The Emotional Counting Stroop Paradigm: A Functional Magnetic Resonance Imaging Probe of the Anterior Cingulate Affective Division

Paul J. Whalen, George Bush, Richard J. McNally, Sabine Wilhelm, Sean C. McInerney, Michael A. Jenike, and Scott L. Rauch

Background: *The emotional counting Stroop (ecStroop) functional magnetic resonance imaging (fMRI) activation paradigm was designed to recruit the anterior cingulate affective division (ACad).*

Methods: *Nine normal, healthy male and female subjects (mean age 24.2 years) reported via button press the number of neutral and negative words that appeared on a screen while reaction time and fMRI data were acquired.*

Results: *We observed a) greater ACad activation for negative versus neutral words during initial presentation blocks; b) lower overall ACad signal intensity during task performance (i.e., both negative and neutral words) compared to the baseline fixation condition; and c) no reaction time increase to negative versus neutral words.*

Conclusions: *In a companion study of a cognitive version of the counting Stroop (Bush et al 1998), these same 9 subjects a) activated the more dorsal anterior cingulate cognitive division; b) also showed the overall decrease in ACad signal intensity; and c) demonstrated a reliable reaction time effect. Taken together, these data offer a within-group spatial dissociation of AC function based upon information content (i.e., cognitive vs. emotional) and/or presence of behavioral interference. We propose that the ecStroop will be a useful fMRI probe of ACad function in anxiety disorders.* Biol Psychiatry 1998;44: 1219–1228 © *1998 Society of Biological Psychiatry*

Key Words: Imaging, anxiety disorders, obsessive–compulsive disorder, emotion

Introduction

Cognitive activation paradigms have been used successfully in conjunction with neuroimaging to examine specific brain systems implicated in psychiatric disorders (e.g., Berman et al 1986; George et al 1994; Rauch et al 1997). Our aim was to develop a probe of anterior cingulate (AC) function for future study of this region in anxiety disorders. Toward that end, we present here functional magnetic resonance imaging (fMRI) data in normal subjects performing an emotional Stroop task modified specifically for fMRI.

A number of cognitive tasks have been modified for the study of selective processing of disorder-specific stimuli in anxiety (see Mathews and MacLeod 1994). One such task, the emotional Stroop, is based on the classic color Stroop interference paradigm (Stroop 1935; see Williams et al 1996). The color Stroop measures a subject's latency to name the color of a word that is incongruent with the meaning of that word (word "red" in blue ink; answer blue). Latency to color-name incongruent words is increased compared to neutral words (i.e., words unrelated to color). Whereas interference is provided by color incongruence in the classic Stroop task, the emotional valence of words (such as "murder") provides the crucial interference in the emotional Stroop. When subjects are presented with colored words relevant to their current concerns, automatic processing of word meaning delays naming of the word's color (see Williams et al 1996). Numerous studies have revealed longer color-naming latencies for anxiety disorder-related words across a number of patient groups performing the emotional Stroop [Mathews and MacLeod 1985, generalized anxiety disorder (GAD); Watts et al 1986, phobias; McNally et al 1990, posttraumatic stress disorder (PTSD); Hope et al 1990, social phobia; McNally et al 1992, panic disorder; Foa et al 1993, obsessive–compulsive disorder (OCD)].

As an adaptation to the fMRI environment, where head movements produced by overt speech (required

From the Psychiatric Neuroimaging Research Group and Nuclear Magnetic Resonance Center, Massachusetts General Hospital, Charlestown, Massachusetts (PJW, GB, SCM, SLR); Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (PJW, GB, SW, MAJ, SLR); Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts (GB); and Department of Psychology, Harvard University, Cambridge, Massachusetts (RJM).

Address reprint requests to Scott L. Rauch, MD, Department of Psychiatry, Massachusetts General Hospital, 13th St., Bldg 149, CNY-9, Charlestown, MA 02129.

Received March 27, 1998; revised July 28, 1998; accepted July 31, 1998.

0006-3223/98/$19.00
PII S0006-3223(98)00251-0

during the color Stroop) are not well tolerated, we have developed the counting Stroop (cStroop; Bush et al 1998) and the emotional counting Stroop (ecStroop; present study) tasks; these are finger-press, numerosity variations of the classic Stroop and the emotional Stroop tasks, respectively. During both these tasks, word stimuli are presented in sets of one to four identical words per trial, and subjects report (via button press) the number of words on the screen. Bush et al 1998 demonstrated that the cStroop produces a reliable interference effect via presentation of number-words that are incongruent with the correct response. For example, a subject presented with the word "four," written two times on the screen, would require more time to respond correctly (by pushing the second button) compared to a similar presentation of a neutral word (i.e., non-number related), such as "bird."

For the present study, we modified the cStroop for presentation of emotionally valenced word stimuli (i.e., ecStroop). Subjects were presented with alternating blocks of neutral and negatively valenced words. For example, during the neutral condition, a subject might see the word "cushion" written three times on the screen and would push the third of four buttons. During the negative condition, a subject might see the word "murder" written four times on the screen and would push the fourth of four buttons. Any delays in reaction time in the negative condition compared to the neutral condition might be interpreted as "emotional interference," and as noted above, patient groups demonstrate striking interference effects during performance of the emotional Stroop in response to disorder-specific stimuli (see Williams et al 1996). In the present validation study in normal subjects, we tested the hypothesis that performance of the ecStroop in normal subjects would recruit an affective subdivision of the AC, as measured by fMRI.

Anatomical tracing studies suggest that the AC can be parcellated into an affective division (ACad) and a cognitive division (ACcd) based on distinct efferent and afferent projection systems (see Vogt et al 1992; Devinsky et al 1995). Accordingly, Bush et al (in press) demonstrated that the cStroop activates the ACcd in normal subjects, similar to the classic color Stroop (e.g., Pardo et al 1990; Carter et al 1995). Hence, in the present study, we used the ecStroop to test for ACad activation in response to presentation of negative words in the same subjects demonstrating ACcd activation during performance of the cStroop (Bush et al 1998). This result would a) provide within-group support for an affective versus cognitive functional subdivision of the AC and b) validate an fMRI probe of ACad function for subsequent use in studies of subjects with anxiety disorders.

