of findings shows that both the left anterior insula and the right OFC differentiate emotional interference and noninterference trials regardless of valence.

Regions That Differentiate Negative and Positive Interference Trials

The combined session emotion interference trial contrast to identify regions that show greater BOLD activation for positive than negative interference trials and vice versa revealed three valence-specific regions that showed a differentially greater response to negative or positive interference trials: the right anterior insula, the right ventral OFC, and the ventral ACC (Figure 3). The right anterior insula and ventral OFC showed a greater BOLD response to negative than positive interference trials, whereas the ventral ACC showed a greater BOLD response to positive than negative interference trials. An Interference × Condition × Valence Session ANOVA of the right anterior insula showed a main effect of Interference, $F(1, 25) = 4.883$, $p < .05$, $\eta^2 = .163$, qualified by an Interference × Condition × Session interaction, $F(1, 25) = 4.498$, $p < .05$, $\eta^2 = .158$. Follow-up paired t tests indicate that the interaction is due to significantly greater BOLD responses for emotion interference than for noninterference trials only in the negative valence session, $t(25) = 2.2$, $p < .05$. In all other conditions, interference and noninterference trials were not significantly different, $t(52) < .94$, $p > .1$.

Similarly, an Interference × Condition × Valence Session ANOVA of the right ventral OFC yielded a main effect of Interference, $F(1, 25) = 9.3$, $p < .01$, $\eta^2 = .28$. qualified by an Interference × Condition interaction, $F(1, 25) = 4.335$, $p < .05$, $\eta^2 = .15$, and an Interference × Valence Session interaction, $F(1, 25) = 4.8$, $p < .05$, $\eta^2 = .16$. Follow-up paired t tests indicate that the interaction is due to significantly greater BOLD responses for emotion interference than for noninterference trials only in the negative valence session, $t(25) = 4.29$, $p < .001$. In all other conditions, interference and noninterference trials were not significantly different, $t(52) < .95$, $p > .1$.

For the ventral ACC, a similar BOLD activation pattern was found yet reversed for positive stimuli; an Interference × Condition × Valence Session ANOVA of the ventral ACC showed a main effect of Condition, $F(1, 25) = 6.1, p < .05$, $\eta^2 = .2$, and Valence Session, $F(1, 25) = 9.78, p < .01$, $\eta^2 = .3$, qualified by an Interference × Valence Session interaction, $F(1, 25) = 5.83, p < .05$, $\eta^2 = .19$. Follow-up paired t tests indicate that the interaction is due to significantly greater BOLD responses for emotion interference than noninterference trials only in the positive valence session, $t(25) = 2.77, p < .01$. In all other conditions, interference and noninterference trials were not significantly different, $t(52) < .1.1, p > .1$. These patterns of BOLD activation indicate that the right anterior insula and ventral OFC are particularly in response to negative interference, whereas the ventral ACC is particularly responsive to positive interference.

Regions That Differentiate Emotional and Neutral Stimuli

The combined session emotion versus neutral noninterference trial contrast, to identify regions that show greater BOLD activation for emotional than neutral stimuli, revealed that the left amygdala differentiates emotional and neutral stimuli. A Condition × Valence Session ANOVA of the ventral ACC yielded a main effect of Condition, $F(1, 25) = 10.9, p < .01$, $\eta^2 = .3$. A follow-up paired t tests reveals that the condition main effect is due to significantly higher BOLD activity to trials with emotional stimuli (regardless of valence) than trials with neutral stimuli, $t(25) = 3.3$, $p < .01$. To determine if this region also differentiates neutral and emotional trials at target set, BOLD responses at target set for trials in the neutral and emotional condition were extracted and compared in a Condition × Valence Session ANOVA. The ANOVA yielded a main effect of emotion, $F(1, 25) = 6.13, p < .05$, $\eta^2 = .22$, which follow-up t tests indicate was due to significantly greater BOLD activity during both probe and target set presentation with emotional than neutral stimuli, $t(25) = 2.476, p < .05$. The left amygdala therefore differentiates emotional from neutral stimuli at both probe and target set.

