

RICE UNIVERSITY

Gender Specific Neural Correlates of Emotion and Cognition

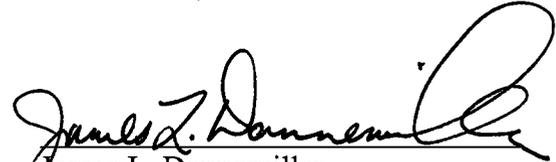
by

Heather M. Lugar

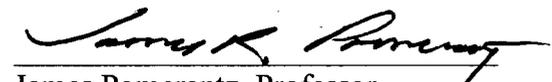
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ABSTRACT

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by

Heather M. Lugar

Evidence suggests that regions within the anterior cingulate cortex (ACC) are sensitive both to emotional and cognitive task demands. This experiment asked whether emotional and cognitive demands are processed separately by ventral and dorsal regions within the ACC, respectively. Results revealed significant individual variability between changes in anxiety and response times with practice during performance of a verb generation task. Correlational analyses of the functional magnetic resonance imaging (fMRI) data were inconclusive. However, exploratory analyses suggest that while the ventral and dorsal subdivisions of the medial prefrontal cortex, which encompasses the ACC, make specialized contributions to the processing of emotion and cognition, respectively, the two subdivisions also appear to interact. These analyses also suggest that there could be a difference in how women and men balance the competing demands of emotion and cognition that might be related to differences in self-concept and neural activity in the default mode network.

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INTRODUCTION

Everyone has experienced the effects of emotion on cognition. Heightened emotion can lead to impulsive decision-making, imprecise problem solving, and ill-chosen words. Much evidence exists from electrophysiological and functional neuroimaging studies, as well as patient studies of lesions and psychopathology, implicating activity in the anterior cingulate cortex (ACC) in both emotional and cognitive processing (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001). In addition, an anatomical division exists between ventral and dorsal portions of the ACC, with each having unique cell structure and projections (Bush, Luu, & Posner, 2000; Vogt, 2005). The ventral ACC is linked to the limbic system, with connections to the amygdala, hypothalamus, and hippocampus, areas implicated in emotional processing, with direct outputs to the autonomic, visceromotor, and endocrine systems. The dorsal ACC has connections with the lateral prefrontal cortex, and the premotor and supplementary motor areas, which are often engaged in difficult cognitive tasks requiring response selection.

It is unclear, however, whether this neuroanatomical distinction extends to a functional delineation in which the ventral portion of the ACC is responsible for affective processing, and the dorsal ACC is responsible for cognitive processing (Allman et al., 2001). On one hand, substantial evidence exists supporting the notion that there is a pure functional distinction in the ACC in which the ventral subdivision is associated specifically with emotional processing, and the dorsal ACC is associated specifically with cognitive processing (Bush et al., 2000; Drevets & Raichle, 1998). For example, in a study requiring cognitive and emotional inhibition, activity in the ACC was compared while the same group of subjects performed two versions of a Stroop-like task—one

involving emotional interference and the other involving cognitive interference (Bush et al., 2000). A double dissociation was revealed in which the emotional interference task activated the ventral but not dorsal ACC, and the cognitive interference task activated the dorsal but not ventral ACC. Furthermore, experiments requiring affective processing, such as recollection of sad memories with simultaneous viewing of sad facial expressions (George et al., 1995) and induction of anticipatory anxiety (Drevets, Videen, Snyder, MacLeod, & Raichle, 1994), report activity primarily in the ventral portion of the ACC. In contrast, studies employing a cognitive task requiring high attentional demands and response selection or inhibition, such as verb generation (Petersen, Fox, Posner, Mintun, & Raichle, 1989), word stem completion (Buckner & Tulving, 1995), reward based decision making (Bush et al., 2002), and visual discrimination (Corbetta, Miezin, Dohmeyer, Shulman, & Petersen, 1991), report activity primarily in the dorsal portion of the ACC.

The ventral/dorsal distinction is further supported by reciprocal suppression, in which the affective (ventral) subdivision of the ACC exhibits deactivations during the performance of demanding cognitive tasks, and the cognitive (dorsal) subdivision exhibits deactivations during the experience of induced and pathological emotional states (Drevets & Raichle, 1998). Deactivations in the ventral ACC have been associated with tasks requiring divided attention and working memory (Coull, Frith, & Grasby, 1995) and visuospatial discrimination (Corbetta et al., 1991), while deactivations in the dorsal ACC have been associated with anticipation of pain (Drevets et al., 1994), film-induced emotion (Lane et al., 1998), and severe depressive episodes (Bench et al., 1992).

Alternatively, it is possible that, while the centers of activation/deactivation may be separable, the overall activity overlaps, and the ventral and dorsal subdivisions of the ACC are functionally interconnected. In an fMRI study exploring the functional organization of the ACC, subjects performed a cognitively demanding task in which they were asked to discriminate between attentional targets and other stimuli in the presence of emotional distracters (Yamasaki, LaBar, & McCarthy, 2002). For analysis, Yamasaki and colleagues divided the ACC into four areas from ventral to dorsal and measured the activity associated with each condition in those four portions of the ACC. They found that the most dorsal slice was only active for targets, supporting the role of the dorsal ACC in cognitive processing. Interestingly, however, they found that the two most ventral slices were not only active in the presence of the emotional distracters, but they also showed an equivalent degree of activation for the targets.

This suggests that there is no clean separation of emotional and cognitive function, at least within the ventral ACC. Evidence also exists suggesting that functioning of the dorsal ACC may not be limited only to cognition, either. By varying their firing rate, inhibitory and excitatory neurons in the dorsal ACC detect targets, identify novel stimuli, recognize conflict, and acknowledge errors, with some of these dorsal, rather than ventral, ACC cells responding preferentially to high-conflict, emotionally laden words (Davis et al., 2005).

Further evidence against a pure distinction between ventral and dorsal was observed in a study by Wang and colleagues (2005) in which subjects' brain activity was compared while they performed a simple number task versus a difficult arithmetic task. In support of the functional distinction within the ACC (Bench et al., 1992; Buckner &

Tulving, 1995; Bush et al., 2000; Corbetta et al., 1991; Coull et al., 1995; Drevets et al., 1994, George et al., 1995; Lane et al., 1998; Petersen et al., 1989), they found that activation in the dorsal portion of the ACC was associated with the cognitively demanding arithmetic task. However, inconsistent with these theories, subjective anxiety ratings correlated positively with this dorsal ACC activation.

Thus, studies examining the functional roles of the ventral and dorsal ACC report conflicting results. However, many of the studies supporting a pure functional division of the ACC have treated emotional and cognitive processing as relatively discrete functions that can be isolated using either emotionally provocative tasks, such as film induced emotion (Lane et al., 1998) or anticipation of pain (Drevets et al., 1994) or cognitively demanding tasks, such as word stem completion (Buckner & Tulving, 1995) or reward based decision making (Bush et al., 2002). The few studies that have examined both emotional and cognitive components of the same task (Wang et al., 2005; Yamasaki et al., 2002) suggest that the relationship between ventral and dorsal ACC may be more complex.

Furthermore, the participants in nearly all of the aforementioned experiments were either mixed sex or same sex groups. Cahill (2005) recently reported that there are significant gender differences in neural activity, and there have been multiple reports of women exhibiting greater ACC activity than men during negative affect conditions (Wager, Phan, Liberzon, & Taylor, 2003). So gender differences could also be a factor contributing to inconsistent results with regard to emotional and cognitive processing in the ACC. In fact, in a follow-up study Wang and colleagues (2007) reported that women's and men's neural responses to psychosocial stress, as measured by performance

of a demanding arithmetic task, produced such distinctly different activity patterns that a machine classification was able to identify gender with over 94% accuracy. While women's stress response was characterized by increased activity in the limbic system, including the dorsal ACC, men showed asymmetrical right prefrontal cortex increases with corresponding decreases in left orbitofrontal cortex.

Butler and colleagues (2007) also recently reported that reciprocal suppression between ventral and dorsal ACC during performance of a difficult mental rotation task, specifically deactivation of the ventral ACC, was observed only in women. They proposed that activations and deactivations in ventral ACC so often associated with performance of cognitively demanding tasks, could be driven by female participants (Butler et al., 2007; Derbyshire, Nichols, Firestone, Townsend, & Jones, 2002; Wager et al., 2003).

However, both studies reporting gender differences in brain function in response to psychological stress (Butler et al., 2007; Wang et al., 2007) involved the performance of tasks, in particular visuospatial and arithmetic, routinely reported to be more easily and more accurately performed by men in comparison to women (Halari et al., 2005). Despite both groups performing similarly in these two studies, other factors that could have differed between women and men in performance of the tasks, such as mental effort or perceived anxiety, might have contributed differently to the accomplishment of a similar outcome (Butler et al., 2007; Wang et al., 2007). Indeed, perceived stress between low and high stress conditions differed between women and men in the experiment conducted by Wang and colleagues (2007). Therefore, it is not known whether the differences reported in these studies reflect a fundamental difference in ACC

activity between genders, or if it is domain specific (Butler et al., 2007). Assessing psychosocial stress in the language domain, in which women are known to have an advantage over men (Halari et al., 2005), could help to discriminate between these two possibilities.

Therefore, the original question remains: Do the ventral and dorsal subdivisions of the ACC have distinct functional roles in emotional and cognitive processing? Subsequent to the design of the study and to data collection, several papers appeared that suggested important gender differences in neural activity in these areas. Therefore, exploratory analyses were also conducted to address a follow-up question: Are these roles between subdivisions of the more expansive, medial prefrontal cortex (mPFC), different between women and men?

The first step is to determine whether emotional and cognitive processing can be dissociated. Many studies have shown that subjects become faster and more accurate in a wide variety of cognitive tasks with repeated performance of the task (Petersen, van Mier, Fiez, & Raichle, 1998; Raichle et al., 1994; Simpson, Snyder, Gusnard, & Raichle, 2001), and it is likely that familiarization with a difficult task may reduce performance anxiety in subjects who have a desire to perform well. Indeed, Simpson and colleagues (2001) observed similar changes in anxiety and response time as subjects practiced a verb generation task. In the Simpson et al. experiment, anxiety level and reaction times were measured during four conditions: (1) single word reading, in which subjects simply read aloud a single list of words; (2) naïve verb generation, in which subjects were initially exposed to the verb generation task and a specific list of words; (3) practiced verb generation, in which subjects repeated the verb generation task with the same list of

words (from the previous naïve run) for nine more blocks; (4) novel verb generation, in which subjects performed the verb generation task with a new set of words. Similar effects were observed in anxiety and reaction time measures. Both were greater in the verb generation than in the read task, and both decreased with practice. Thus, anxiety and reaction times were confounded, making it difficult to assess the individual contributions of each to the neural activity reported in the ACC. The authors concluded that the ACC activity represented a combined effect of participant anxiety levels and the attentional demands of the task.

Although results from Simpson et al. (2001) indicate that anxiety and performance are confounded in the cognitively demanding verb generation task, it is possible that they might be dissociable in a less demanding task, such as single word reading. Indeed, Simpson and colleagues (2001) reported lower anxiety and quicker reaction times in the single read run in comparison to verb generation, but they did not examine the effects of practice on the read task. Therefore, it is possible that anxiety and performance could be dissociated by comparing practice effects across the two tasks, with read showing a decrease in reaction time with practice, but not anxiety, and verb generation showing a decrease in both. To examine this possibility, changes in anxiety and performance with practice were measured during verb generation and single-word reading in the following preliminary experiment.

Preliminary Experiment

Method

Participants

Forty-eight subjects (24 female mean age 20.43 years, SD = 1.67; male mean age 20.96 years, SD = 2.86) from the Rice University community participated in the study. Subjects reported being neurologically healthy, having normal or corrected-to-normal vision, and were native English speakers. Informed consent was obtained from each subject in accordance with the guidelines of the Rice University Institutional Review Board.

Design and Materials

A 2 x 4 repeated measures design was originally employed in which task (verb generation vs. read) and run (run 1 vs. run 2 vs. run 3 vs. run 4) were within-subjects independent variables. Exploratory analyses were also conducted in which gender was a between-subjects variable in a 2 x 4 x 2 design.

Stimuli were 160 concrete nouns ranging in frequency from 1, least frequent, to 299, most frequent (Francis & Kucera, 1982), with the number of letters per word ranging from 3 to 11. The words were divided into four lists of 40 words that were equated for frequency, mean of 46.27, and number of letters, mean of 5.07. Each list was counterbalanced across conditions, verb generation and read, and all subjects, male and female. White stimuli were presented on a black background in Helvetica font, size 36, on a Macintosh computer using PsyScope (Cohen, MacWhinney, Flatt, & Provost, 1993), and each word was presented for 100 milliseconds at an average rate of 1 per 5 seconds with a fixation cross presented in between the words. A chin rest was used to

maintain the subject's distance 30 inches from the computer screen. Words subtended approximately 0.72° of visual angle vertically and between 1.43° and 5.20° horizontally.

Procedure

All subjects completed four blocks of the read task and four blocks of the verb generation task. The read task always preceded the verb generation task because previous pilot data indicate that subjects attempt to passively generate verbs during the read task if they have performed the verb generation task immediately prior. During the first read task, subjects were simply asked to read the words aloud as quickly and accurately as they could. Subjects read the same list of words for three runs. During the fourth run, a novel list of 40 nouns was presented in which subjects were asked to read the words aloud. During the verb generation task, subjects were presented with a new set of 40 nouns, and they were asked to generate verbs associated with the nouns presented to them. Subjects generated verbs to the same list of words for three runs. During the fourth run, subjects were presented with a final, new set of 40 nouns in which they were asked to generate verbs.

Between runs, subjects completed the state portion of the State-Trait Anxiety Inventory (STAI; Spielberger, 1983), a widely used self-report measure of anxiety. The state portion of the STAI consists of 20 statements, and subjects selected from the following four options the degree to which each statement described how they felt during the run just completed: 1) Not at all 2) Somewhat 3) Moderately so or 4) Very much so. There are 10 anxiety-absent statements, such as "I feel relaxed" and 10 anxiety-present statements, such as "I feel nervous", and the range of scores is 20 to 80. An example of the behavioral paradigm is shown in Figure 1.