Methods and Materials

Subjects

Subjects were 9 healthy, right-handed adults (5 male, 4 female; mean age 24.2 years, standard deviation 2.4 years). Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield 1971). All subjects had normal or corrected-to-normal vision. No subject was taking medication. A brief clinical screen consisting of several questions concerning prior and current hospitalizations, medications, diagnoses, and head injuries determined that no subject had a history of neurological, major medical, or psychiatric disorder. Written informed consent was obtained following the guidelines of the Subcommittee on Human Studies at the Massachusetts General Hospital.

Procedure

Subjects were presented with a keypad while in the fMRI scanner. The keypad consisted of four buttons arranged horizontally and representing one, two, three, and four from left to right. Subjects performed the task bimanually using the middle and index finger of their left hand for buttons one and two, respectively, and the index and middle finger of their right hand for buttons three and four, respectively. On each trial, subjects viewed sets of one to four identical words on a screen and were instructed to report (via button press) the number of words in each set. The appearance of one to four words per trial was balanced within each run across conditions. Subjects were instructed to "work as quickly as possible, but do not sacrifice accuracy for speed."

Subjects completed two runs each of the ecStroop. As Figure 1 depicts, each run consisted of four 30-sec blocks of categorized neutral (Neu) words [household items (e.g., cushion)] alternating with four blocks of negative (Neg) words (e.g., murder). Runs started and ended with a 30-sec baseline fixation (Fix) block, where subjects were simply asked to stare at a fixation point on an otherwise blank screen. Subjects completed 20 trials during each stimulus presentation block (intertrial interval = 1.5 sec). Thus, subjects viewed each stimulus type (i.e., Neg or Neu) 80 times per run, seeing each word five times. During a single scanning session, all 9 subjects completed two runs each of the cStroop (Bush et al 1998) prior to completing the two ecStroop runs described here. All ecStroop words (Neg and Neu) were novel compared to those presented in the cStroop. Thus, data presented here represent those of subjects who were well practiced on the task components of counting and button pressing, but had not seen the to-be-presented words.

Stimuli

This task is amenable to use with disorder-specific words related to various psychiatric disorders. Since we next planned to use this probe in a study of OCD, half of the Neg word blocks consisted of general negative words, and half consisted of words specific to OCD (always blocked separately, as were their matched Neu words; see Table 1). Such a design will allow investigators to test the generalizability of information-processing biases (i.e., negative valence vs. disorder specificity) in future studies of anxiety disorders.

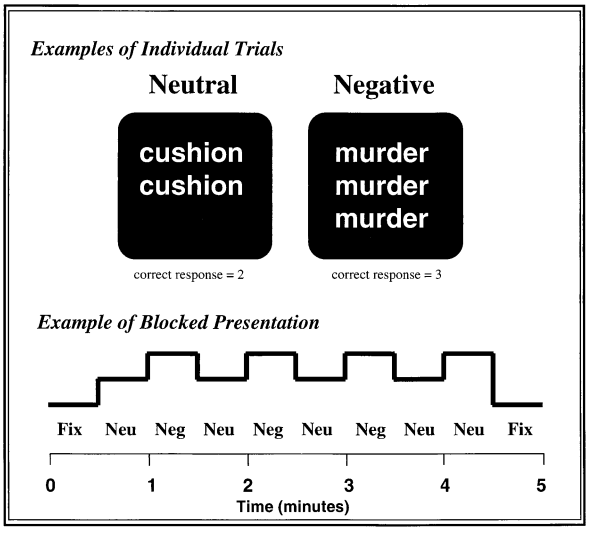

Figure 1. Summary of stimulus presentation paradigm. The top portion of this figure presents representative examples of a single neutral and negative trial. See Table 1 for a list of words used for each condition. For each trial, subjects counted the number of words on the screen and reported their answer via button press (the answer was always 1, 2, 3, or 4). The lower portion of this figure depicts how these 1.5-sec trials were blocked for a single run. Immediately following a 30-sec fixation block (Fix), subjects completed alternating 30-sec blocks where neutral (Neu) and negative (Neg) words were presented. Stimulus presentation blocks were then immediately followed by a 30-sec Fix block. For the second run the block order was counterbalanced. In addition, the appearance of one to four words per trial was balanced across conditions within each run.

General negative and OCD-related words were always blocked together for presentation, as were the corresponding neutral words. The validity of included Neg and Neu words had been determined previously (see Wilhelm et al 1996). The hierarchy for selection of word stimuli emphasized first disorder relevance followed next by inclusion of words in a single category (see Williams et al 1996). By selecting words that were particularly arousing to OCD patients (Wilhelm et al 1996) and requiring that neutral words also belong to a single category (i.e., household items), we constructed lists that were matched for frequency of usage (Francis and Kucera 1982), word length (i.e., number of characters), and semantic category (i.e., household items vs. negatively valenced words). Neutral and negative words were not matched for part of speech. Order of presentation of Neg and Neu words was counterbalanced across 8 subjects. That is, 4 subjects were presented with Neu word blocks followed by Neg word blocks during their first run, and the order was reversed for the other 4 subjects. In addition, presentation order of general negative and OCD-related word blocks was independently counterbalanced across these 8 subjects. The addition of the 9th subject did not change the results.

Table 1. Word Stimuli Used for Present ecStroop Study

Neutral		Negative	
		General negative	OCD-related
tables	mirror	violence	filthy
closet	bowl	deceit	dirty
corridor	cabinet	murder	toilet
fan	cellar	contempt	sweat
cushion	glass	painful	shit
curtain	dishwasher	hazard	mess
pan	mailbox	torture	guilty
porch	mixer	danger	disease

Apparatus

Word stimuli were presented via standardized software (MacStim, Inc.), using a Macintosh 100-MHz PowerPC computer with a Radius interface (model 0355, Videovision) and projected via a Sharp XG-2000V color LCD projector through a collimating lens onto a hemicircular tangent screen. This rear-projection screen (Dalite Corp.) was secured vertically within the magnet bore at neck level after the subject had been positioned. Stimuli on the screen were visible via a 1.5 × 3 in. mirror positioned approximately 6 in. from and directly above the subject's eyes.

Functional magnetic resonance images were collected with a General Electric Signa 1.5-T high-speed imaging device (modified by Advanced NMR Systems, Wilmington, MA) using a quadrature head coil. Our Instascan software is a variant of the echoplanar technique first described by Mansfield (1977). Head stabilization was achieved using a plastic bite bar, molded to each subject's dentition.