DISCUSSION

This experiment sought to determine the neural circuitry involved in the facilitation of interference resolution for emotional information, with the additional goal of distinguishing neutral from both negative and positive emotion interference processing regions in pFC and insula. Our

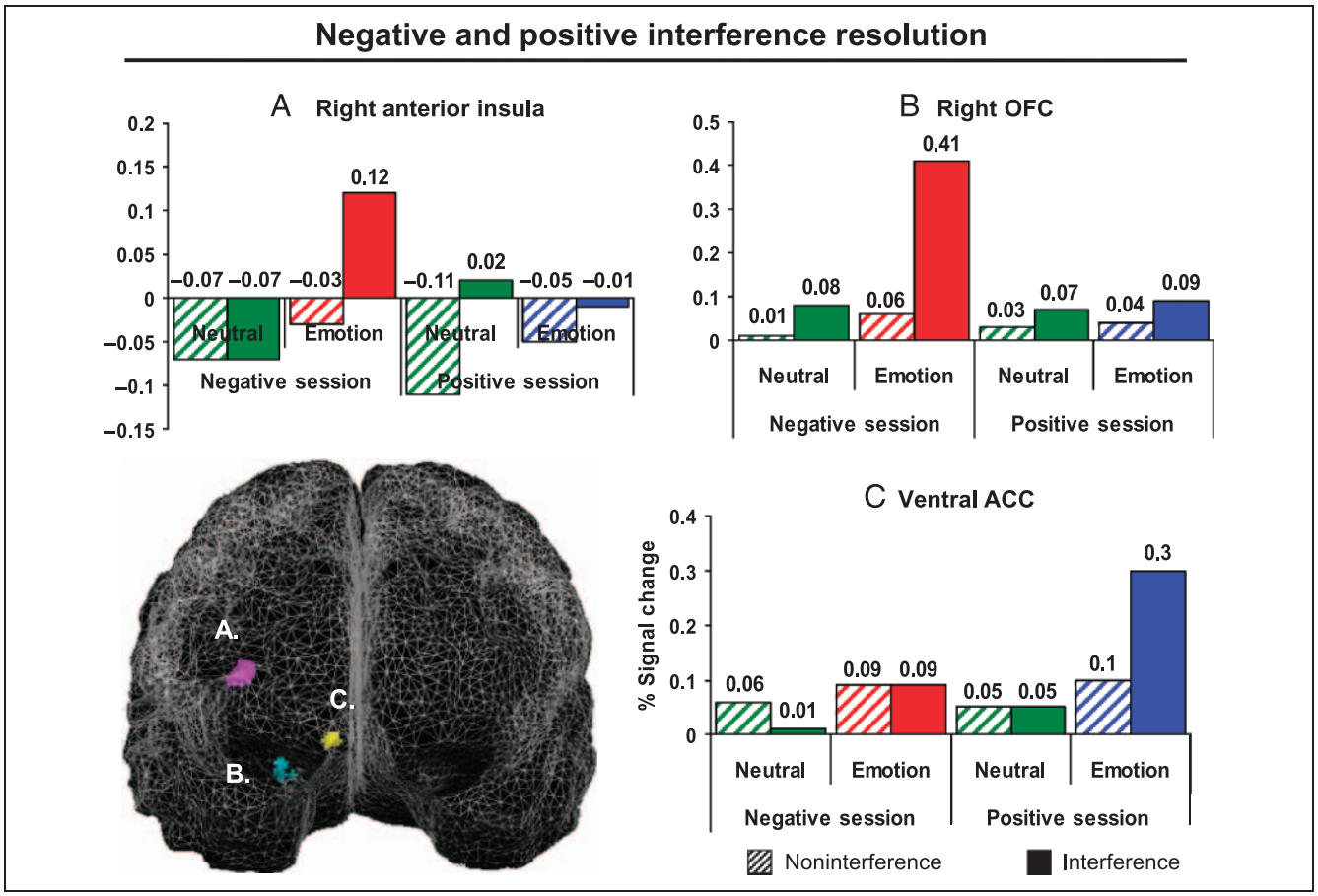

Figure 3. Right insula, OFC, and ventral ACC ROIs and corresponding graphs are identified by letters A through B. Graphs are percent signal change for interference and noninterference trials in neutral and emotion condition in each valence session for each of the labeled ROIs.

behavioral results replicate prior findings showing interference resolution facilitation for emotional information in WM: Interference levels for negative and positive information were lower than neutral interference levels (Levens & Phelps, 2008). Previously, we outlined three possible routes by which emotion may facilitate interference resolution: (1) different neural mechanisms may mediate interference resolution for emotional and neutral information, (2) additional neural mechanisms to those that mediate interference resolution for neutral information may be involved for emotional information, or (3) the same neural mechanisms that mediate interference resolution for neutral information may respond differently to emotional information. On the basis of prior imaging and lesion research, we hypothesized that that IFG would mediate both neutral and emotional interference resolution, and the insula would mediate emotional interference resolution specifically. We also hypothesized that in addition to the IFG and the insula, other regions such as the OFC and ACC might contribute to the emotional facilitation of interference resolution.