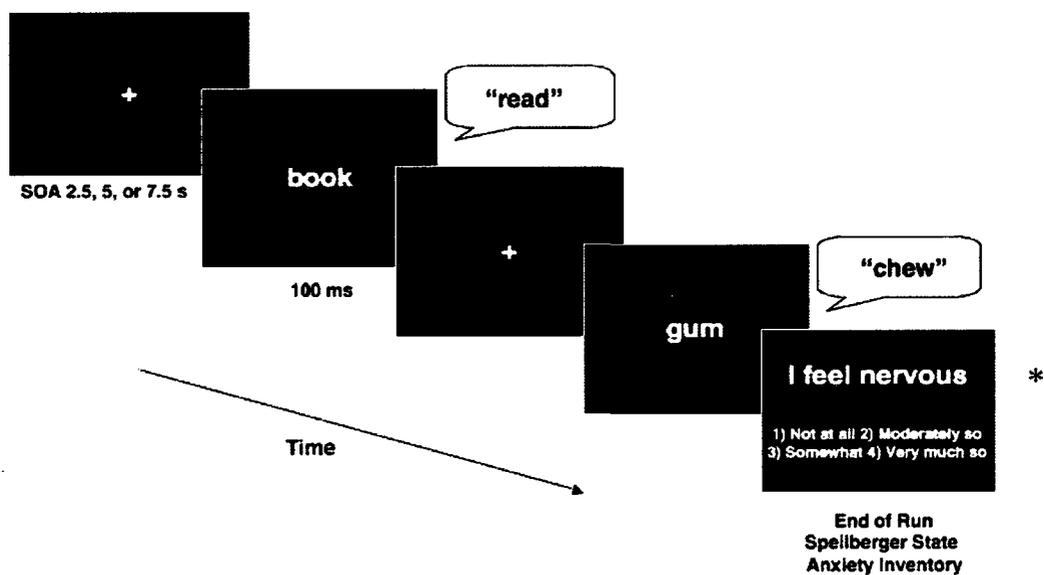


Figure 1. Schematic of the verb generation paradigm. * Spielberger statements that are written in present tense were not modified. Participants in our experiment were specifically asked to read the statements as they applied to the run just completed.

Voice response latency was recorded as a measure of performance on the tasks. Voice responses were digitally recorded and response times were automatically extracted (Nelles, Lugar, Coalson, Meizin, Petersen, & Schlaggar, 2003) and coded as either correct or incorrect. Read responses were scored as correct if they were properly pronounced and incorrect if mispronounced or omitted. Verb generation responses were considered correct if a single verb was produced in present tense and was in some way associated with the noun. Responses were scored as incorrect if they were anything other than a verb, a verb that was not associated with the noun, or if there was no response at all.

Results – Original Hypotheses

Anxiety

STAI data were analyzed using a 2 x 4 (task x run number) repeated measures analysis of variance (ANOVA). Results are shown in Figure 2.

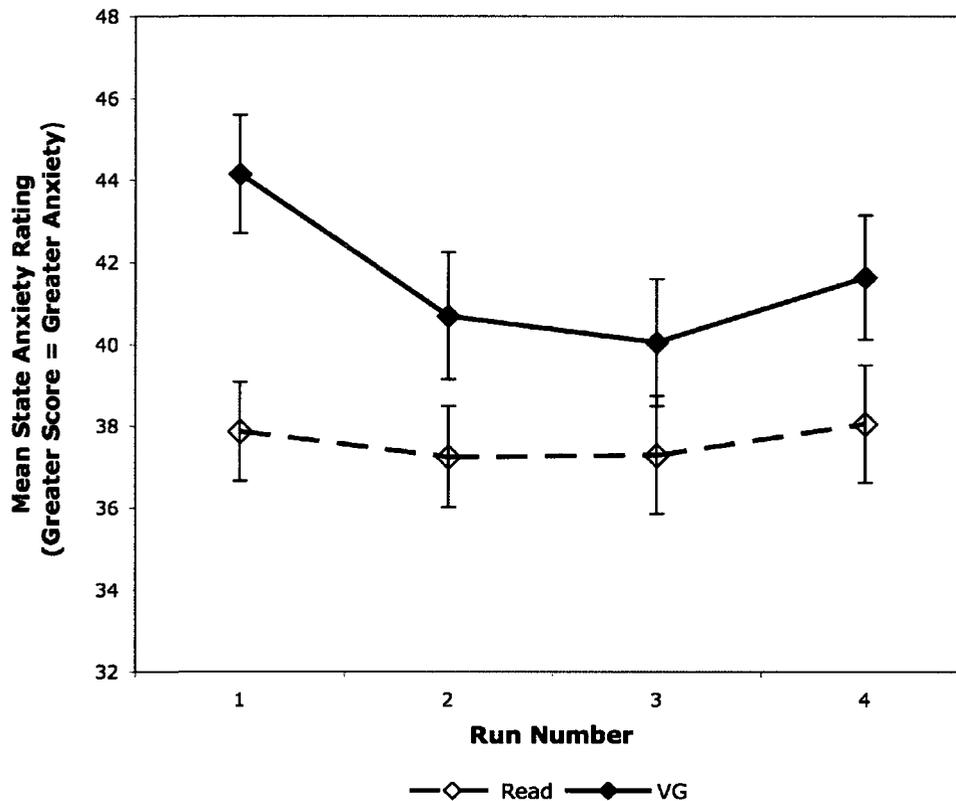


Figure 2. Mean anxiety level by run on read and verb generation tasks for 48 behavioral participants showing a main effect of task, main effect of run, and an interaction of task x run.

As expected, there was a main effect of task for anxiety, $F(1, 47) = 31.45, p < .001$, with subjects reporting greater anxiety in the verb generation than the read task. Subjects also reported differential effects of anxiety between the two tasks, as reflected in the main effect of run $F(3, 141) = 4.76, p = .003$. Finally, there was a significant interaction of

task x run, $F(3, 141) = 3.49, p = .017$, in which the reaction time reduction across runs was greater for verb generation than read.

Performance

Reaction times for correct responses were analyzed using a 2 x 4 (task x run number) repeated measures ANOVA. Results are shown in Figure 3.

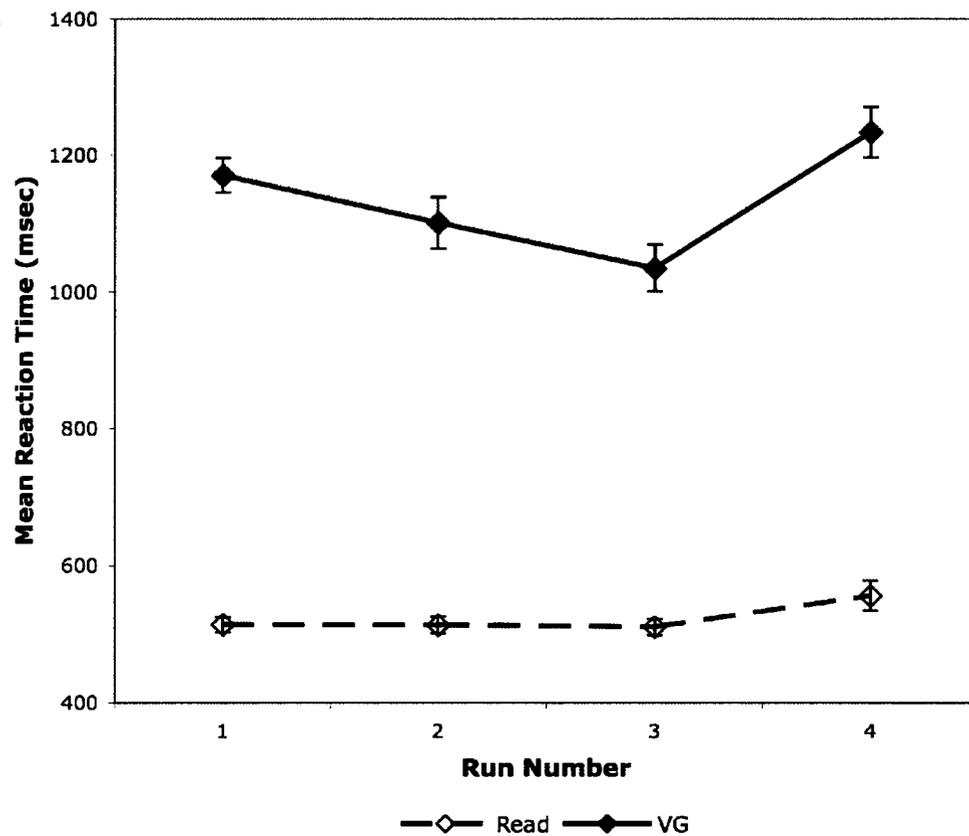


Figure 3. Mean reaction time by run on read and verb generation tasks for 48 behavioral participants showing a main effect of task, main effect of run, and an interaction of task x run.

There was a main effect of task for reaction time, $F(1, 47) = 580.22, p < .001$, in which subjects' reaction times were longer in verb generation than read, and a main effect of run, $F(3, 141) = 16.88, p < .001$, in which subjects showed a decrease in reaction time across runs for both tasks. There was also an interaction of task by run, $F(3, 141) = 8.20, p < .001$, in which the reaction time reduction across runs was greater for verb generation than read.

Results from the analysis of error rates were similar to those observed for response times (see Table 1). Main effects of task, $F(1, 47) = 52.38, p < .001$, run, $F(3, 141) = 4.52, p = .005$, and an interaction of task by run, $F(3, 141) = 3.41, p = .020$ were observed.

Table 1. Mean error rates per run for both tasks in the preliminary study

Run	Task	
	Read	Verb Generation
1	0.012	0.053
2	0.014	0.032
3	0.009	0.028
4	0.016	0.023

Results – Exploratory (Gender Differences)

Anxiety

STAI data were also analyzed using a 2 x 4 x 2 (task x run number x gender) repeated measures analysis of variance (ANOVA). Results are shown in Figure 4.

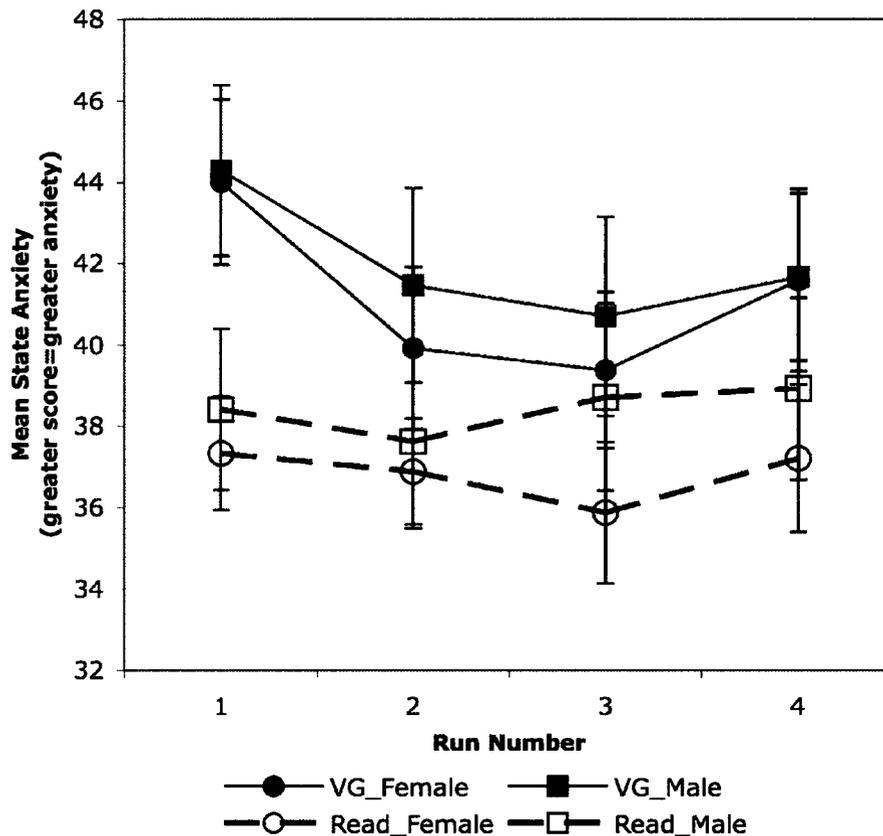


Figure 4. Mean anxiety level by run on read and verb generation tasks for 48 behavioral participants (24 female, 24 male) showing a main effect of task, main effect of run, and an interaction of task x run but no gender effects.

As with initial analyses, there was a main effect of task for anxiety, $F(1, 46) = 30.98, p < .001$ and a main effect of run $F(3, 138) = 4.70, p = .004$. Finally, there was a significant interaction of task x run, $F(3, 138) = 3.45, p = .018$, in which the effect of run differs

between verb generation and read. The simple effects will be examined in a following section. No significant effect of gender was observed, $F(1, 46) = 0.22, p = .639$, nor was there an effect of task by gender, $F(1, 46) = 0.30, p = .590$, run by gender, $F(3, 138) = 0.40, p = .751$, or task by run by gender, $F(3, 138) = 0.44, p = .723$.

Performance

Reaction times for correct responses were analyzed using a 2 x 4 x 2 (task x run number x gender) repeated measures ANOVA. Results are shown in Figure 5.

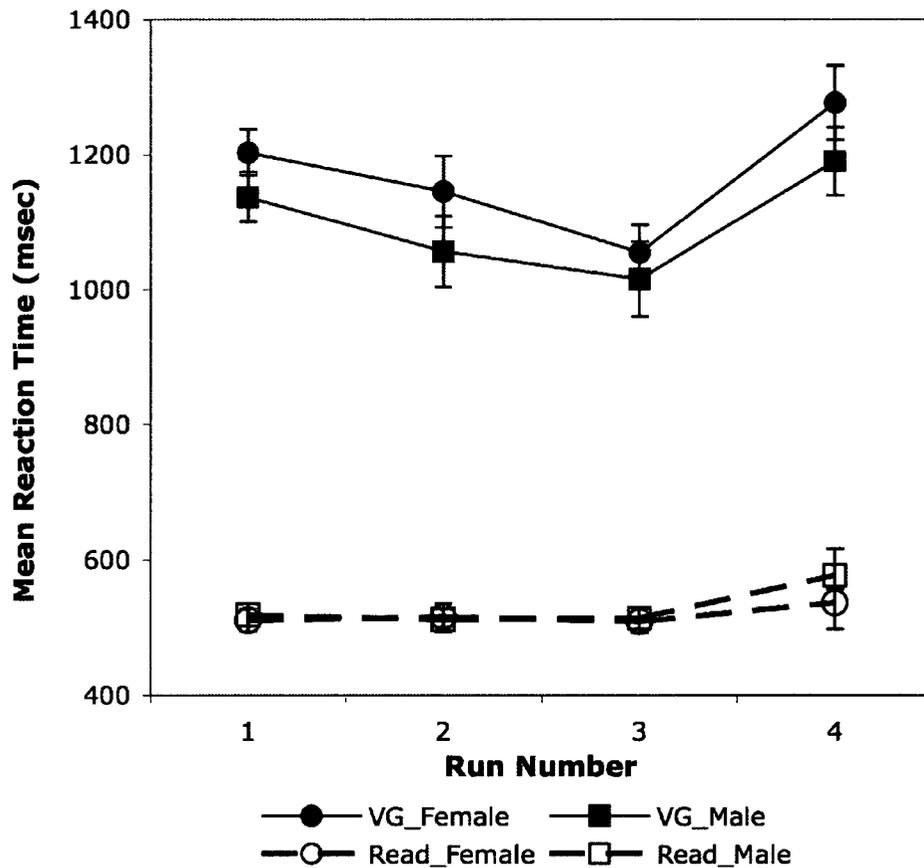


Figure 5. Mean reaction time by run on read and verb generation tasks for 48 behavioral participants showing a main effect of task, main effect of run, and an interaction of task x run but no gender effects.