Functional MRI Data Acquisition

Our standard image acquisition protocol was utilized and has been previously described elsewhere (Cohen and Weisskoff 1991; Kwong 1995). An initial sagittal localizer [spoiled gradient recall acquisition in a steady state (SPGR), 60 slices, resolution 0.898 × 0.898 × 2.8 mm] was performed to provide a reference for subsequent slice selection. Following automated shimming (Reese et al 1995) to maximize field homogeneity, a magnetic resonance (MR) angiogram (SPGR, resolution 0.78125 × 0.78125 × 9.0 mm) was acquired to identify large- and medium-diameter vessels. Then a set of T1-weighted high-resolution transaxial anatomic scans (resolution 3.125 × 3.125 × 9 mm) were acquired. For the functional series, asymmetric spin-echo (ASE) sequences were used to minimize macrovascular signal contributions. Functional ASE data were acquired as 12 contiguous, interleaved, horizontal, 9-mm-thick slices that paralleled the intercommissural plane (voxel size 3.125 × 3.125 × 9 mm; 150 images per slice, repetition time/echo time/flip angle = 2000 msec/70 msec/90°). Ten initial functional ASE images were collected (and discarded) prior to the first fixation epoch to eliminate initial magnetization effects.

Functional MRI Data Analysis

Data analysis began with quantification of subject motion and subsequent correction (Jiang et al 1995) based on the registration algorithm of Woods et al (1992). Both functional and high-resolution structural data were then placed into normalized Talairach space (Talairach and Tournoux 1988).

TALAIRACH TRANSFORMATION. First, high-resolution structural data (sagittal localizer scan) were transformed into Talairach space. Three landmarks were identified on a given individual's anatomic scans consisting of the anterior commissure, posterior commissure, and an additional point within the interhemispheric fissure to define the midsagittal plane. High-resolution structural data were then reformatted into a normalized sagittal orientation space (anterior–posterior commissure line aligned with y axis; midsagittal plane in y–z plane). Using this normalized scan, brain extents (left and right lateral, frontal, posterior, superior, inferior) were measured. These extents determined the x, y, and z spatial scaling factors used for linear transformation into Talairach space. The scaling was accomplished in a "piece-wise" fashion for each of the six brain regions created by three bisection lines through the 1) anterior–posterior commissure in the y plane (basal line), 2) anterior commissure in the z plane, and 3) posterior commissure in the z plane. Then, this individual's normalized sagittal orientation scan was subsampled in the Talairach space and resliced coronally at a 3.125 mm (x) by 3.125 mm (y) by 3.125 mm (z) resolution.

Second, the "native" functional acquisition data were subsampled into Talairach space using the transformation determined on the individual's high-resolution structural data (detailed above). Before doing so, a) the individual's functional data were "registered" to their anatomic MR angiogram data; b) the center point (x,y,z) of the functional data set was determined; and c) other necessary points of reference [i.e., slice orientation, angle (if oblique), and resolution] were derived from the functional slice prescription.

KOMOGOROV–SMIRNOV STATISTICAL MAPPING. Following Talairach transformation, coronally sliced functional data from individuals were baseline normalized and concatenated (i.e., data from the entire cohort were assembled to form a single time series normalized to a common baseline). Nonparametric statistical maps were calculated for relevant contrasts using the Kolmogorov–Smirnov (KS) statistic (Press et al 1988), displayed in pseudocolor and scaled according to significance. The threshold for statistical significance for AC activation ($p < 1.0 \times 10^{-4}$) represents a Bonferroni-corrected .05 probability level based upon the size of a predefined region of the ACad consisting of approximately 500 voxels (areas 24a, 24b, 32; see Vogt et al 1995). KS maps were superimposed on the high-resolution sagittal localizer SPGR images that had likewise been placed into Talairach space and resliced in the coronal plane (as described above).

We planned our analyses of ACad activation and behavioral reaction time effects to test all presentation blocks of Neg versus Neu words. In addition, we planned to test only the first four presentation blocks of each run (i.e., first presentation blocks of each word type). Our rationale for these analyses relied upon our previous finding that responses to emotionally valenced stimuli within limbic regions diminish with repeated stimulus presentation in normal subjects (Whalen et al 1998). In addition to the ACad, other regions of interest included the amygdala (Rauch et al 1996; Shin et al 1997; Whalen et al 1998), sublenticular substantia innominata (Whalen et al 1998), insular cortex, and orbitofrontal cortex (see Rauch et al 1996; Shin et al in submission). These regions were searched using Bonferroni correction thresholds ($p < .05$) relevant to their size (e.g., $p < 6.6 \times 10^{-4}$ for the amygdala at 76 voxels; see Whalen et al 1998).

Table 2. Mean (SD) Reaction Times in Milliseconds for Nine Subjects during Negative versus Neutral ecStroop Word Presentations

	Block 1	Block 2	Block 3	Block 4
Neg	650	686	640	653
	(113)	(130)	(105)	(96)
Neu	653	684	644	652
	(104)	(116)	(86)	(104)

Values reflect average response time across two runs, paralleling the time course for AC activation presented in Figure 2B.

Results

Behavioral Reaction Time Data

A Condition × Block repeated-measures analysis of variance (ANOVA) demonstrated no significant main effects for Condition or Block and no interaction (all *p*s $> .10$). Table 2 presents mean reaction times in milliseconds across presentation blocks. As noted in the Materials and Methods section, we tested individual presentation blocks for early reaction time differences that may have rapidly habituated; we found no such significant differences (all *p*s $> .10$). There was also no significant difference in reaction time to general negative vs. OCD-related words ($p > .10$)

Functional MRI Data

NEGATIVE VERSUS NEUTRAL WORDS. Figure 2A presents a KS statistical map depicting significant activation within the left ACad [$p = 2.1 \times 10^{-5}$; x = −3, y = 39, z = 15, ~Brodmann Area (BA) 32] when the initial two negative word blocks of each run were compared to the corresponding counterbalanced two neutral word blocks. Figure 2B presents fMRI signal intensity data changes over time for the ACad locus presented in Figure 2A. These data depict increased signal intensity during negative words when compared to that during neutral words. Note the consistent relationship through the first four blocks of each run, consonant with the above-reported KS probability value showing significant activation when only the first two blocks of each word type are considered. Indeed, the probability value for the negative versus neutral contrast decreased to levels that did not exceed our a priori Bonferroni-corrected significance level for the ACad (see Methods and Materials) when all presentation blocks were considered ($p = .003$) or when only the final two blocks of each word type within each run were