Consistent with prior interference resolution research, we found bilateral IFG activation, similar to that identified by D'Esposito et al. (1999) and Jonides et al. (1998), that differentiated interference and noninterference trials across all valence types. This finding, in conjunction with previous interference resolution in WM research (Nee et al., 2007; Badre & Wagner, 2005; Thompson-Schill et al., 2002; D'Esposito et al., 1999; Jonides et al., 1998), indicates that the left and right IFG resolve interference for both neutral and emotional verbal stimuli. Because the IFG responds to both neutral and emotional interference, there do appear therefore to be overlapping neural mechanisms mediating neutral and emotional interference resolution.

We also found a series of regions that differentiate neutral and emotional interference. One region, the MFG, showed greater BOLD activation to neutral than emotional interference trials. This MFG region has been implicated in previous interference resolution studies (Nee et al., 2007); however, it is not clear whether this region mediates interference resolution or WM control processes more generally. Regions in the left anterior insula and right OFC, in contrast, showed greater BOLD activation to emotional than neutral interference trials, regardless of valence. Both of these regions have been implicated previously in emotion processing (Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Rolls, 1996, 2004; Wager & Feldman Barrett, 2004; Craig, 2002). This pattern of BOLD activation indicates that although there do appear to be overlapping neural mechanisms mediating neutral and emotional interference resolution, namely, the right and the left IFG, there also appear to regions in the left pFC that specifically respond to neutral interference and regions in the left anterior insula and right OFC that respond differentially to emotional than neutral interference.

Our finding that the left anterior insula mediates emotional interference resolution is broadly supported by Wager and Feldman Barrett (2004) who in a meta-analysis of insula imaging studies found that the anterior insula is jointly activated by cognitive control tasks and by tasks that elicit affective processing, both of which are elements of the emotion recency-probes task. Wager and Feldman Barrett concluded that the anterior insula forms a network with surrounding cortical and subcortical regions that serves to develop subjective emotional motivational states and to translate these states into specific action plans. Our findings support this conclusion because any emotional conflict must be resolved before an action can be executed, and the left anterior insula in this task may be enacting a specific emotion interference resolution strategy.

In addition to the insula regions, we also found a region in the right OFC that differentiated between interference and noninterference trials for both negative and positive stimuli. Consistent with our findings, prior research indicates that one of the primary roles of the OFC in information processing is the regulation and control of emotion, including the temporal monitoring of emotional information for reward and contingency changes (Rolls, 1996, 2004; Rule, Simammura, & Knight, 2002). According to Craig (2002, 2003), it is via a connection to the OFC that the anterior insula affects the evaluation of valence and affect. Thus, a neural signal sent to the anterior insula may comprise temporal and contextual information regarding when the emotional word was encountered. This signal, which would be available to interference resolution processes in the anterior insula, would help resolve the source recognition/familiarity conflict induced in this paradigm, thereby reducing interference for emotional information. We concluded, therefore, that the OFC aids emotion interference resolution, confirming the second part of our hypothesis that, in addition to the anterior insula, other neural regions are recruited to enable the facilitation of interference resolution.

We also found valence-specific regions in the right anterior insula, the right ventral OFC, and the right ventral ACC that show selectively greater BOLD activity to negative or positive interference: the right anterior insula and ventral OFC to negative stimuli and the right ventral ACC to positive stimuli. The right anterior insula and the right OFC have both been consistently associated with the processing of negative stimuli in previous fMRI studies (Nitschke et al., 2006). Similarly, BOLD activity in the ventral ACC has been associated with the processing of positive stimuli (Sharot, Riccardi, Raio, & Phelps, 2007; Moran, Macrae, Heatherton, Wyland, & Kelley, 2006) and the recall of positive information (Cooney, Joormann, Atlas, Eugène, & Gotlib, 2007). One possibility, therefore, is that these three regions may be recruited as valence-specific components of emotional interference resolution.