There was a main effect of task for reaction time, $F(1, 46) = 601.89, p < .001$, and a main effect of run, $F(3, 138) = 16.60, p < .001$. There was also an interaction of task by run, $F(3, 138) = 8.11, p < .001$, in which the effect of run differed between verb generation and read. An examination of the simple effects follows. Again, there was no effect of gender, $F(1, 46) = 0.71, p = .403$, nor were there interactions of task by gender, $F(1, 46) = 2.75, p = .104$, run by gender, $F(3, 138) = 0.24, p = .870$, or task by run by gender, $F(3, 138) = 0.50, p = .685$.

Results from the analysis of error rates were similar to those observed for response times (see Table 2). Main effects of task, $F(1, 46) = 33.10, p < .001$, run, $F(3, 138) = 4.42, p = .005$, and an interaction of task by run, $F(3, 138) = 4.052, p = .009$ were observed. In this case, women made more errors than men, $F(3, 138) = 4.31, p = .044$, but there were no significant interactions with gender, task by gender, $F(1, 46) = 1.48, p = .230$, run by gender, $F(3, 138) = 0.37, p = .779$, or task by run by gender, $F(3, 138) = 0.21, p = .893$.

Table 2. Mean error rates per run for both tasks by gender in the preliminary experiment

Run	Females		Males	
	Read	Verb Generation	Read	Verb Generation
1	0.015	0.064	0.008	0.041
2	0.011	0.037	0.016	0.026
3	0.016	0.039	0.003	0.016
4	0.020	0.011	0.011	0.034

Because participants were not instructed about whether or not to provide the same verb in response to subsequent presentations of the same noun, it is possible that anxiety levels and reaction times might differ between subjects who frequently repeated the same verb during practice conditions as compared to those participants who tended to generate

a new verb for each subsequent presentation. So, with regard only to the third presentation of the nouns, responses were coded 1-3. One represents generation of a verb for the first and only time in response to the third presentation of the noun, and 3 represents the same verb being produced in response to all three presentations of the noun. Overall, it seems that providing the same response a second and third time was a common strategy used by participants, so there was very little variability. The mean repetition rate for women was 2.44 (SD = 0.23) and mean rate for men was 2.49 (SD = 0.25). The percentage of new verbs provided in response to the third presentation of nouns was 15% (SD = 9%) for women and also 15% (SD = 10%) for men. Women and men did not differ in verb repetition rate or novel verb generation, and neither variable produced was significantly correlated with changes in state anxiety or reaction time with practice at the $p = .05$ level.

Absence of Practice Effects in the Read Task

When more carefully examining potential practice effects in the read task using a repeated measures ANOVA, there was no effect of run (run 1 vs. run 2 vs. run 3 vs. run 4) in the anxiety scores, $F(3, 138) = 0.45, p = .718$, and there was no effect of run in the reaction time data for read when excluding run 4, $F(2, 92) = 0.11, p = .896$, which showed an overall increase in reaction time in comparison to the other three runs. A direct comparison of run 1 to 3 failed to reveal a significant difference, $t(47) = 0.38, p = .706$ (two-tailed). While an increase in reaction time was expected in run 4 (novel words) compared to run 3 (practiced words), this difference is difficult to interpret in the absence of changes across runs 1-3. Based on these calculations, it was concluded that the read

task failed to reveal the expected practice effects, so it was excluded from the final analysis.

Relationship Between Anxiety and Performance in the Verb Generation Task

The similar patterns observed in the anxiety and performance data at the group level in the verb generation task suggest that these variables are not dissociable. However, it is possible that the two may be dissociated at the individual level. To assess the relationship between anxiety and reaction time decreases across individuals, a difference score was calculated by subtracting naïve scores of run 1 from practiced scores of run 3, for both anxiety and reaction time. Run 3, rather than run 4, was chosen as the comparison to run 1, so as not to confound the effects of word list with practice effects. In addition, anxiety levels were greater in naïve (run 1) than novel (run 4) conditions. Correlations between changes in anxiety and changes in reaction time were computed separately by gender for the verb generation task as well as averaged across gender. None of these correlations was significant, $r_{female} = .09, p = .832, r_{male} = .13, p = .759, r_{average} = .01, p = .981$. As shown in Figure 6, there was quite a bit of variability among individuals. For example, some individuals exhibited a dissociation between anxiety and reaction time with practice in which there was a decrease in anxiety but either an increase or no change in reaction time. The reverse was also true, with some subjects showing an increase in anxiety and a decrease in reaction time.

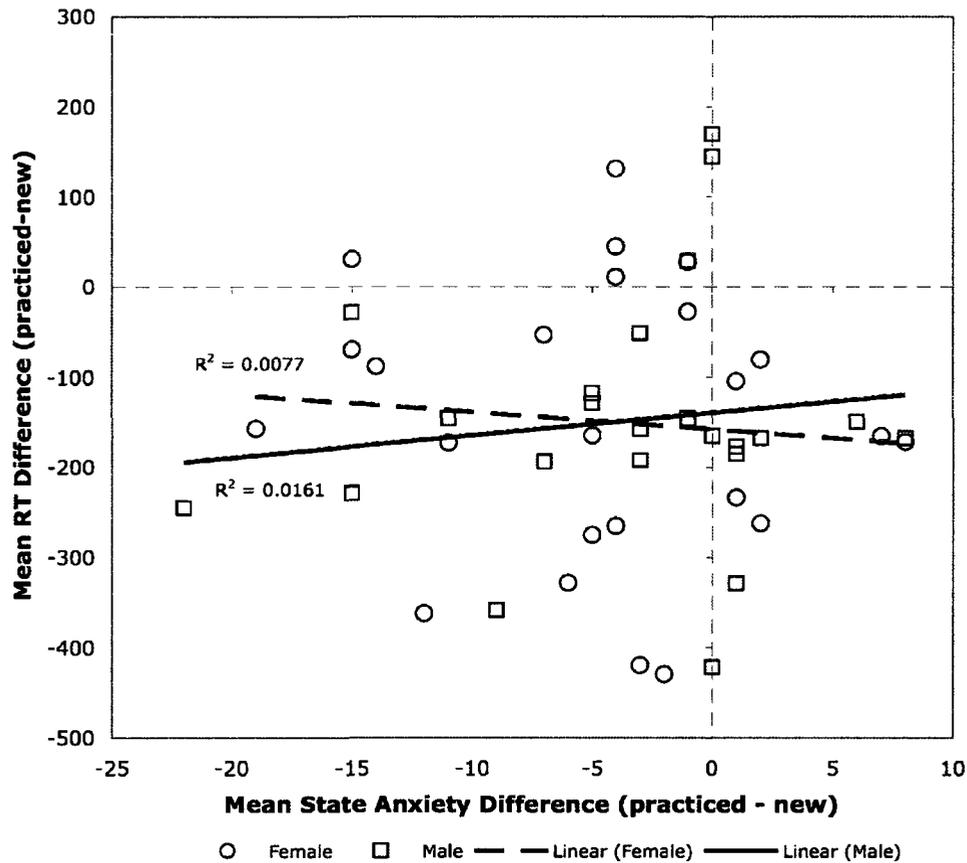


Figure 6. No correlation was revealed in difference scores (practiced minus new) in 48 behavioral subjects for mean state STAI (x axis) and reaction times (y axis) for verb generation, indicating individual variability.

Discussion

Thus, behavioral results failed to dissociate anxiety and response time at the group level in women or men. Anxiety and reaction times were greater for the verb generation than the read task in both females and males, and both measures decreased with practice in the verb generation task but not the read task. Difference scores calculated to assess the magnitude of change between anxiety scores and reaction times in the verb generation task, however, revealed no correlation. Therefore, while changes

in anxiety and reaction time may not be dissociable at the group level, they may be dissociable at the individual level when additional variables are considered (e.g., fMRI data). Ultimately, examining this individual variability using fMRI should allow the assessment of specific contributions of the ventral and dorsal subdivisions to ACC activity during cognitively demanding tasks that may unintentionally elicit performance anxiety.

Given the great inter-individual variability found between changes in anxiety levels and response times in the preliminary experiment, two additional behavioral measures, the trait portion of the Spielberger's State Trait Anxiety Inventory scale (1983) and the International Personality Item Pool (IPIP) Big 5 Personality Inventory (Goldberg, 1999), were administered to participants in the fMRI experiment to explore the possibility that some of these individual differences may be attributable to more enduring differences in individual dispositions. The state portion of the STAI, which was administered in the preliminary experiment to measure transient changes in anxiety levels, should be complemented by the results of the trait STAI in the fMRI experiment, given that trait STAI measures an individual's general tendency to perceive various situations as threatening (Spielberger, 1983).

Personality refers to stable individual differences in disposition, character, habits, and reactions (Kumari, ffytche, Williams, & Gray, 2004). Personality traits have been shown to account for individual differences in affective responsiveness. More specifically, high scores in extraversion are strongly associated with positive affect and high scores in neuroticism are strongly associated with negative affect (Costa & McRae, 1980; Eysenck, 1990). Given the strong affective component to at least these two factors

of the Big 5, extraversion and neuroticism, activity within the ventral portion of the ACC may reflect this relationship between affect and personality (Gray, Braver, & Raichle, 2002). Indeed, activity in the ventral ACC has previously been found to correlate with extraversion (Johnson et al., 1999), neuroticism (Gray et al., 2005), and stable individual differences in negative affect (Zald, Mattson, & Pardo, 2002), which is in line with the proposed functional specialization of the ventral and dorsal ACC.

Finally, anxiety and latency effects may be dissociated by examining different types of neural signals that can be measured using fMRI. Using a mixed-blocked/event-related design (Donaldson, 2004; Donaldson, Petersen, Ollinger, & Buckner, 2001; Visscher et al., 2003), two types of neural signals can be measured, and both types have been observed in the ACC (Burgund, Lugar, Miezin, & Petersen, 2003; Donaldson et al., 2001). *Transient signals* are signals that are time-locked to the presentation of individual events. These signals have been shown to decrease with repeated presentation of a stimulus (Buckner et al., 1998; Burgund et al., 2003; Koutstaal et al., 2001; van Turennout, Ellmore, & Martin, 2000), and thus may underlie decreases in response latency with repetition.

In contrast, *sustained signals* are signals that endure throughout an entire task block and do not depend on the presence or absence of particular events. Because of their extended time courses, sustained signals seem likely candidates for reflection of underlying emotional states and personality traits, which might also have a prolonged duration, relative to event processing. Indeed, it has been suggested that the ventral ACC may reflect sustained activity, rather than transient, due to its role in monitoring the internal emotional state, viscera, internal milieu, and autonomic responses (Phan, Wager,

Taylor, Liberzon, 2002). The proposed fMRI experiment was designed to examine the role that these two signals may serve in ventral and dorsal functioning within the ACC.

It should be noted here that the original proposal was designed to examine the functional contributions of the ventral and dorsal subdivisions of the ACC to emotion and cognition using the mixed blocked/event-related fMRI design by measuring changes in state anxiety and reaction times. However, given aforementioned reports in the literature, gender, trait anxiety, and the IPIP Big Five Personality Inventory were later added as factors for exploratory purposes. Results of the original proposal are followed by these exploratory results. Further review of the relevant literature will be reserved for the Discussion section.

fMRI Experiment

Method

Participants

Sixteen adult subjects (8 female mean age 23.95 years, SD = 2.15; 8 male mean age 25.88 years, SD = 4.55) from the Rice University community were asked to participate in the study. All subjects reported having normal or corrected-to-normal vision, no history of neurological or psychiatric disorders, and were native English speakers. Informed consent was obtained from each subject in accordance with the guidelines and approval of the Rice University and Baylor College of Medicine Institutional Review Boards.

Behavioral Procedure

Behavioral Paradigm. The behavioral procedure and materials were similar to those used in the preliminary experiment described above with the following exceptions.

Because the read task failed to reveal practice effects, it was replaced with additional verb generation runs to increase power. In total, ten runs of verb generation were completed. Subjects produced verbs to a new set of nouns four times (runs 1, 4, 7, 10), performing a second and third practice run (runs 2, 5, 8 and 3, 6, 9, respectively) with each of the first three sets of words. A baseline of the state STAI measure was collected immediately after subjects were placed into the scanner, but prior to MR data acquisition. Thereafter, state STAI was collected after completion of each of the ten BOLD runs, in which subjects performed the verb generation task while we collected reaction times.

Trait STAI and IPIP. After exiting the scanner, subjects completed the trait portion of the STAI. Like the state STAI, the trait STAI consists of 20 statements, and subjects selected from the following four options the degree to which each statement described how they *generally* felt: 1) Not at all 2) Somewhat 3) Moderately so or 4) Very much so. There are 10 anxiety-absent statements, such as “I feel satisfied with myself” and 10 anxiety-present statements, such as “I feel inadequate,” and the range of scores is 20 to 80. In contrast to the state STAI, which measures transitory changes in anxiety, the trait STAI measures a relatively stable trait that is associated with the likelihood that individuals interpret various situations as threatening or dangerous.

Participants then completed the 50-item, abbreviated IPIP Big Five Personality Inventory (Goldberg, 1999). Participants were asked to read each statement, such as “Am the life of the party,” and rate how accurately they believed it described them: 1) Very inaccurate 2) Moderately accurate 3) Neither inaccurate nor accurate 4) Moderately Accurate 5) Very accurate. There are ten items per big-five factor: Extraversion (E), Agreeableness (A), Conscientiousness (C), Emotional Stability (ES), and Intellect (I).

Scores range from 0-60 with each factor. Those with high scores in extraversion tend to be optimistic, energetic, and sociable. Extraversion is generally associated with positive affect. The opposite pole of the extraversion scale is introversion. Introverts tend to be quiet, generally requiring little stimulation, with a preference for being alone. People who are agreeable tend to be considerate, generous, and cooperative. Those who score high in conscientiousness are described as organized, ambitious, and reliable. Emotional stability, which is the opposite pole of neuroticism, is the dimension measured in the IPIP. Those who are neurotic tend to be emotionally reactive, anxious, and depressed. Neuroticism is associated with unstable, negative affect. People high in emotional stability, by contrast, are characterized by less negative affect, and tend to be more emotionally calm and stable. Finally, people who score high in intellect/imagination are imaginative, open to experience, and intellectually curious.