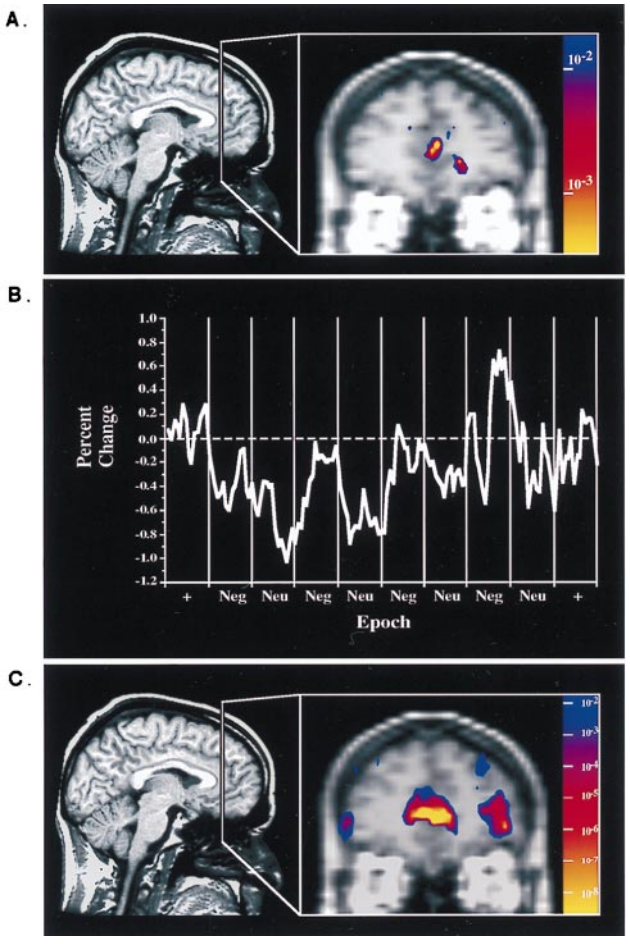

Figure 2. Modulation of the anterior cingulate affective division (ACad) during performance of the emotional counting Stroop (ecStroop). **(A)** The coronal image on the right (y = 39) displays a KS statistical map depicting significant activation within the left ACad during initial negative word presentation blocks compared to neutral word presentation blocks ($p < 10^{-4}$). This image is presented according to radiological convention (i.e., right = left; left = right; top = superior; bottom = inferior). The colorized statistical map is superimposed over the averaged high-resolution structural data for all subjects. Both functional and structural data have been placed in a normalized space according to the coordinate system of Talairach and Tournoux (1988). All figures were smoothed using a Hanning nine-voxel 1:2:1 kernel filter. Note that susceptibility from the sinus space causes signal dropout in the most inferior portions of this slice (i.e., inferior AC and medial orbitofrontal cortex). The sagittal image on the left depicts the anterior–posterior location of the coronal slice presented on the right. **(B)** Presentation of fMRI signal intensity changes over time (i.e., repeated stimulus presentations) for the locus presented in **(A)**. Y-axis values represent percent change from the mean signal intensity during fixation blocks. Data recorded across counterbalanced blocks comprising two runs have been temporally rearranged and averaged to create this pseudo-time series representing AC response across 9 subjects. fMRI signal intensity was significantly higher during negative word presentation blocks compared to neutral word blocks. Note the global decrease in signal intensity during task performance compared to the preceding and following fixation blocks. **(C)** Decreased fMRI signal during task performance (Neg and Neu blocks) compared to the fixation condition (i.e., Fix minus Neg and Neu blocks). KS statistical map depicts significant deactivation within a large portion of the ACad during all negative and neutral word presentation blocks compared to fixation blocks. Image parameters are as in **(A)**.

compared ($p > .10$). No significant activation occurred throughout the rest of the AC, including the ACcd.

The comparison of initial negative versus neutral blocks also produced activation of the left superior parietal lobule [$p = 2.32 \times 10^{-6}$; x = −25, y = −69, z = 31; BA 7 (sulcal)]. This finding should be interpreted cautiously as the statistical threshold applied here is appropriate only for the search volume within the ACad.

We observed no significant activation to negative versus neutral words (all corrected *p*s > .05) within other limbic regions of interest such as the amygdala, sublenticular substantia innominata, insular cortex, or orbitofrontal cortex for either planned test (i.e., initial or all stimulus presentations). There was also no significant difference in ACad activation to general negative versus OCD-related words.

FIXATION VERSUS NEGATIVE AND NEUTRAL WORDS: SIGNAL DECREASES TO THE TASK ITSELF. The time course presented in Figure 2B also illustrates the fact that ACad signal intensity during task performance (i.e., both Neu and Neg blocks) was significantly lower than that during the baseline Fix blocks that preceeded and followed stimulus presentations ($p = 1.1 \times 10^{-6}$). This effect was most pronounced in initial presentation blocks, with signal intensity during negative block 4 showing the only sustained rise above mean fixation levels. Figure 2C presents the KS statistical map for this Fixation versus Task (i.e., all Neu and Neg blocks) contrast, showing that this significant "deactivation" during task performance was observed over a large portion of the ACad and frontal cortical regions. Note that the subgenual AC (BA 25) and the orbitofrontal cortex were not visualized in the present study due to signal dropout associated with susceptibility from the sinus space.

NEUTRAL WORDS VERSUS FIXATION: ACTIVATION TO THE TASK ITSELF. Though not the focus of the present study, the ecStroop task itself (Neutral vs. Fixation contrast) produced significant activation of bilateral frontal cortex (right: x = 53, y = 21, z = 28, ~BA 9; left: x = −50, y = 9, z = 31, ~BA 8); bilateral midcingulate/supplementary motor area (right: x = 9, y = −6, z = 46; left: x = −3, y = −6, z = 50, BA 6/24); left superior parietal lobule (x = −31, y = −57, z = 43, BA 7); bilateral fusiform gyrus (right: x = 40, y = −57, z = −9; left: x = −40, y = −57, z = −9, BA 37); bilateral visual

association cortex (right: x = 25, y = −87, z = 9; left: x = −21, y = −87, z = 6, BA 18); and left primary visual cortex (x = −6, y = −90, z = −3, BA 17). For designation of these brain regions we used a conservative Bonferroni correction for whole brain (all $ps < 1 \times 10^{-7}$).