An alternate explanation is that these regions are being recruited as the result of a negative or positive valence session mood formation. Given that this imaging study was conducted over 2 days, with one valence session on

each day, it is possible that a negative or positive mood formed in response to viewing the emotional stimuli. Although insula activity is generally more associated with the processing of emotional stimuli as a region particularly central to emotional awareness, it may be showing increased BOLD activity to emotional interference trials as part of a mood formation as well (Craig, 2002). The right OFC and ventral ACC have also been previously implicated in negative and positive mood effects respectively (Elliot, Agnew, & Deakin, 2010; Subramaniam, Kounois, Parrish, & Jung-Beeman, 2008). In a related study, Lewis et al. (2004) presented subjects with positive and negative words to study and then subsequently manipulated their mood to be either positive or negative at recall. Functional imaging during study and recall revealed valence-specific activity that predicted mood congruent recollection in the ventral ACC for positive valence and in the ventral OFC for negative valence—patterns of activation very similar to the present study's findings. The right ventral OFC and the ventral ACC, therefore, not only appear to be associated with mood congruent memory facilitation but also may be associated with mood congruent emotional interference resolution facilitation as well.

Finally, to examine emotion processing regions that might contribute to the emotional facilitation of interference resolution, we examined regions that show greater BOLD activation to emotional than neutral stimuli overall. The left amygdala emerged as a region that shows greater BOLD activity to emotional relative to neutral stimuli at probe onset and during target set presentation, suggesting that this region may be involved in processing emotional information at encoding in this task. This finding is consistent not only with prior research that has shown that the amygdala is central for processing emotional information and task relevance (Sander, Grafman, & Zalla, 2003; Phelps, LaBar, & Spencer, 1998; LeDoux, 1996) but also with research that has shown that the left amygdala, in particular, processes emotional verbal information (Engelien et al., 2006; Isenberg et al., 1999). On the basis of the present set of findings, we cannot conclude what the role of the left amygdala may have in the emotional facilitation of interference resolution. Future research will be needed to determine if the amygdala is critical for emotional interference resolution.

The goal of this study was to determine the neural circuitry underlying the emotional facilitation of interference resolution in WM. The present findings suggest that multiple regions involved in cognitive control and emotion processing, namely, IFG, anterior insula, OFC, and amygdala, may lead to the facilitation of interference resolution seen behaviorally. In accordance with these findings, we propose an emotional interference resolution network comprising regions of the anterior insula, amygdala, and right OFC. In this emotional interference resolution network, the right anterior insula and OFC and the ventral ACC contribute valence-specific memory enhancements that aid negative and positive interference resolution, respectively. For example, the amygdala may differentiate emotional from neutral stimuli, whereas the OFC may produce a signal that amplifies the value that the insula gives emotional stimuli relevant to interference resolution. The anterior insula then integrates signals from the left amygdala and right OFC to enact a specific emotion interference strategy that reduces interference for emotional as compared with neutral information. This proposed network is preliminary but is supported by the results of Wager and Feldman Barrett's (2004) insula meta-analysis, which concludes that the anterior insula mediates representations of affect-driven cognitive control strategies via intra-insular, OFC, and subcortical structure connections. Future lesion research on patients with insula, unilateral amygdala, and OFC damage using this same paradigm is needed to confirm the roles of these regions in our proposed network. Nevertheless, the present findings clarify the role of the anterior insula in the resolution of emotion interference and identify ventral pFC structures that appear to be involved in the selection of relevant emotional information amidst competing alternatives in WM.

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Note

1. Recent yes-response trials may serve as an additional control for interference trials as they have a recency manipulation, yet no interference between source recognition and familiarity. To confirm that the regions identified in our emotional interference resolution analysis are due to interference resolution, as opposed to the effects of recency, we conducted a post hoc analysis contrasting regions showing greater BOLD activity to interference than recent yes-response trials. A behavioral analysis of RTs for recent yes-response trials replicate prior behavioral results—recent yes-responses were significantly lower than interference trial reactions in both the neutral condition negative and positive valence sessions, $t(24) = 3.9, p < .001$ and $t(26) = 5.9, p < .001$, and the emotion condition negative and positive valence sessions, $t(24) = 2.09, p < .05$ and $t(26) = 3.57, p < .001$, respectively. A combined session conjunction analysis of interference and recent yes-response trials to identify regions that show a greater BOLD response to interference than recent yes-response trials across all stimulus types (neutral, positive, and negative stimuli) resulted in four ROIs: a right IFG ROI (41, 16, 1), a left IFG ROI (−40, 13, 8), a right insula ROI (28, −2, 1), and a right temporal lobe ROI (37, −10, −9). These ROIs are nearly identical to the IFG and insula ROIs that differentiate interference and noninterference trials across all stimulus types, confirming that the results of the interference versus noninterference trial contrasts are due to interference resolution, as opposed to recency effects.

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