Calculation of Change with Practice. To assess the magnitude of change with practice in individual participants, a single difference score was calculated for reaction time, state anxiety, and fMRI signal changes in which the new condition was subtracted from the practiced condition. In the behavioral measures, negative scores reflect decreases (improvement) in response time and state anxiety with practice, and positive scores reflect increases (decrements). In fMRI signal difference scores, two patterns of change result in a negative score and two patterns of change result in a positive score, as shown in Figure 7.

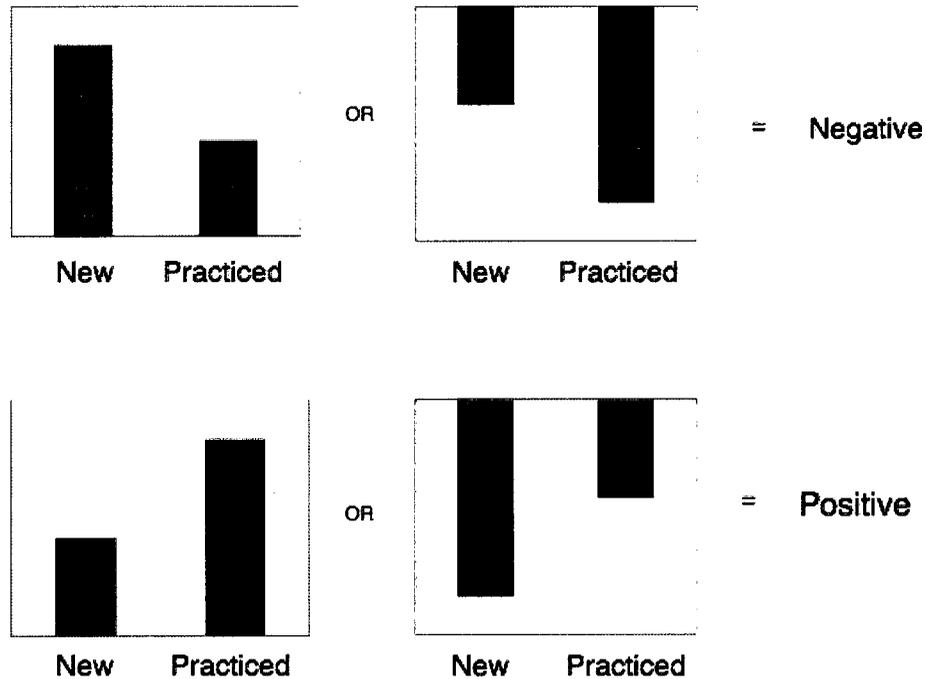


Figure 7. Examples of how difference scores were calculated for both behavioral and fMRI data, resulting in either negative or positive values.

Negative scores (going “down”) characterize practice with either a positive activation becoming less positive (decreasing in magnitude) or negative (dropping below baseline), or a negative (deactivation) signal becoming more negative (greater deflection from baseline). Positive scores (going “up”) describe the opposite patterns in which, with practice, positive activations become even greater in magnitude, negative signals (deactivations) become positive, or negative signals (deactivations) become less negative (less deflection from baseline).

fMRI Procedure

Data Acquisition. A Siemens 3.0-Tesla Allegra scanner (Erlangen Germany) was used to acquire MRI data, and an MP-RAGE T1 weighted scan was collected at the beginning of the scan session. Blood Oxygenation Level Dependent (BOLD) data collected included 16 contiguous axial images per TR (2.5), parallel to the anterior-posterior commissure plane. To establish a steady state, functional data collection began after the first four frames.

A mixed blocked/event-related design (Donaldson et al., 2001; Visscher et al., 2003) was used in which two experimental blocks alternated with three control blocks within a single BOLD scan, for a total of ten functional scans. Stimuli were presented in a jittered, event-related fashion with 20 nouns presented in each of the two experimental blocks. The onset of the stimuli was time-locked with the onset of the scanner, and subjects were given an instructional cue prior to each experimental block.

A Macintosh computer and PsyScope (Cohen et al., 1993) were used to present a stimulus display projected at the end of the bore into the subjects' view via a mirror. To control for eye movement, during both control and experimental blocks, participants were asked to focus on a fixation cross projected on the screen visible to them and to maintain fixation even while stimuli were presented during experimental blocks. Subjects were provided with headphones and a microphone to dampen the noise of the scanner and allow communication between the experimenter and the participant, and overt responses to the verb generation task were recorded for scoring.

fMRI Data Analysis. Automated software was used to correct for motion artifact within and across runs in each participant using a rigid body translation and rotation

(Friston, Williams, Howard, Frackowiak, & Turner, 1996; Snyder, 1996). To correct for changes in signal intensity introduced by acquisition order, sinc interpolation was used to temporally realign image slices in time to the midpoint of the first slice to account for differences in acquisition time across slices. BOLD data were registered to the MP-RAGE data for each individual and then transformed into standard stereotactic space using 2 mm isotropic voxels (Talairach & Tournoux, 1988).

fMRI data were based on the general linear model (GLM) implemented with in-house software (Friston, Jezzard, & Turner, 1994; Josephs, Turner, & Friston, 1997; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000; Worsley & Friston, 1995; Zarahn, Aguirre, & D'Esposito, 1997) to produce estimates of the magnitude of effects. The GLM was coded for errors (only correct responses were included in the analysis), the instructional cues at the beginning and end of task blocks, the effects of a linear trend (to account for within-run drift), constant term (to account for run mean), and finally to separate transient and sustained signals. For transient effects, no assumptions were made regarding the shape of the hemodynamic response. Rather, the hemodynamic response function (% BOLD signal change as a function of time) was modeled over the first seven time points following the presentation of each stimulus. Sustained effects, by contrast, were coded as an assumed square wave shape producing a single magnitude estimate for each task block. For the analyses of both transient and sustained activity, signals during the verb generation task blocks were compared to signals during fixation-only control periods.

Because the anterior cingulate spans a large portion of the medial surface of the brain (Vogt, Finch, & Olson, 1992), we did not define a priori regions. To identify

regions exhibiting transient and sustained activity, separate voxel-wise, one-way repeated measures ANOVAs were performed, with practice (new vs. practiced) as the within subjects factor and gender (female vs. male) as the between subjects factor. The resulting sphericity corrected statistical images were then smoothed by a 4 mm radius hard sphere kernel, and region coordinates were identified by using a peak-finding and region-finding algorithm, in which region peak activation met a statistical threshold of $p < .005$ (uncorrected) in transient signals and $p < .025$ (uncorrected) in sustained signals (Talairach & Tournoux, 1988). Peaks less than 10 mm apart were averaged together, a 10 mm sphere was placed over the center of each peak, and all voxels within each sphere were masked to meet a statistical threshold of $p < .01$ (uncorrected) for transient signals and $p < .05$ (uncorrected) in sustained signals.

Strict criteria were established in determining whether or not regions were to be included in the final analyses. All reported time courses peaked at either time point 3 or 4, the absolute magnitude of those peaks was 0.1% change or greater, and the “tails” (time points 1, 2, 5-7) of the time courses were smaller in magnitude than the peaks. Regions whose peaks were in white matter, instead of gray, were excluded from further analyses.

As with the behavioral data, difference scores were also calculated for the functional data by subtracting activation values of the new condition from the practiced condition. Most positive activation time courses peaked at time point 3, and most negative/deactivation time courses peaked at time point 4, 2.5 seconds later, thus exhibiting a different pattern between positive and negative time courses that has been previously reported by Meltzer and colleagues (2008). Since there were some

exceptions, however, the “peak” time point used to compute difference scores for the transient regions was chosen on a region-by-region basis by selecting the time point with greatest absolute magnitude. Since time is not a factor in sustained activity, only a single value per task block is produced and was used in the computation of differences scores for sustained activity.

Results

Behavioral Results – Original Hypotheses

Assigning Conditions. Runs 1, 4, 7, and 10 were coded as the “new” condition, in which each set of words was presented for the first time. Because there were no significant differences in either state anxiety or response time between the second and third practice sets, all p 's > .60, runs 2, 3, 5, 6, 8, and 9 were collapsed and coded as the “practiced” condition.

Anxiety. State STAI data were analyzed using a 2 level repeated measures analysis of variance (ANOVA). Results are shown in Figure 8A. Contrary to the preliminary study, the main effect of practice in state anxiety failed to reach significance, $F(1, 15) = 1.88, p = .190$.

Performance. Reaction times for correct responses were analyzed using a 2 level repeated measures ANOVA. Results are shown in Figure 8B. As in the preliminary study, there was a main effect of practice for reaction time, $F(1, 15) = 7.96, p = .013$, in which subjects' reaction times were longer in the new condition than in the practiced one.

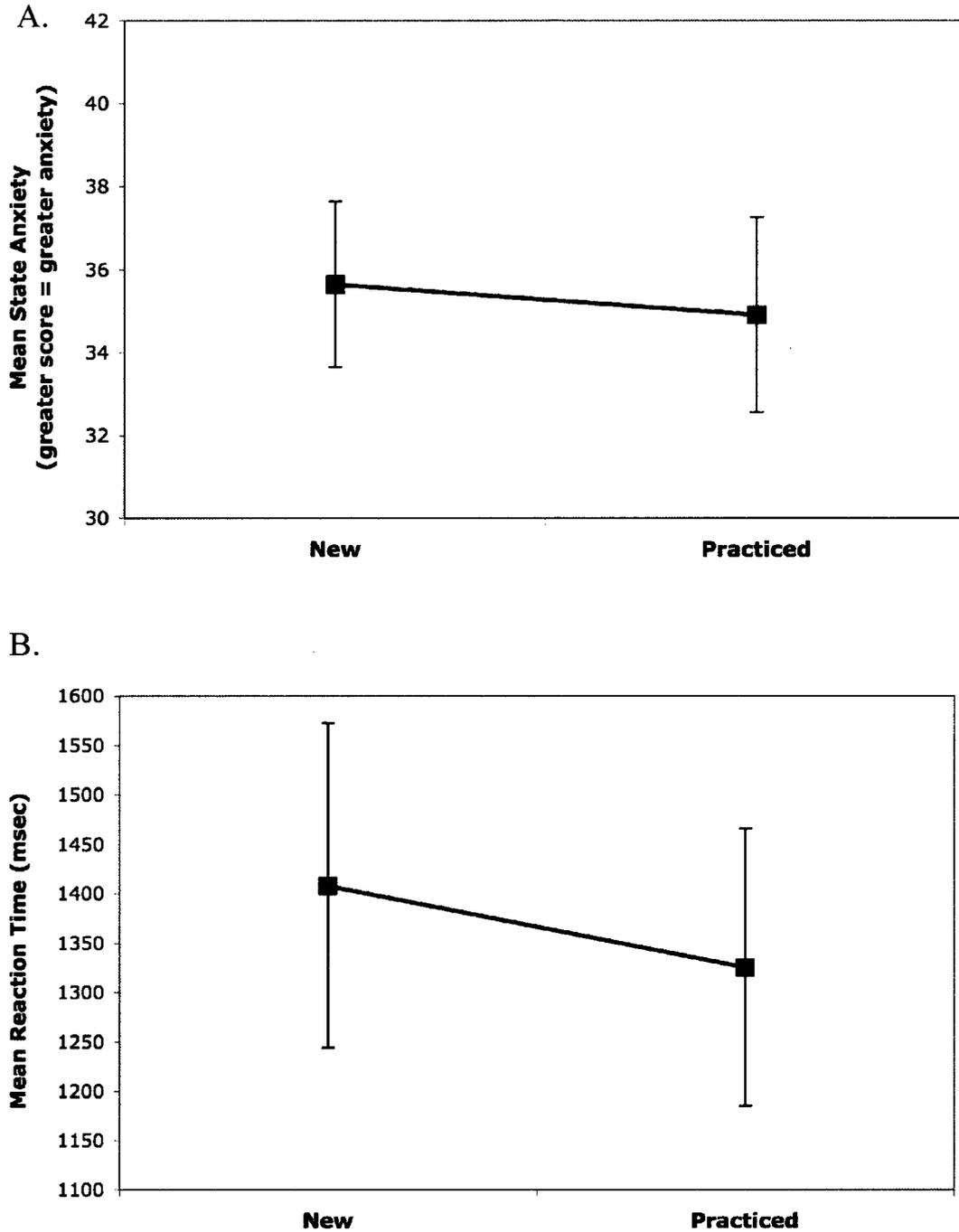


Figure 8. Behavioral results for verb generation in 16 fMRI subjects reflecting A) A non-significant downward trend with practice in mean anxiety level. B) A main effect of practice in mean reaction time.

Results from the analysis of error rates were similar to those observed for response times (see Table 3). There was a main effect of practice, $F(1, 15) = 9.35, p = .008$, in which error rates were higher in the new than in the practiced condition.

Table 3. Mean error rate by practice level for fMRI verb generation task

Level	Mean Error Rate
New	0.066
Practiced	0.041

Relationship Between Anxiety and Performance. As in the preliminary study, the fMRI experiment revealed similar patterns observed in the anxiety and performance data at the group level, but there was substantial variability at the individual level, $r = .12, p = .777$, as shown in Figure 9.