Discussion

The present study aimed to test the validity of the ecStroop as an fMRI activation paradigm designed to recruit the ACad in response to negatively valenced words. Use of both general negative and disorder-specific words enables the ecStroop to be used as a neuroimaging probe of ACad function in anxiety disorders. In this cohort of normal subjects, greater ACad activation occurred for negative versus neutral words during initial presentation blocks, in the absence of a significant behavioral effect (i.e., no reaction time increase to Neg vs. Neu words).

The Emotional Counting Stroop as a Probe of ACad Function in Normal Subjects

Although AC activation during interference tasks is becoming well-established in neuroimaging (see Bush et al 1998), its specific function in these tasks remains unclear; candidate functions include sensory selection/response competition (Pardo et al 1990), error detection (Dehaene et al 1994; but see also Carter et al 1998), and/or stimulus anticipation (Murtha et al 1996). Nevertheless, Stroop interference tasks consistently implicate the AC, specifically the ACcd (see Bush et al 1998). Modifying the color-naming Stroop interference task as a word-counting Stroop task for the fMRI environment (i.e., cStroop), Bush et al (1998) demonstrated both ACcd activation and a reliable response latency interference effect. The present study extends this work by addressing the role of the AC in the processing of emotionally valenced stimuli during the performance of a similar word-counting task (i.e., ecStroop).

Affective versus Cognitive Subdivisions of the AC

Figure 3 presents a summary diagram of activation loci for the ecStroop (present study) and the cStroop (Bush et al 1998) within the AC. Activation observed in response to the ecStroop occurs within the ACad. This functional subdivision comprises an anterior portion of the AC (areas 24a, 24b, 32; see Vogt et al 1995) that has extensive connections with limbic and paralimbic regions, such as the amygdala and orbitofrontal cortex (see Devinsky et al 1995). What we refer to here as the ACad represents the "pregenual" region of the AC (see Mayberg 1997; Drevets and Raichle 1998). Note that the "subgenual" region of the AC (BA 25), identified as an affective and/or visceromotor region (see Vogt et al 1992; see also Drevets et al 1997; Mayberg 1997; Drevets and Raichle 1998), was not visualized in the present fMRI study due to characteristic signal dropout attributable to susceptibility effects.

Numerous studies report activation of the ACad in response to emotional manipulations in normal subjects and patient groups. George et al (1994) observed activation of this region in a positron-emission tomography (PET) study of normal subjects performing a "sad Stroop" task. Symptom provocation studies of distinct anxiety disorders [Rauch et al 1994, OCD; Rauch et al 1995, simple phobia (SP); Rauch et al 1996, PTSD] also activate the ACad. Interestingly, Mayberg (1997) describes a territory of the ACad as an affective "regulatory" area and documents that in depressed patients, pretreatment activity levels in this region predict response to antidepressant medication.

Figure 3 further illustrates that in the same subjects demonstrating ACad activation during ecStroop performance, activation in response to the cStroop (Bush et al 1998) occurs in the ACcd, a more dorsal and posterior, "supragenual" portion of the AC (areas 24a′, 24b′, 32′; see Vogt et al 1995). This territory has extensive connections with prefrontal, premotor, and supplementary motor areas (see Devinsky et al 1995). Importantly, both our modified cStroop (Bush et al 1998) and the color Stroop (e.g., Pardo et al 1990; Carter et al 1995) activate the ACcd, as do numerous attentional and interference paradigms (see Bush et al 1998).

The within-group demonstration of ACad activation to the ecStroop and ACcd activation to the cStroop suggests that spatial localization will be an important variable to consider in attempting to reconcile the function of the AC. Though a unifying theory of AC function may exist, differing subterritories may subserve different types of information processing (see Vogt et al 1992).

Overall Level of Task-Related ACad Signal Intensity

An unexpected finding was that, although signal intensity during presentation of negative words was consistently higher than that during neutral words, the overall level of fMRI signal within the ACad was below that observed during the fixation condition (low-level baseline). When task condition blocks were compared to the fixation baseline, a decrease in fMRI signal intensity was noted throughout the ACad region (Figure 2B–C), but not within the ACcd. We also observed this same ACad "deactivation" during performance of the cStroop (Bush et al unpublished observations). Interestingly, "deactivation," observed during performance of the ecStroop (present study) and cStroop (Bush et al 1998), was also observed in other "limbic" structures, such as insular cortex (present