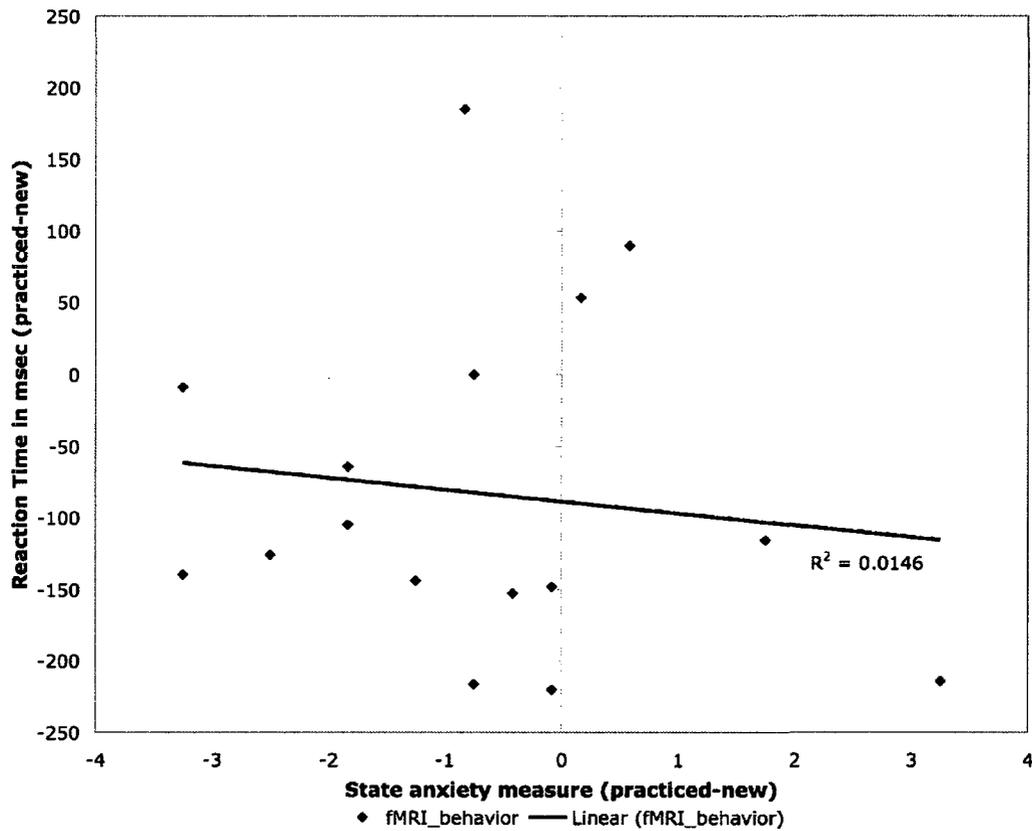


Figure 9. Using difference scores (practiced minus new), for 48 behavioral subjects, mean state STAI (x axis) and reaction times (y axis) for verb generation are plotted and reveal high individual variability.

fMRI Results - Original Hypotheses

Transient Activity. Only three regions showed a main effect of time, in which activity was independent of practice effects. These regions are shown in Table 4.

Table 4. Peak coordinates of significant transient BOLD responses (main effect of time)

Location	Region	BA	x	y	z	Voxels	Peak Z	<i>P</i> (time)
Frontal	R Insula	13	34	20	5	113	7.12	<0.0001
Temporal	R Superior temporal gyrus	41	45	-26	11	81	5.82	<0.0001
	L Transverse temporal gyrus	41	-41	-31	12	119	6.54	<0.0001

Note. Approximate Brodmann area (BA) and peak locations (x, y, z in mm) in the Talairach and Tournoux (1988) atlas with number of voxels and associated significance (Peak Z score and *p*-value). R = Right; L = Left; time = main effect of time.

Regions showing an interaction of practice by time are shown in Table 5. All regions exhibiting a practice effect revealed greater changes in magnitude, either activations or deactivations, for new than for practiced conditions.

Table 5. Peak coordinates of significant transient BOLD responses (interaction of practice x time)

Location	Region	BA	x	y	z	Voxels	Peak Z	P(pxt)	RegSource
<i>New > Practice</i>									
Frontal	R Middle frontal gyrus	10	36	46	14	81	3.16	<0.0001	pxt
	R Middle frontal gyrus	8	22	33	40	78	2.94	<0.0001	pxt
	R Middle frontal gyrus	8	22	23	41	87	3.03	<0.0001	pxt
	L Middle frontal gyrus	8	-26	29	38	114	6.50	0.0001	time
	R Insula	13	42	11	2	148	6.46	0.0060	time
	L Inferior frontal gyrus	9	-45	5	27	110	6.59	0.0120	time
	R Precentral gyrus	4	58	-5	20	50	3.01	0.0001	pxt
	L Precentral gyrus	4	-48	-15	38	314	4.54	<0.0001	pxt
Med front/Ant cing	R Medial frontal gyrus	10	14	45	13	55	6.00	0.0016	time
	R Anterior cingulate	32	2	20	33	242	7.23	0.0043	time
	R Anterior cingulate	32	16	36	14	92	3.11	<0.0001	pxt
	L Anterior cingulate	24	-6	9	42	388	9.36	0.0007	time
	L Cingulate gyrus	24	-3	7	45	96	3.27	<0.0001	pxt
	L Medial frontal gyrus	6	-1	-2	57	252	4.71	<0.0001	pxt
	L Medial frontal gyrus	6	-2	-3	57	436	9.53	<0.0001	time
	L Medial frontal gyrus	6	-5	-25	72	77	2.98	<0.0001	pxt
Parietal	R Precuneus	39	40	-64	37	162	3.22	<0.0001	pxt
	L Precuneus	19	-44	-70	40	58	2.86	<0.0001	pxt
Med par/Post cing	R Cingulate gyrus	31	3	-42	39	79	3.02	<0.0001	pxt
	R Cingulate gyrus	31	5	-55	27	280	7.79	<0.0001	time
	R Precuneus	31	17	-47	31	358	7.53	<0.0001	time
	R Precuneus	31	10	-64	26	169	4.10	<0.0001	pxt
	L Precuneus	31	-13	-68	25	288	4.30	<0.0001	pxt
Med occ	L Posterior cingulate	31	-7	-57	26	204	7.52	0.0240	time
	L Lingual gyrus	18	-1	-81	7	269	4.54	<0.0001	pxt
	L Lingual gyrus	18	-8	-72	1	223	3.89	<0.0001	pxt
	R Cuneus	18	1	-82	25	57	3.16	<0.0001	pxt
Sub-lobar	R Cuneus	18	5	-85	16	160	4.02	<.0001	pxt
	R Putamen	15	8	2	143	3.22	0.0006	pxt	
	R Putamen	14	7	5	187	6.69	0.0310	time	
	R Thalamus	10	-4	11	41	5.77	0.0021	time	
	R Thalamus	11	-19	7	155	8.39	0.0092	time	
	L Thalamus	-9	-19	10	52	2.93	<0.0001	pxt	
	L Thalamus	-10	-21	9	206	8.47	0.0190	time	

Note. See notes for Table 4. Absolute magnitudes are reported. RegSource = Region Source, region based analysis from which region was defined. Med = medial; front = frontal; ant = anterior; post = posterior; ant cing = anterior cingulate; occ = occipital.

Three of these regions fell within the boundaries of the ACC, two dorsal and one ventral. As expected, the two dorsal ACC regions exhibited positive activation (Figure 10A and B), and the ventral ACC region displayed a deactivation (Figure 10C).

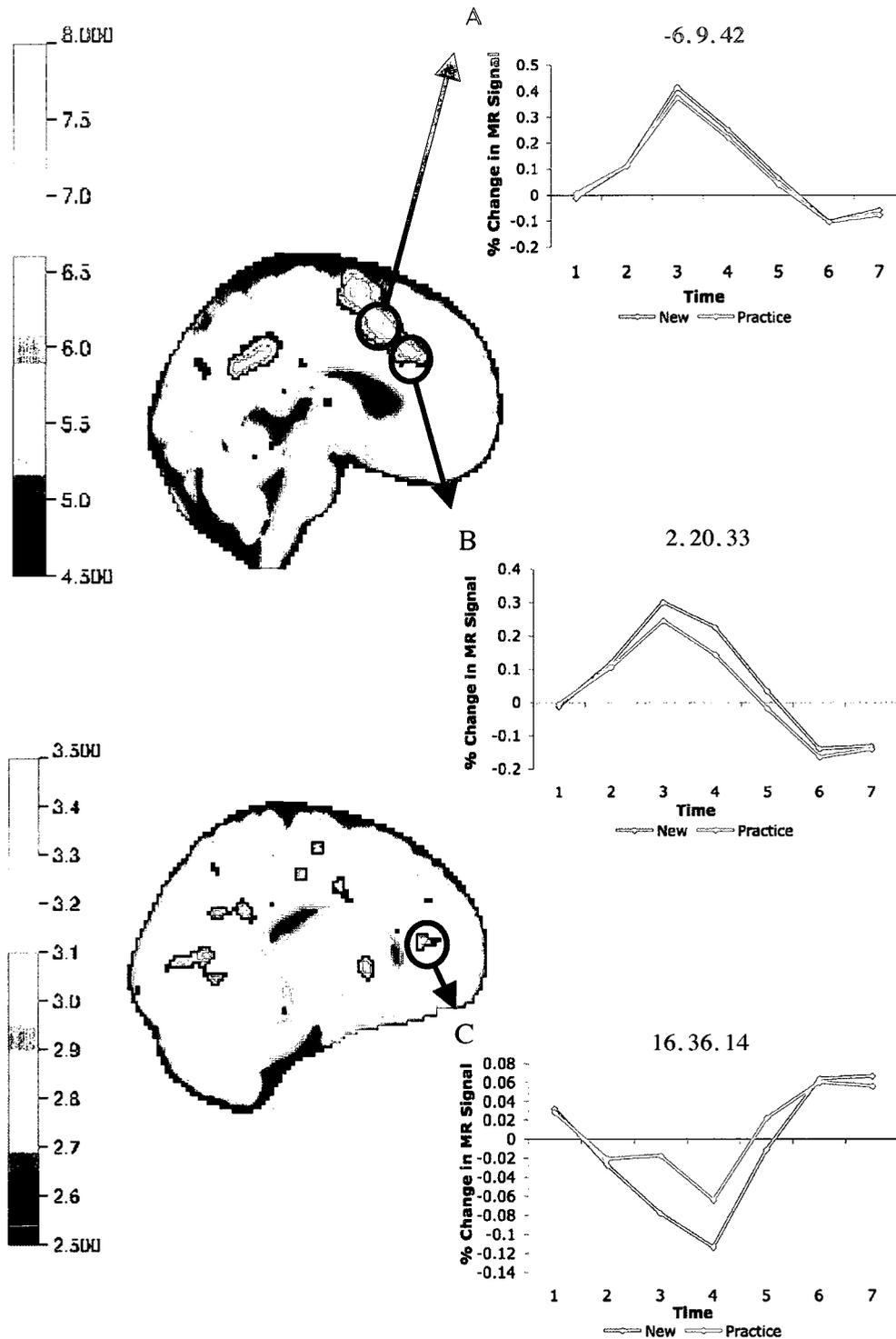


Figure 10. Original experiment revealed three ACC regions showing transient effects: two dorsal (Figure 10A and B) and one ventral (Figure 10C). Regions of interest are circled and their corresponding time courses are displayed.

One of these ventral/dorsal pairs exhibited reciprocal suppression with practice, $r = .60$, $p = .014$, in which change in positive activation in the dorsal ACC region (coordinates 2, 20, 33) was inversely correlated with change in deactivation in the ventral ACC region (coordinates 16, 36, 14), as is often reported in imaging studies associated with performance on a cognitive task (Buckner & Tulving, 1995; Bush et al., 2002; Corbetta et al., 1991; Coull et al., 1995; Drevets & Raichle, 1998; Petersen et al., 1989).

Sustained Activity. Regions exhibiting significant sustained activation with practice are listed in Table 6. There were no regions in the ACC exhibiting significant sustained activation.

Table 6. Peak coordinates of significant sustained BOLD responses (effect of practice)

Location	Region	BA	x	y	z	Voxels	Peak Z	P(Practice)
Frontal	L Precentral gyrus	4	-49	-11	45	65	2.27	0.0003
Med front/Ant cing	R Cingulate gyrus	32	13	23	30	117	2.30	0.0002
	R Subcallosal gyrus	25	3	9	-14	54	2.31	0.0009
	R Subcallosal gyrus	47	16	18	-11	62	2.28	0.0029
Parietal	L Medial frontal gyrus	8	-13	29	40	179	3.13	<0.0001
	L Inferior parietal lobule	40	-52	-28	39	100	2.40	<0.0001
Med occ	R Lingual gyrus	18	9	-72	-4	72	2.52	<0.0001
Occipital	L Fusiform gyrus	18	-23	-91	-12	94	2.39	0.0005
Cerebellum	R Anterior lobe-culmen		20	-54	-7	141	2.76	<0.0001

Note. See notes for Tables 4 and 5.

Relationship Between Behavior and Neural Activity. Brain regions within the ACC exhibiting transient activation are shown in Table 7, along with their behavioral correlates for state anxiety and reaction time. None of these correlation coefficients reached statistical significance at the $p < .05$ level.

Table 7. Correlations between behavioral measures and BOLD responses in ACC regions

Coordinates			Reaction Time	State Anxiety
x	y	z		
-6	9	42	0.26	-0.41
2	20	33	-0.38	-0.36
16	36	14	0.37	0.38

Note. Peak locations (x, y, z in mm) in the Talairach and Tournoux (1988) Atlas. $r = .50$ at $p < .05$.

Conclusion - Original Hypotheses

While the absence of a statistically significant behavioral correlation with brain activity should be interpreted with caution, based on these results, the data did not allow us to examine the originally proposed question. Because no significant correlations were revealed between changes in activation within regions of the ACC and changes in either state anxiety or reaction time, the functional roles of the ventral and dorsal portions of the ACC in emotional and cognitive processing could not be assessed.

Given recently published research regarding gender effects in affective processing in the ACC despite similar behavioral performance (Butler et al., 2007, Wang et al., 2007), exploratory analyses of the fMRI data were conducted in which gender was added as a between-subjects factor. To examine potential differences in disposition that might help to explain variability between individuals, trait anxiety and the IPIP Big Five Personality Inventory were also added as additional behavioral measures in these exploratory analyses.

Behavioral Results - Exploratory (Gender Differences)

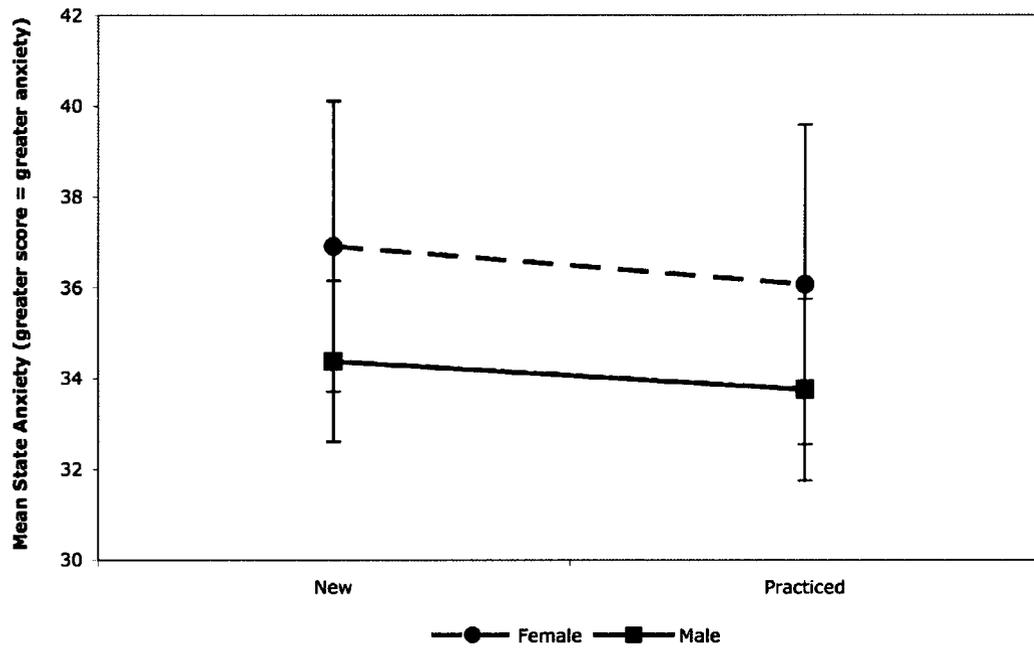
Anxiety. State STAI data were analyzed using a 2 x 2 (practice x gender) repeated measures analysis of variance (ANOVA). Results, divided by gender, are shown in Figure 11A. Contrary to the preliminary study, the main effect of practice in state anxiety

failed to reach significance, $F(1, 14) = 1.76, p = .206$. Furthermore, no effect of gender was observed, $F(1, 14) = 0.34, p = .571$, nor was there an interaction of practice by gender for anxiety, $F(1, 14) = 0.04, p = .846$.¹

Performance. Reaction times for correct responses were analyzed using a 2 x 2 (practice x gender) repeated measures ANOVA. Results are shown in Figure 11B. As expected, there was a main effect of practice for reaction time, $F(1, 14) = 7.99, p = .013$, in which subjects' reaction times were longer in the new condition than in the practiced one. Again, no main effect of gender was observed, $F(1, 14) = 1.65, p = .220$, nor was there an interaction of practice by gender for reaction times, $F(1, 14) = 1.05, p = .324$.¹

¹Although it appears as though there is a main effect of gender, standard error was high, so the gender effect did not reach statistical significance.

A.



B.

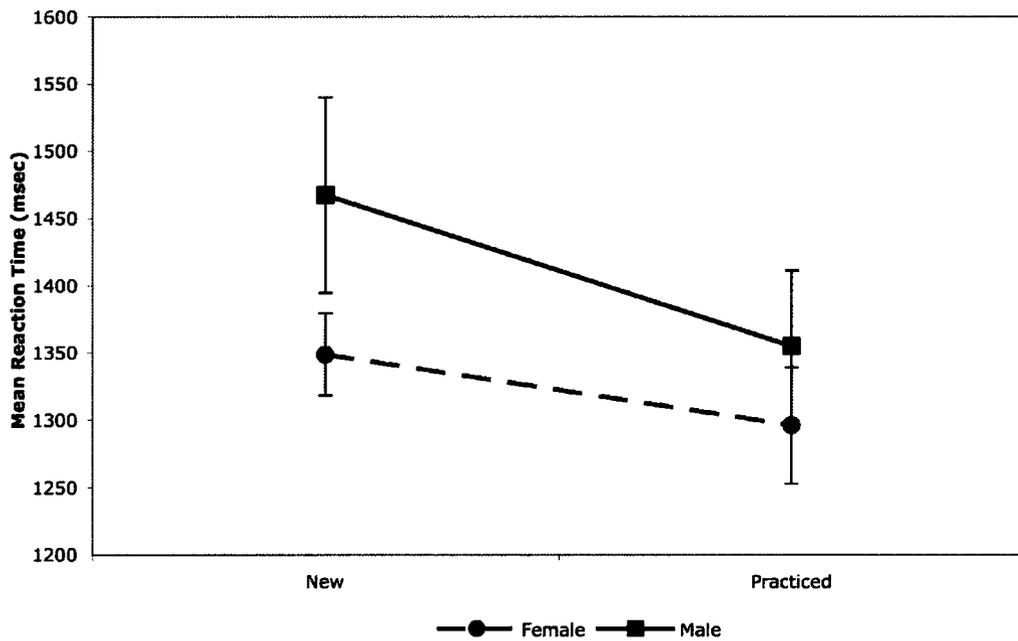


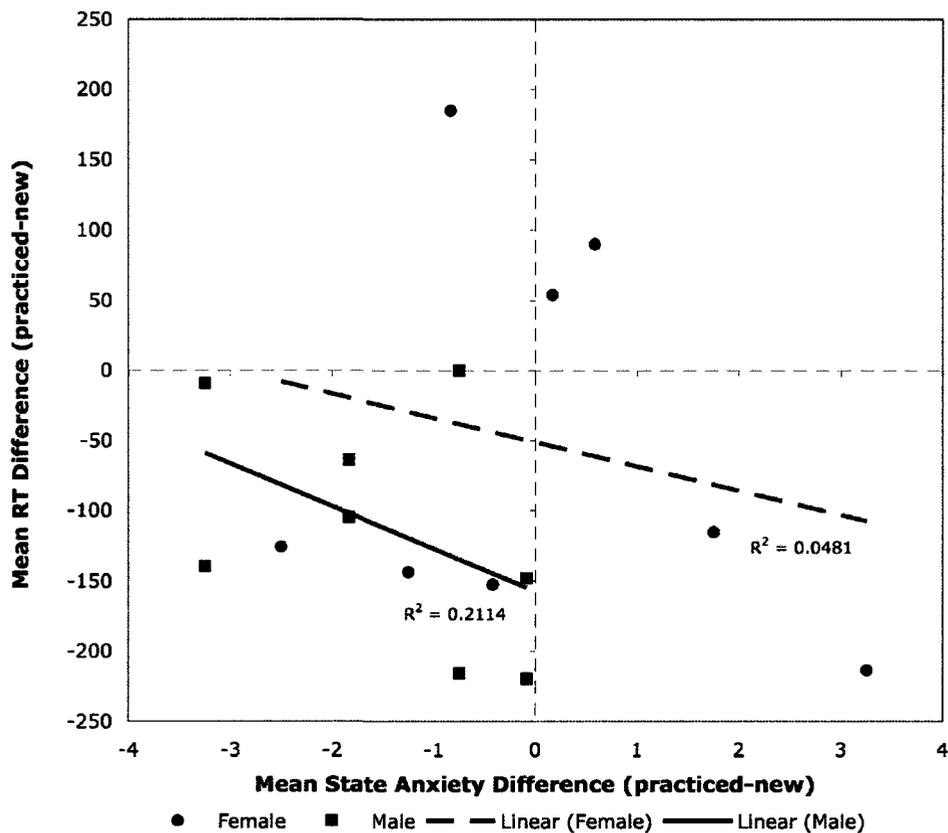
Figure 11. Behavioral results for verb generation in 16 fMRI subjects (8 female and 8 male), divided by gender, reflecting A) A non-significant downward trend with practice in mean anxiety level. B) A main effect of practice in mean reaction time. There was no effect of gender.

Results from the analysis of error rates were similar to those observed for response times (see Table 8). There was a main effect of practice, $F(1, 14) = 9.18, p = .009$, but there was no main effect of gender in the errors for these subjects, $F(1, 14) = 2.47, p = .138$, nor was there an interaction of practice by gender, $F(1, 14) = 0.74, p = .405$.

Table 8. Mean error rate by practice level for the verb generation task by gender in fMRI experiment

Level	Females	Males
New	0.084	0.048
Practiced	0.052	0.031

Relationship Between Anxiety and Performance. As in the preliminary study, the fMRI experiment revealed similar patterns observed in the anxiety and performance data at the group level, but there was substantial variability at the individual level, $r_{female} = .22$, $p = .601$, $r_{male} = .46$, $p = .251$, $r_{average} = .12$, $p = .777$, as shown in Figure 12. Individual behavior from both the preliminary experiment and the fMRI experiment is shown in Figure 13.



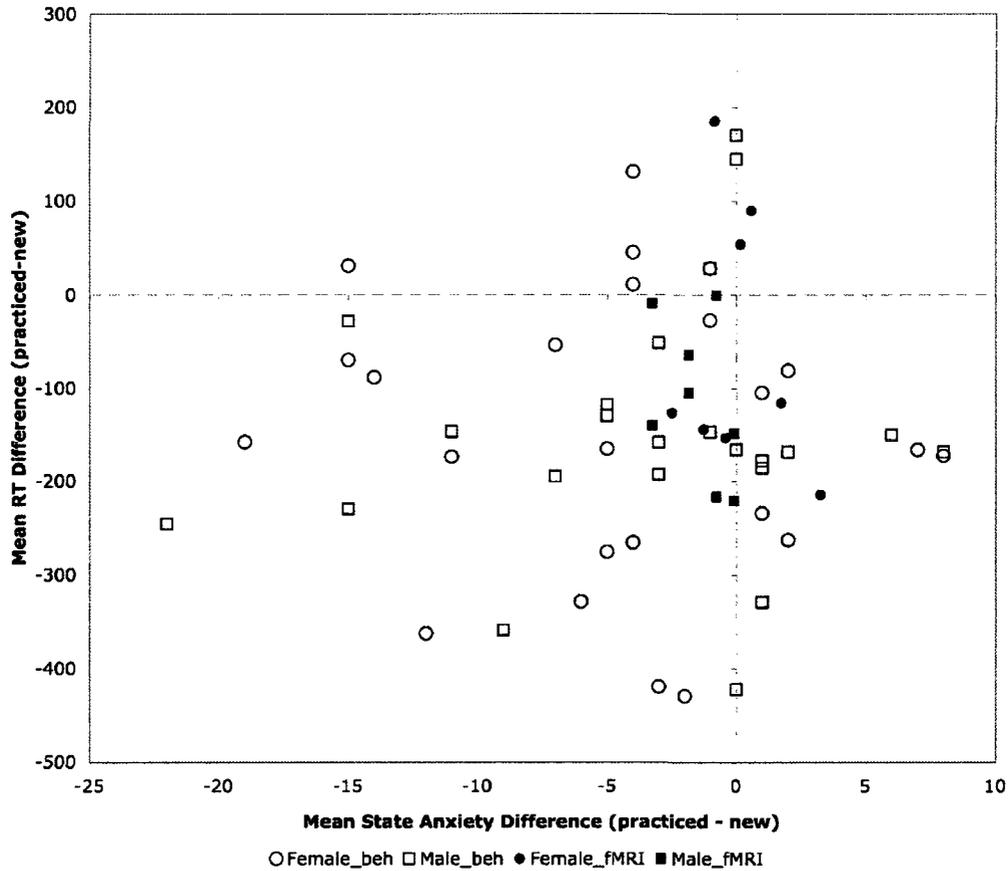


Figure 13. Mean difference scores (practiced minus new) of 16 fMRI subjects by gender for state STAI and reaction time in verb generation in comparison to 48 behavioral subjects by gender, both showing individual variability.

Trait Anxiety and IPIP. The mean and standard deviation for trait anxiety and the Big 5 dimensional scores are shown in Table 9. There were no significant differences between genders on any scales.

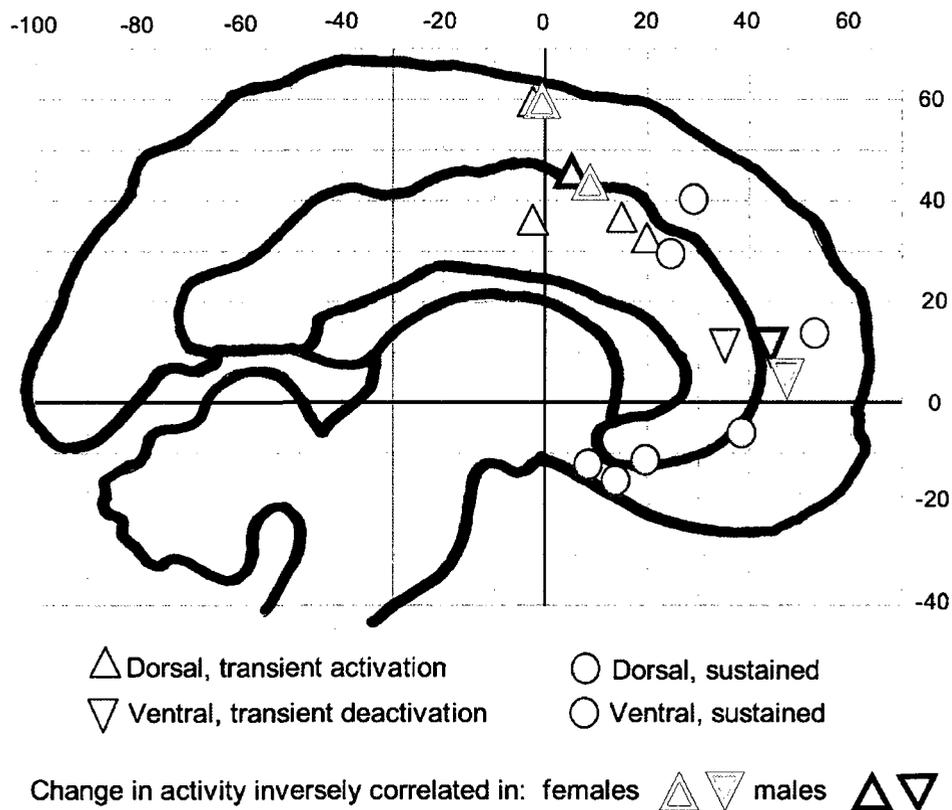
Table 9. Mean score (SD) for trait anxiety and dimensions of the Big 5 Personality Inventory

Measure	Females		Males	
Trait Anxiety	37.0	(11.6)	30.3	(4.2)
Extraversion	32.8	(5.8)	34.0	(9.0)
Agreeableness	44.0	(6.7)	42.8	(3.7)
Conscientiousness	29.8	(8.1)	30.8	(5.9)
Emotional Stability/neuroticism	31.6	(10.8)	38.1	(1.8)
Intellect/Imagination	39.9	(4.4)	39.5	(4.6)

In females but not males, trait anxiety and emotional stability were highly negatively correlated $r_{female} = -.96, p < .001, r_{male} = .02, p = .960; \chi^2_{c(F)}(1, N = 16) = 9.10, p = .003$. It is not surprising that trait anxiety and emotional stability are correlated in women, given that both measures assess general levels of anxiety/negative affect. Similarly, correlations were observed in women between the state anxiety difference score (change with practice) and emotional stability, $r_{female} = -.81, p = .016$, and the difference score in state anxiety with trait anxiety $r_{female} = .74, p = .034$. These results are also consistent with Spielberger's (1983) claim that trait and state anxiety are more highly correlated in social evaluative situations than when a physical threat exists; individuals with high trait anxiety are especially sensitive to increases in state anxiety in situations in which they feel that they are being judged by other people. Other behavioral measures found to correlate in women include agreeableness and conscientiousness $r_{female} = .72, p = .046$. Marginal correlations in the men were observed with the state anxiety difference score and emotional stability, $r_{male} = .70, p = .053$, and extraversion and agreeableness, $r_{male} = .71, p = .050$.

fMRI Results - Exploratory (Gender Differences)

Regions of Interest. Based on results from the original analyses, regions of interest were broadened from the ACC to include all regions in the medial prefrontal cortex (mPFC) exhibiting transient or sustained activation. A schematic of these medial prefrontal regions is displayed in Figure 14.