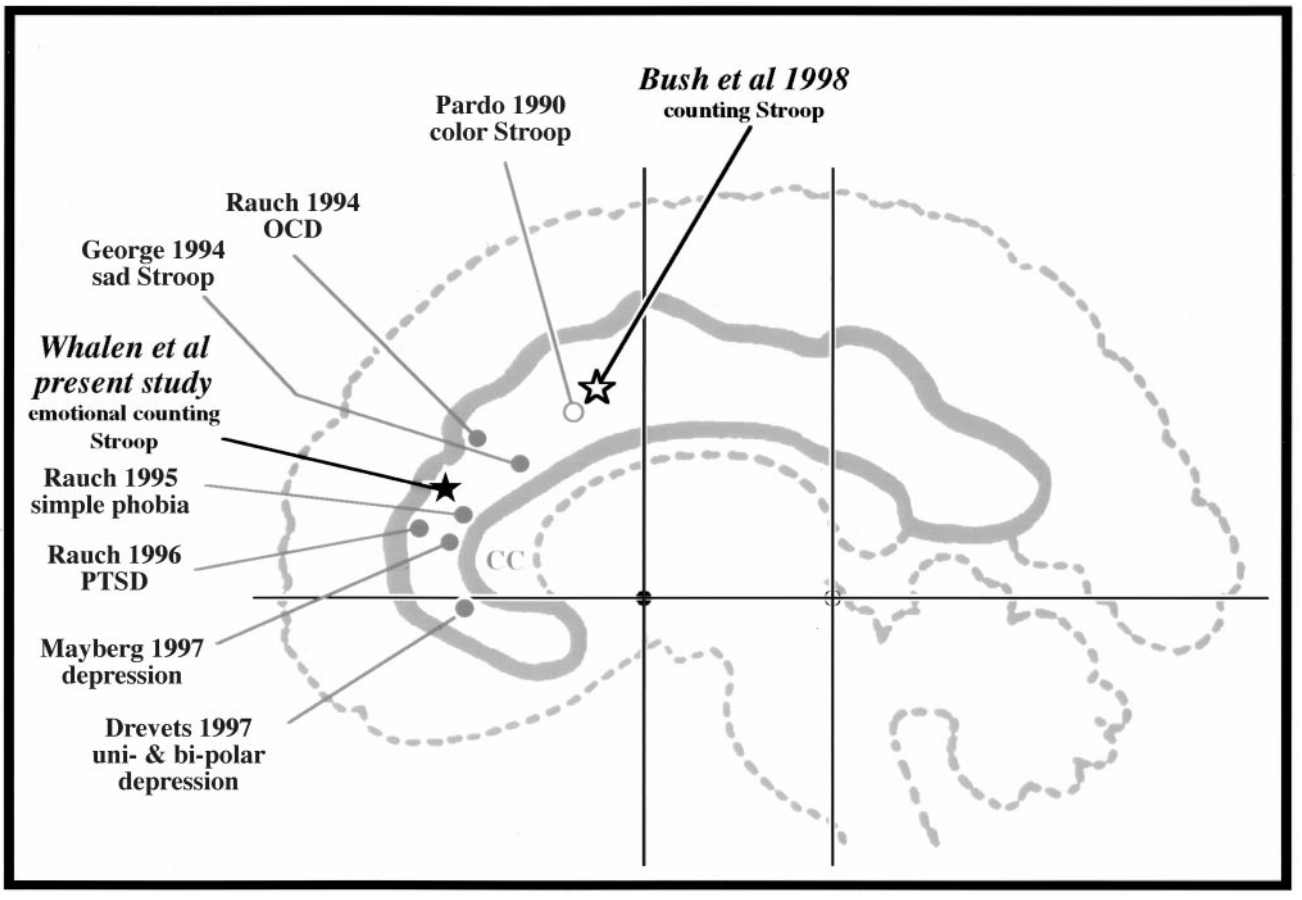

Figure 3. Schematic illustration of a representative sagittal section through the cingulate cortex depicting activation loci for the ecStroop and cStroop as well as selected emotional and cognitive studies. Studies involving emotional tasks or manipulations are represented by solid symbols, and tend to cluster in the rostral anterior cingulate affective division (ACad). Cognitive/motor tasks are represented by open symbols, and are within the more dorsal anterior cingulate cognitive division (ACcd). Highlighted in black ink are the activations from the present study within the ACad during performance of the emotional counting Stroop (ecStroop), and the within-group activation of the ACcd during performance of the cognitive counting Stroop (cStroop). Shaded in gray are selected cognitive and emotional studies referred to by first author, year of publication, and subject matter. For a more thorough presentation of cognitive versus emotional AC activation loci see Figure 6 in Bush et al (1998). CC = corpus callosum.

study, data not presented) and amygdala/hippocampus (Bush et al data not presented).

Shulman et al (1997) recently documented what appears to be a similar phenomenon in a pooled analysis of multiple PET cognitive activation paradigms, presenting similar areas of "deactivation" during active task conditions compared to fixation and passive task conditions. Also, Shulman et al (1997) show that decreases relative to fixation are not dependent upon motor responding, suggesting the present effect is more likely due to cognitive processes associated with word presentations.

Hence, overall ACad signal intensity appears to be modulated by processing of word presentations during the cStroop and ecStroop. Although other explanations are possible (see Shulman et al 1997 for a detailed discussion), we hypothesize that lower ACad signal intensity during stimulus presentations reflects active inhibition of this limbic region in the service of allocating resources toward effective cognitive performance (see Drevets and Raichle 1998). Importantly, though we propose that this region was biased against in normal subjects, significant signal changes to negative versus neutral words demonstrate the continued capacity of the ACad to monitor the presence of emotional information.

ACad Activation and Behavioral Interference in Normal Subjects

In recording behavioral data during fMRI we found no significant increase in response latency to negative words despite activation of the ACad. This result is consistent with 1) a lack of reaction time increase found for normal control subjects studied with the color-naming emotional Stroop for comparison with patient groups (see Williams

et al 1996); and 2) the fact that manual button-press Stroop analogs typically produce lesser interference effects compared to vocal response tasks (see MacLeod 1991). Still, McKenna and Sharma (1995) did find an early reaction time effect in normal subjects that eventually habituated in a button-press emotional color Stroop task.

The lack of a reaction time effect while the ACad was activated offers additional information toward an understanding of AC function. A measurable interference effect is not necessary to observe activation of the AC. Note that these same 9 subjects did exhibit a significant increase in response latency and a concomitant increase in activation of the ACcd during performance of the cStroop (Bush et al 1998). Recall also that in the cStroop, the interference manipulation was cognitive in nature (i.e., number–word incongruence). Activation of the AC to both the cStroop and ecStroop is consistent with its purported role in reconciling competing information streams (see Devinsky et al 1995). The dissociation of ACcd and ACad activation between these tasks suggests that information content (i.e., cognitive vs. emotional) accounts for differences in spatial location within the AC. On the other hand, differences in spatial location might be related to the presence (e.g., ACcd activation) or absence (e.g., ACad activation) of behavioral interference. Since patients with anxiety disorders demonstrate reliable reaction-time interference effects to disorder-specific words (see Williams et al 1996), future study of such patient populations will offer important information concerning the relationships between ACad and ACcd activation, measured interference, and information content.

The ecStroop as a Probe of AC Function in Anxiety Disorders

Provocation paradigms have been used in conjunction with functional neuroimaging in an effort to delineate the mediating anatomy of the symptoms that characterize anxiety disorders (see Rauch and Shin 1997 for review). Building on the symptom provocation work of others (Reiman et al 1989; Zohar et al 1989), initial studies in our laboratory indicated significant activation within the ACad during provoked versus control conditions for OCD (Rauch et al 1994), simple phobia (Rauch et al 1995), and posttraumatic stress disorder (Rauch et al 1996); however, the interpretations of these experiments were limited by the absence of normal control groups. Hence, although the ACad was recruited during the symptomatic state, it remained unclear whether this activation was greater than that during physiological (i.e., nonpathological) anxiety. Few studies have directly compared brain activation profiles between anxiety disorder and normal control groups during exposure to disorder-specific stimuli. Some data have suggested greater activation of AC within the anxiety disorder group (Shin et al 1997), whereas other findings have suggested greater activation within the normal control group (Shin et al in submission). Moreover, several symptom provocation studies of anxiety disorders have not yielded significant AC activation (e.g., Reiman et al 1989; Fredrikson et al 1995).

Accordingly, the role of normal AC function is unclear, making hypotheses about aberrant AC activation difficult. For example, if ACad activation in response to negative words is related to the level of emotional response, then one would predict that disorder-specific word stimuli should produce greater ACad activation in patients compared to matched control subjects. On the other hand, if ACad activation is related to a normal compensatory or regulatory response (Mayberg 1997) to emotionally valenced stimuli, then one would predict that patients would demonstrate an inability to effectively recruit the ACad, resulting in diminished AC activation during the ecStroop compared to control subjects. Consistent with this notion, Shin et al (in submission) report that PTSD subjects exhibit lesser ACad activation to disorder-specific stimuli compared to trauma-exposed normal subjects. We also note that anterior cingulotomy (Cosgrove and Rauch 1995), a surgical procedure for relieving severe intractable anxiety, entails lesions within the ACcd while leaving ACad tissue intact.

The additional observation of overall decreased ACad signal intensity during task performance in normal subjects presents another avenue for potential aberrance in anxiety. We hypothesize that signal decreases in limbic regions during cognitive processing represent a beneficial bias in normal subjects that could decrease the "weighting" of affective information in the service of optimizing cognitive performance. Thus, one possibility is that pathological anxiety will be associated with a failure to demonstrate decreased ACad signal during task performance compared to the fixation baseline, suggesting that affective processing continues to receive equal weighting even in the face of cognitive performance demands. Future studies employing a) perfusion methodologies for comparison of absolute values of flow between patients and control subjects during baseline conditions and b) additional fixation epochs and/or a passive viewing baseline condition would more rigorously address these issues.

Generalizability of the Present Results

The present study provides a potentially useful probe for the study of normal AC function and its application to patient studies. Generalizability of our results is qualified by the following points. Recall that subjects were well practiced on the counting and button-pressing aspects of

the task, since all subjects completed two runs of the cStroop in the scanner before beginning the ecStroop. Thus, results like these might depend upon a practice session in the scanner before subsequent scanning. Moreover, all words for the ecStroop differed from those for the cStroop. Accordingly, replication of our findings might require a practice session involving words different from those subsequently used during scanning.

We matched negative and neutral words for frequency, word length, and categorical inclusion (stimulus parameters that have been shown to produce Stroop effects; see Williams et al 1996). Our emphasis dictated the use of words that were most emotionally relevant to a particular disorder (OCD), producing a word list that was not matched for part of speech. That is, whereas all neutral words were nouns, general negative words included seven nouns and one adjective, while OCD-related words included five nouns and three adjectives. Though we cannot rule out that presence of adjectives could have produced greater activation of the ACad in the negative versus neutral contrast, the fact that OCD-related words (containing three adjectives) did not produce greater ACad signal compared to general negative words (containing only one adjective) mitigates this possibility.

Conclusion

The extant literature concerning emotional Stroop performance in patient groups predicts a reliable reaction time effect in patients with anxiety disorders for disorder-specific versus neutral words. Studying subjects who do show an interference effect to emotional stimuli will offer valuable data concerning the role of the ACad versus ACcd in the parallel processing of emotional information and cognitive task performance. Thus, future studies involving patients with anxiety disorders and the ecStroop fMRI probe promise important insights regarding the pathophysiology of these diseases as well as normal AC function.

This work was supported by a Harvard Medical School Clinical Research Training Program (CRTP) Fellowship to PJW (MH-16259; Robert McCarley, Stuart Hauser, Program Directors); Harvard/MIT Div. of Health Sci. Clinical Investigator Training Program Fellowship, in collaboration with Beth Isreal Hospital and Pfizer, Inc. to GB; MH-01215 and National Alliance for Research on Schizophrenia and Depression Award to SLR; and the David Judah Fund to MAJ.

We thank Terry Campbell, Mary Foley, and Michael Vevea for technical assistance; and Lisa Shin, Bruce Rosen, Cary Savage, David Kennedy, Robert Weisskoff, and Brent Vogt for advice and comments.

This work was presented at the Research Symposium on "Brain Neurocircuitry of Anxiety and Fear: Implications for Clinical Research and Practice" in Boston, Massachusetts, on March 26, 1998. The symposium was jointly sponsored by the Anxiety Disorders Association of America and the National Institute of Mental Health through an unrestricted educational grant provided by Wyeth-Ayerst Laboratories.

References

Berman KF, Zec RF, Weinberger DR (1986): Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: II. Role of neuroleptic treatment, attention and mental effort. *Arch Gen Psychiatry* 43:126–135.

Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL (1998:) The counting Stroop: An interference task specialized for functional neuroimaging—Validation study with functional MRI. *Hum Brain Mapping* 6:270–282.

Carter CS, Mintun M, Cohen JD (1995): Interference and facilitation effects during selective attention: An H_2150 PET study of Stroop task performance. *Neuroimage* 2:264–272.

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JA (1998): Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.

Cohen MS, Weisskoff RM (1991): Ultra-fast imaging. *Magn Reson Imaging* 9:1–37.

Cosgrove GR, Rauch SL (1995): Psychosurgery. In: Gildenberg PL, editor. *Neurosurgery Clinics of North America: Functional Neurosurgery*, vol 6. Philadelphia: W.B. Saunders, pp 167–181.

Dehaene S, Posner MI, Tucker DM (1994): Localization of a neural system for error detection and compensation. *Psychol Sci* 5:303–305.

Devinsky O, Morrell MJ, Vogt BA (1995): Contributions of anterior cingulate cortex to behaviour. *Brain* 118:279–306.

Drevets WC, Raichle ME (1998): Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: Implication for interactions between emotion and cognition. *Cogn Emotion* 12:353–385.

Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M,et al (1997): Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386:824–827.