Note. Brain schematic adapted from “Cognitive and Emotional Influences in Anterior Cingulate Cortex.” *Trends in Cognitive Sciences*, 4, p. 217.

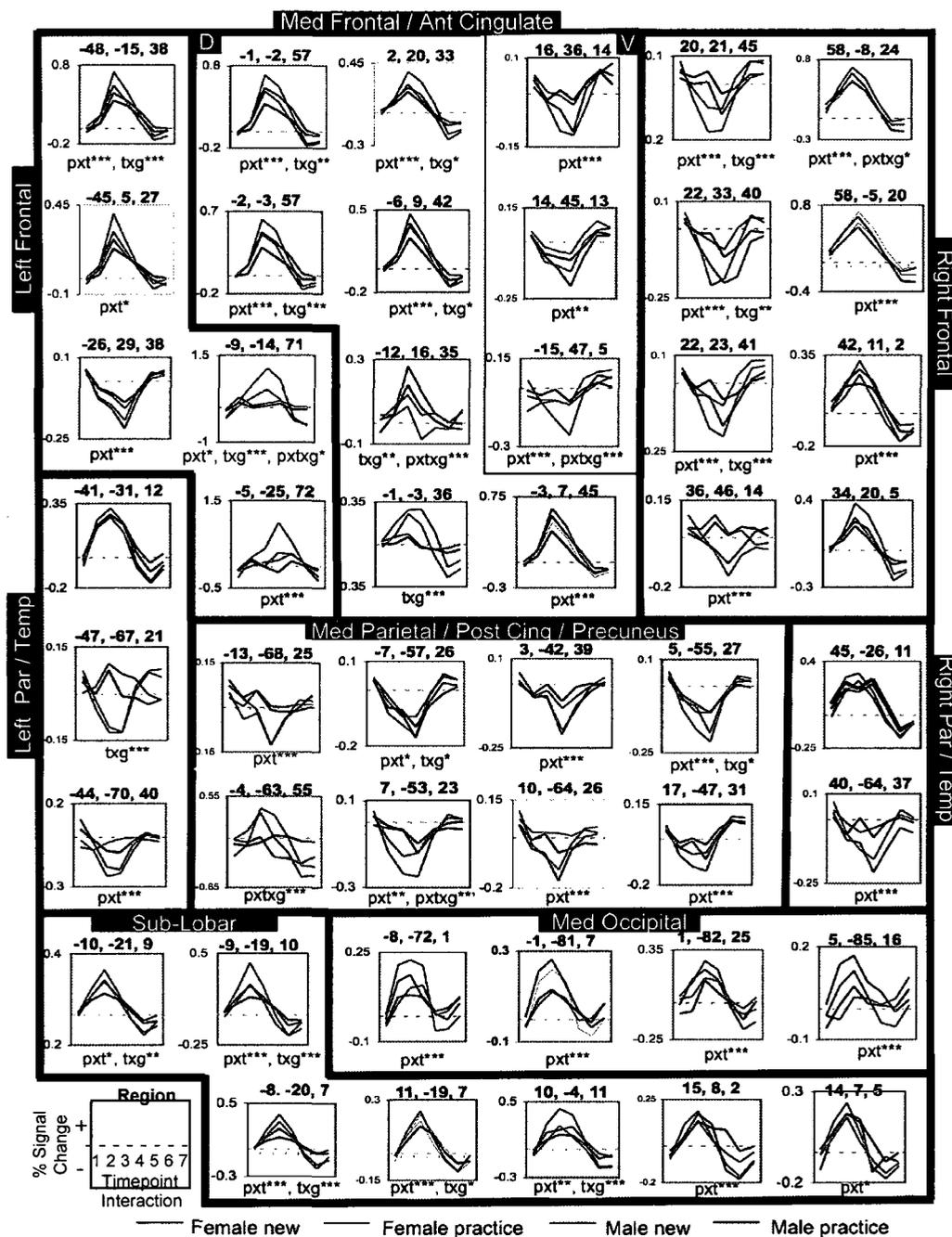
Figure 14. Schematic of medial slice of brain with all medial frontal regions from fMRI experiment exhibiting either transient or sustained BOLD activation plotted.

Transient Activity. All regions exhibiting interaction effects with gender, including those regions generated by the main effect of time and the practice by time analyses, are shown in Table 10. The time courses for all regions exhibiting significant transient activation are displayed in Figure 15. Although not all regions reached statistical significance, most regions exhibited greater changes in magnitude, either activations or deactivations, for new than for practiced conditions, with many also reflecting greater activity in women as compared to men. Exceptions include a region of the dorsal mPFC in which there was greater positive activation in men as compared to women, and bilateral posterior cingulate, in which there were greater deactivations in men than in women.

Table 10. Peak coordinates of significant transient BOLD responses (practice x time, time x gender, practice x time x gender)

Location	Region	BA	x	y	z	Voxels	Peak Z	P(pxt)	P(txg)	P(pxtxg)	RegSource
<i>New > Practice, Female > Male</i>											
Frontal	R Middle frontal gyrus	8	22	33	40	78	2.94	<0.0001	0.0220	-	pxt
	R Middle frontal gyrus	8	22	23	41	87	3.03	<0.0001	0.0001	-	pxt
	R Superior frontal gyrus	8	20	21	45	227	4.29	0.0009	<0.0001	-	txg
Med front/Ant cing	L Precentral gyrus	4	-48	-15	38	314	4.54	<0.0001	0.0024	-	pxt
	R Anterior Cingulate	32	2	20	33	242	7.23	0.0043	0.0500	-	time
	L Anterior cingulate	24	-6	9	42	388	9.36	0.0007	0.0410	-	time
	L Medial frontal gyrus	6	-1	-2	57	252	4.71	<0.0001	0.0048	-	pxt
Med par/Post cing	L Medial frontal gyrus	6	-2	-3	57	436	9.53	<0.0001	0.0006	-	time
	R Cingulate gyrus	31	5	-55	27	280	7.79	<0.0001	0.0130	-	time
Sub-lobar	R Thalamus	10	-4	11	41	41	5.77	0.0021	0.0097	-	time
	R Thalamus	11	-19	7	155	155	8.39	0.0092	0.0350	-	time
	L Thalamus	-9	-19	10	52	52	2.93	<0.0001	0.0004	-	pxt
	L Thalamus	-8	-20	7	53	53	2.99	0.0008	<0.0001	-	txg
	L Thalamus	-10	-21	9	206	206	8.47	0.0190	0.0040	-	time
<i>New > Practice, Male > Female</i>											
Med par/Post cing	L Posterior cingulate	31	-7	-57	26	204	7.52	0.0240	0.0320	-	time
	R Posterior cingulate	31	7	-53	23	70	3.39	0.0036	<0.0001	-	txg
<i>Female > Male, New = Practice</i>											
Med front/Ant cing	L Cingulate gyrus	24	-1	-3	36	73	3.59	-	<0.0001	-	txg
Temporal	L Middle temporal gyrus	39	-47	-67	21	31	2.89	-	<0.0001	-	txg
<i>3-Way Interaction of Practice x Time x Gender</i>											
Med front/Ant cing	L Medial Frontal Gyrus	32	-15	47	5	35	2.85	0.0004	-	<0.0001	pctxg
	L Cingulate Gyrus	32	-12	16	35	42	2.86	-	0.0023	<0.0001	pctxg
	L Medial frontal gyrus	6	-9	-14	71	118	3.43	0.0180	-	0.0170	txg
Med par/Post cing	L Precuneus	7	-4	-63	55	53	2.84	-	-	<0.0001	pctxg
Med occ	L Lingual gyrus	18	-8	-72	1	223	3.89	<0.0001	-	0.0200	pxt

Note. See notes for Table 4 and 5. Regions from Table 5 with gender effects are listed again with relevant statistics. Pxt = practice x time; txg = time x gender; pctxg = practice x time x gender.



Note. Time courses are on different scales to magnify differences. pxt = practice x time; txg = time x gender; pxtxg = practice x time x gender. Significance of effect, * $p < .05$, ** $p < .005$, and *** $p < .0005$.

Figure 15. All time courses for regions exhibiting a main effect of time for transient BOLD signals, arranged by brain area with coordinates identified per region. Significant interactions are noted.

A significant three-way interaction between time, practice, and gender was observed in one region of the ventral mPFC (coordinates -15, 47, 5) just anterior to the ACC, $F(6, 78) = 11.83, p < .001$, in which women exhibited a deactivation in the new condition that returned to baseline in the practiced condition, but men's activation for this region remained flat across practice conditions. However, overall transient activations in the dorsal ACC, as well as deactivations in the ventral ACC, provide limited support for the concept of reciprocal suppression within the ACC (Buckner & Tulving, 1995; Bush et al., 2002; Corbetta et al., 1991; Coull et al., 1995; Drevets & Raichle, 1998; Petersen et al., 1989). Using difference scores, correlation calculations revealed a significant inverse correlation between the aforementioned ventral region and two regions within the dorsal mPFC in women, $r_{female} = .80, p = .017$ and $r_{female} = .89, p = .003$ (coordinates -15, 47, 5 and -1, -2, 57/-6, 9, 42), and between a different ventral/dorsal pair in men, $r_{male} = .71, p = .048$ (14, 45, 13 and -3, 7, 45). No other ventral and dorsal pairs exhibiting reciprocal suppression were revealed, as measured by changes with practice.

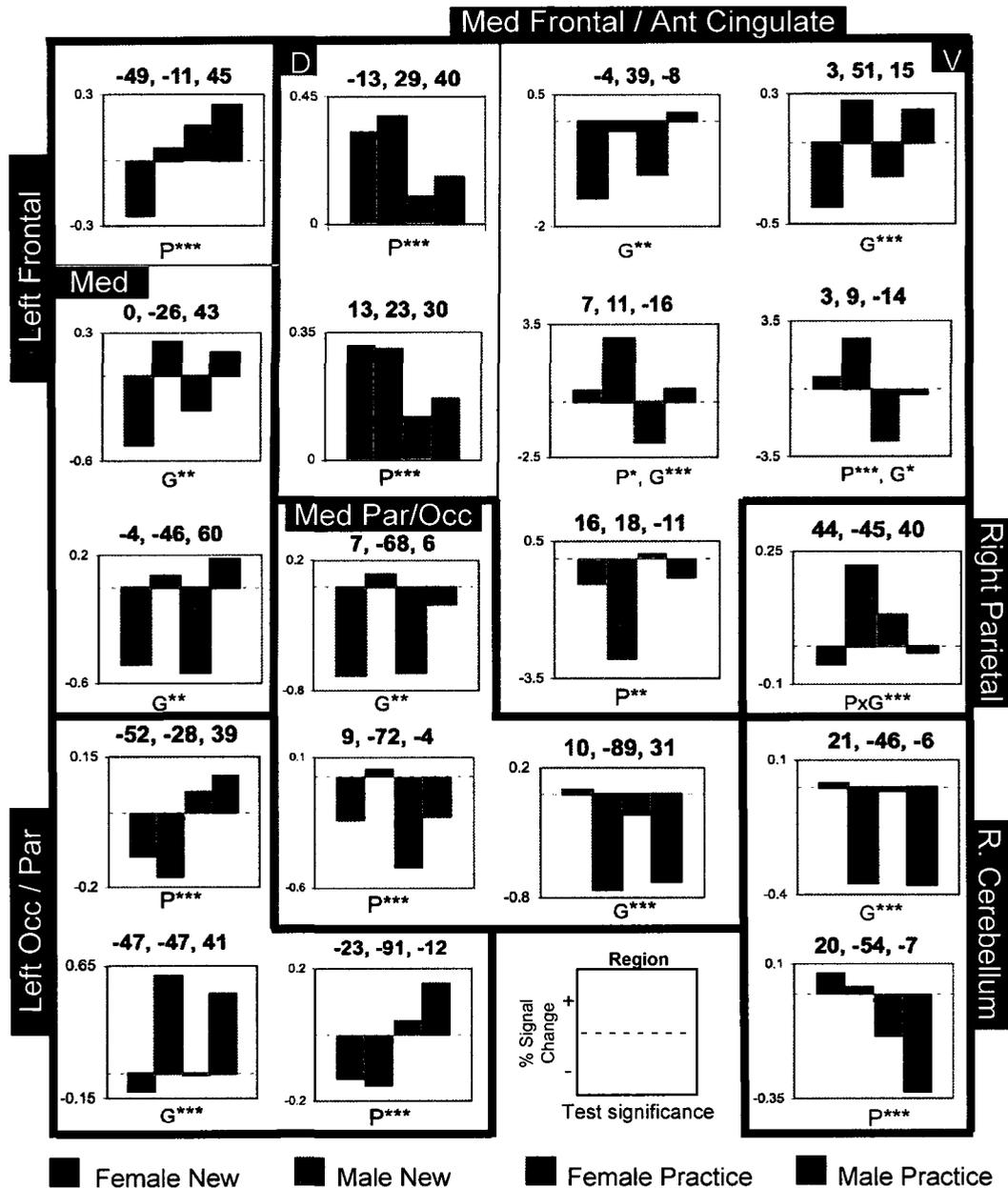
Sustained Activity. Regions exhibiting significant sustained activation, with an effect of gender, are listed in Table 11. Bar graphs representing the sustained activity per region are shown in Figure 16. Women and men exhibited similar activity in bilateral regions of the dorsal mPFC, with greater activity in the new than in the practiced condition. There is a striking contrast between practice and/or gender conditions in most of the other regions, however. Whereas most of the transient regions displayed a similar pattern of activity, in which the direction of the signal was most often similar across practice conditions and gender, with primary differences being only in magnitude, many sustained signals change direction with practice and/or between genders. Interestingly,

the bilateral dorsal medial prefrontal regions exhibit the most uniform activity across gender, whereas the ventral medial prefrontal regions seem to be the most variable.

Table 11. Peak coordinates of significant sustained BOLD responses (main effect of practice, main effect of gender, interaction of practice x gender)

Location	Region	BA	x	y	z	Voxels	Peak Z	P(Practice)	P(Gender)	P(PxG)
<i>Practice</i>										
Med front/Ant cing	R Subcallosal gyrus	25	3	9	-14	54	2.31	0.0009	0.0270	-
<i>Gender</i>										
Frontal	L Paracentral lobule	31	0	-26	43	94	2.26	-	0.0022	-
	L Paracentral lobule	5	-4	-46	60	77	2.43	-	0.0023	-
Med front/Ant cing	R Medial frontal gyrus	9	3	51	15	119	2.34	-	0.0003	-
	R Medial frontal gyrus	25	7	11	-16	39	2.44	0.0057	<0.0001	-
	L Anterior cingulate	32	-4	39	-8	97	2.28	-	0.0029	-
Parietal	L Inferior parietal lobule	40	-47	-47	41	62	2.32	-	0.0005	-
Med occ	R Lingual gyrus	18	7	-68	6	132	2.56	-	0.0017	-
	R Cuneus	19	10	-89	31	96	2.42	-	0.0002	-
Cerebellum	R Anterior lobe-culmen		21	-46	-6	55	2.41	-	0.0002	-
<i>Practice x Gender</i>										
Parietal	R Inferior parietal lobule	40	44	-45	40	70	2.38	-	-	<0.0001

Note. See notes for Table 4 and 5. Region from Table 6 that also exhibits a gender effect is listed again with relevant statistic. PxG = Practice x Gender.