Foa E, Ilai D, McCarthey PR, Shoyer B, Murdock T (1993): Information processing in obsessive-compulsive disorder. *Cogn Ther Res* 17:173–189.

Francis WN, Kucera H (1982): *Frequency Analysis of English Usage.* Boston: Houghton Mifflin.

Fredrikson M, Wik G, Annas P, Ericson K, Stone-Elander S (1995): Functional neuroanatomy of visually elicited simple phobic fear: Additional data and theoretical analysis. *Psychophysiology* 32:43–48.

George MS, Ketter TA, Parekh PI, Rosinsky N, Ring H, Casey BJ, et al (1994): Regional brain activity when selecting a response despite interference: An H_2150 PET study of the Stroop and the emotional Stroop. *Hum Brain Mapping* 1:194–209.

Hope DA, Rapee RM, Heimberg RG, Dombeck MJ (1990): Representations of the self in social phobia: Vulnerability to social threat. *Cogn Ther Res* 14:477–485.

Jiang A, Kennedy D, Baker J, Weisskoff R, Tootell R, Woods R, et al (1995): Motion detection and correction in functional MR imaging. *Hum Brain Mapping* 3:224–235.

Kwong KK (1995): Functional magnetic resonance imaging with echo planar imaging. *Magn Reson Q* 11:1–20.

MacLeod CM (1991): Half a century of research on the Stroop effect: An integrative review. *Psychol Bull* 109:163–203.

Mansfield P (1977): Multi-planar image formation using NMR spin echoes. *J Physics* C10:L55–L58.

Mathews AM, MacLeod C (1985): Selective processing of threat cues in anxiety states. *Behav Res Ther* 23:563–569.

Mathews AM, MacLeod C (1994): Cognitive approaches to emotion and emotional disorders. *Ann Rev Psychol* 45:25–50.

Mayberg H (1997): Limbic-cortical dysregulation: A proposed model of depression. *J Neuropsychiatry Clin Neurosci* 9:471–481.

McKenna FP, Sharma D (1995): Intrusive cognitions: An investigation of the emotional Stroop task. *J Exp Psychol Learn Mem Cogn* 21:1595–1607.

McNally RJ, Kaspi SP, Riemann BC, Zeitlin SB (1990): Selective processing of threat cues in post-traumatic stress disorder. *J Abnorm Psychol* 99:398–402.

McNally RJ, Riemann BC, Louro CE, Lukach BM, Kim E (1992): Cognitive processing of emotional information in panic disorder. *Behav Res Ther* 30:143–149.

Murtha S, Chertkow H, Beauregard M, Dixon R, Evans A (1996): Anticipation causes increased blood flow to the anterior cingulate cortex. *Hum Brain Mapping* 4:103–112.

Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia* 9:97–113.

Pardo JV, Pardo PJ, Janer KW, Raichle ME (1990): The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proc Nat Acad Sci USA* 87: 256–259.

Press WH, Flanner BP, Teukolsky SA, Vetterling WT (1988): *Numerical Recipes in C: The Art of Scientific Computing*. New York: Cambridge University Press.

Rauch SL, Shin LM (1997): Functional neuroimaging studies in posttraumatic stress disorder. In: Yehuda R, McFarlane AC, editors. *Psychobiology of Posttraumatic Stress Disorder*. New York: The New York Academy of Sciences, pp 83–98.

Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, et al (1994): Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using 15-O-labeled CO2 and positron emission tomography. *Arch Gen Psychiatry* 51:62–70.

Rauch SL, Savage CR, Alpert NM, Miguel EC, Baer L, Breiter HC, et al (1995): A positron emission tomographic study of simple phobic symptom provocation. *Arch Gen Psychiatry* 52:20–28.

Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, et al (1996): A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry* 53: 380–387.

Rauch SL, Savage CR, Alpert NM, Dougherty D, Kendrick A, Curran T, et al (1997): Probing striatal function in obsessive-compulsive disorder: A PET study of implicit sequence learning. *J Neuropsychiatry Clin Neurosci* 9:568–573.

Reese TG, Davis TL, Weisskoff RM (1995): Automated shimming at 1.5T using echo-planar image frequency maps. *J Magn Reson Imaging* 5:739–745.

Reiman EM, Raichle ME, Robins E, Mintun MA, Fusselman MJ, Fox PT, et al (1989): Neuroanatomical correlates of a lactate-induced anxiety attack. *Arch Gen Psychiatry* 46:493–500.

Shin LM, Kosslyn SM, McNally RJ, Alpert NM, Thompson WL, Rauch SL, et al (1997): Visual imagery and perception in posttraumatic stress disorder: A positron emission tomographic investigation. *Arch Gen Psychiatry* 54:233–241.

Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, et al (in submission): Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related posttraumatic stress disorder: A positron emission tomographic investigation.

Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, et al (1997): Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *J Cogn Neurosci* 9:648–663.

Stroop JR (1935): Studies of interference in serial verbal reactions. *J Exp Psychol* 18:643–662.

Talairach J, Tournoux P (1988): *Co-planar Stereotaxic Atlas of the Human Brain*. Stuttgart:Thieme Medical Publishers.

Vogt BA, Finch DM, Olson CR (1992): Functional heterogeneity in cingulate cortex: The anterior executive and posterior evaluative regions [review]. *Cereb Cortex* 2:435–443.

Vogt BA, Nimchinsky EA, Vogt LJ, Hof PR (1995): Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. *J Comp Neurol* 359:490–506.

Watts FN, McKenna FP, Sharrock R, Trezise L (1986): Colour naming of phobia-related words. *Br J Psychol* 77:97–108.

Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA (1998): Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci* 18:411–418.

Wilhelm S, McNally RJ, Baer L, Florin I (1996): Directed forgetting in obsessive-compulsive disorder. *Behav Res Ther* 34:633–641.

Williams JMG, Mathews A, MacLeod C (1996): The emotional stroop task and psychopathology. *Psychol Bull* 120:3–24.

Woods RP, Cherry SR, Mazziotta JC (1992): Automated algorithm for aligning tomographic images. II. Cross-modality MRI-PET registration. *J Comput Assist Tomogr* 16:620–633.

Zohar J, Insel TR, Berman KF, Foa EB, Hill JL, Weinberger DR (1989): Anxiety and cerebral blood flow during behavioral challenge. *Arch Gen Psychiatry* 46:505–510.