Note. Graphs are on different scales to magnify differences. P = practice, G = gender; P x G = practice x gender. Significance of effect, * $p < .05$, ** $p < .005$, and *** $p < .0005$.

Figure 16. Bar graphs per region reflecting significant sustained BOLD activation, arranged by brain area with coordinates identified per region. Significant interactions are noted.

There is a single ventral ACC region at -4, 39, -8, exhibiting a main effect of gender, in which there is a significant deactivation in the women that is far less pronounced in the men, $F(1,14) = 13.40, p = .003$. This sustained deactivation pattern is consistent with the gender differences in the ventral ACC recently reported by Butler and colleagues (2007). A similar pattern of gender differences was also revealed by the main effect of gender analysis in another medial prefrontal region at 3, 51, 15, $F(1,14) = 23.64, p < .001$. Both a main effect of practice and a main effect of gender were revealed in two other medial frontal regions at 7, 11, -16 and 3, 9, -14 with activity in both regions moving in a downwardly direction with practice in both women and men.

Unlike Butler and colleagues (2007), however, we did not find an inverse correlation between difference scores in the ventral and dorsal regions of the mPFC in either women or men within the sustained signals. This could simply be a result of computational differences, given that they only had a single condition, and therefore used a single value directly representing the level of activation, while our calculations were based on difference scores between new and practiced conditions. Given, however, that we found deactivations in women but positive activations in men in a few ventral medial prefrontal regions, and positive activation in the dorsal regions for both sexes, does suggest that reciprocal suppression between the ventral and dorsal regions may exist in the sustained signals only in women.

Relationship Between Behavior and Neural Activity. Because there were no predictions regarding behavior and neural activity across the whole brain, examination of the relationship between behavioral measures and neural activation were limited to

regions within the mPFC.² Interesting patterns between behavior and functional activations emerged between genders in the mPFC. Medial prefrontal brain regions exhibiting transient activation are shown in Table 12, along with their behavioral correlates. There were no regions in the ACC or mPFC that exhibited transient activation associated with reaction time differences. However, all three ventral medial prefrontal regions in females at 16, 36, 14 and 14, 45, 13 and -15, 47, 5, exhibited very similar relationships with behavioral measures. As shown in Table 12, activation in each of these three regions in the women exhibited a negative correlation with trait anxiety, all p 's < 0.02, and a positive correlation with emotional stability, p 's < 0.03. In region 16, 36, 14, the relationship was significantly different from that in men for trait anxiety, $r_{female} = -.88, p = .004, r_{male} = .06, p = .888, \chi^2_{c(F)}(1, N = 16) = 6.06, p = .014$, and emotional stability, $r_{female} = .85, p = .008, r_{male} = .15, p = .723, \chi^2_{c(F)}(1, N = 16) = 4.04, p = .045$ (Paul, 1989). Activity in ventral region -15, 47, 5 also correlated with changes in state anxiety in females, $r_{female} = .78, p = .02$ (as shown in Figure 17), but not males, $r_{male} = -.20, p = .635, \chi^2_{c(F)}(1, N = 16) = 4.91, p = .027$. There was a positive correlation with changes in state anxiety levels in the men, $r_{male} = .78, p = .022$, but it was not significantly different from women. The association of negative affect within the ventral mPFC is consistent with the proposed ventral/dorsal distinction.

² Correlations between behavioral measures and regions outside the mPFC are available upon request.

Table 12. Significant correlations between peak transient BOLD signal in mPFC and behavioral measures

BA	x	y	z	Region	v/d	RT		State		Trait		Extra		Agree		Cons		Emot/Stab		Intell/Imag			
						F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
10	14	45	13	R Medial frontal gyrus	v	-	-	-	-	-0.79	-0.45	-	-	-	-	-	-	-	0.87	0.59	-	-	
32	16	36	14	R Anterior cingulate	v	-	-	0.41	0.78	-0.88	0.06	0.76	-0.51	-	-	-	-	-	0.85	0.15	-	-	
32	-15	47	5	L Medial frontal gyrus	v	-	-	0.78	-0.20	-0.76	-0.14	-	-	-	-	-	-	-	0.77	0.07	-	-	
32	-12	16	35	L Cingulate gyrus	d	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
32	2	20	33	R Anterior cingulate	d	-	-	-	-	0.78	-0.18	-	-	-	-	-	-	-	-0.78	-0.04	-	-	
24	-6	9	42	L Anterior cingulate	d	-	-	-	-	-	-	-	-	-	-	-	-0.36	-0.73	-	-	-0.72	0.24	
24	-3	7	45	L Cingulate gyrus	d	-	-	-	-	-	-	-	-	-	-	-	-0.04	-0.72	-	-	-	-	
24	-1	-3	36	L Cingulate gyrus	d	-	-	-	-	-	-	-	-	-	-	-0.71	0.56	-	-	-	-	-	
6	-1	-2	57	L Medial frontal gyrus	d	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.73	-0.17
6	-2	-3	57	L Medial frontal gyrus	d	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note. Approximate Brodmann area (BA) and peak locations (x, y, z in mm) in the Talairach and Tournoux (1988) atlas with number of voxels and associated significance (Peak Z score and *p*-value). R = Right; L = Left; time = main effect of time. v/d = ventral/dorsal; F = female; M = male; RT = reaction time; Anx = Anxiety; Agree = Agreeableness; Consc = Conscientiousness; Emot/Stab = Emotional Stability; Intel/Imag; Intellect/Imagination. Correlations that are significant within gender at *p* < .05 are outlined in black and correlation value for other gender is listed next to it. Significant differences in correlation coefficients between gender are in red (Paul, 1989). Hyphen, *p* > .05.

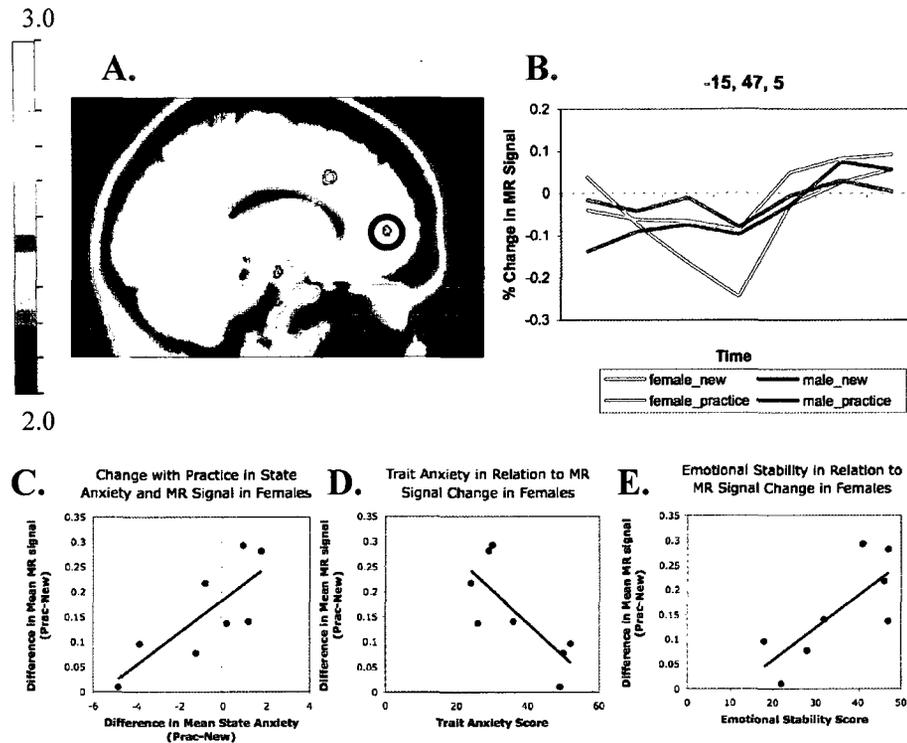


Figure 17. Ventral mPFC region exhibiting significant interaction of practice x time x gender. A) Statistical brain map of transient effects (practice x time x gender) with region of interest (-15, 47, 5) circled. B) Temporal profile of region circled in A. C) Significant correlation in female participants between difference scores (practiced minus new) of region and mean state anxiety. D) Significant correlation in female participants between difference of region and trait anxiety. E) Significant correlation in female participants between difference scores of region and emotional stability.

As shown in Figure 18, a dorsal ACC region (2, 20, 33) in women but not men exhibited a pattern between transient activation and negative affect that mirrors the pattern seen in the ventral mPFC, $r_{female} = .78, p = .022, r_{male} = -.18, p = .700, c^2_{c(F)}(1, N = 16) = 4.78, p = .029$. Discovery of transient activation in the dorsal ACC associated with negative affect challenges the proposed functional division of the ACC.

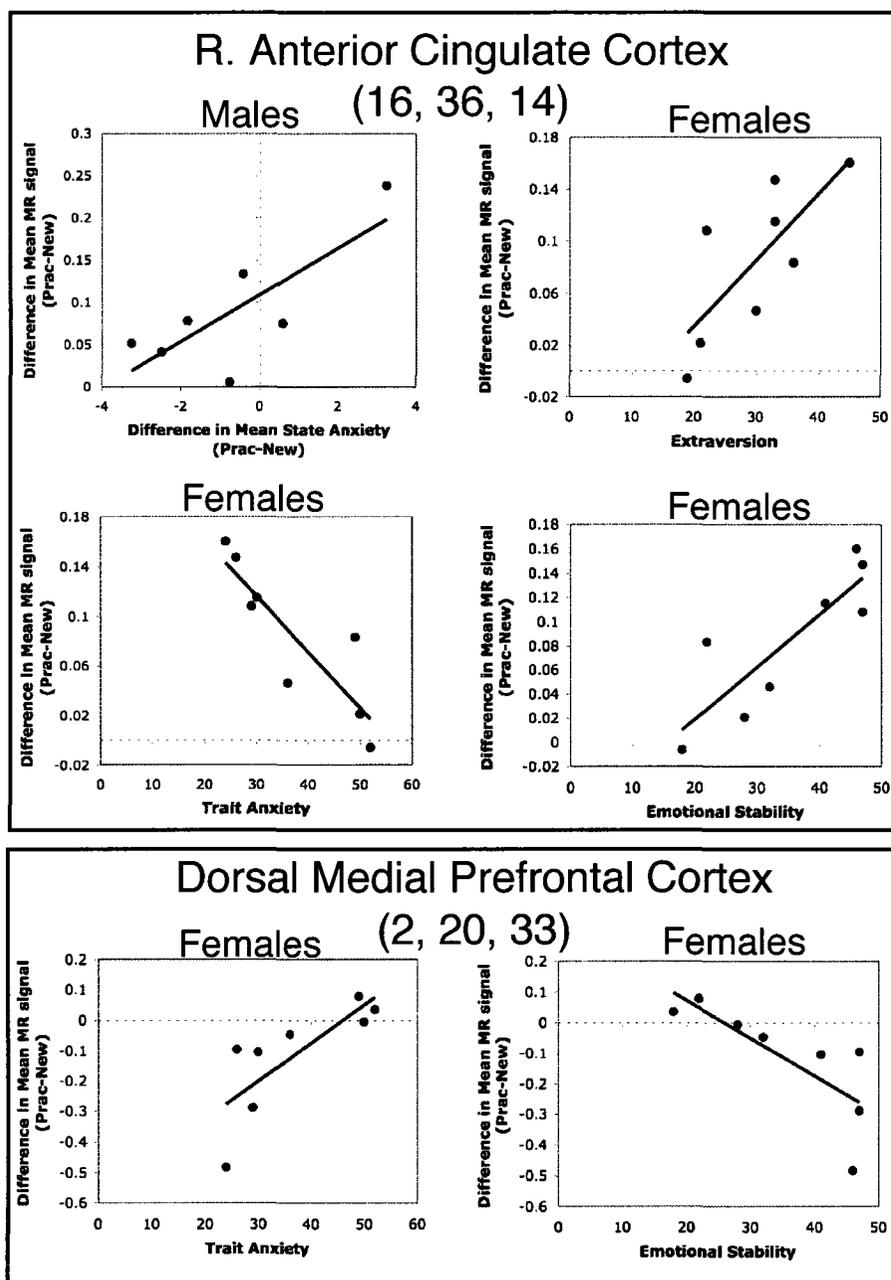


Figure 18. Ventral ACC region (16, 36, 14) and dorsal mPFC region (2, 20, 33) showing significant correlations between difference with practice in transient percent MR signal change (y-axis) and behavioral measure (x-axis) for males and females.

Again, no correlations were revealed between reaction times and sustained activations in any ACC regions (see Table 13). However, as shown in Figure 19, deactivation in a ventral ACC region -4, 39, -8 revealed significant correlations that were opposite to the behavioral pattern revealed in the transient ventral ACC region. In females, the sustained ventral ACC deactivation was negatively correlated with state anxiety, $r_{female} = -.85, p = .008$ (a relationship that significantly differed from that in men, $r_{male} = .43, p = .288, \chi^2_{c(F)}(1, N = 16) = 7.73, p = .005$), and emotional stability, $r_{female} = -.85, p = .008$, and positively correlated with trait anxiety, $r_{female} = .88, p = .004$.

Table 13. Significant correlations between peak sustained BOLD signal in mPFC and behavioral measures

BA	x	y	z	Region	RT		State		Trait		Extra		Agree		Cons		Emot/Stab		Intell/Imag			
					v/d	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
47	16	18	-11	R Subcallosal gyrus	v	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
25	3	9	-14	R Subcallosal gyrus	v	-	-	-0.33	-0.81	-	-	-	-	-	-	-	-	-	-	-	-	
25	7	11	-16	R Subcallosal gyrus	v	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
9	3	51	15	R Medial frontal gyrus	v	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
32	-4	39	-8	L Anterior cingulate	v	-	-	-0.85	0.43	0.88	0.58	-	-	-	-	-	-0.85	-0.22	-	-	-	
8	-13	29	40	L Medial frontal gyrus	d	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
32	13	23	30	R Cingulate gyrus	d	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.18	
																						0.81

Note. See notes for Table 11.

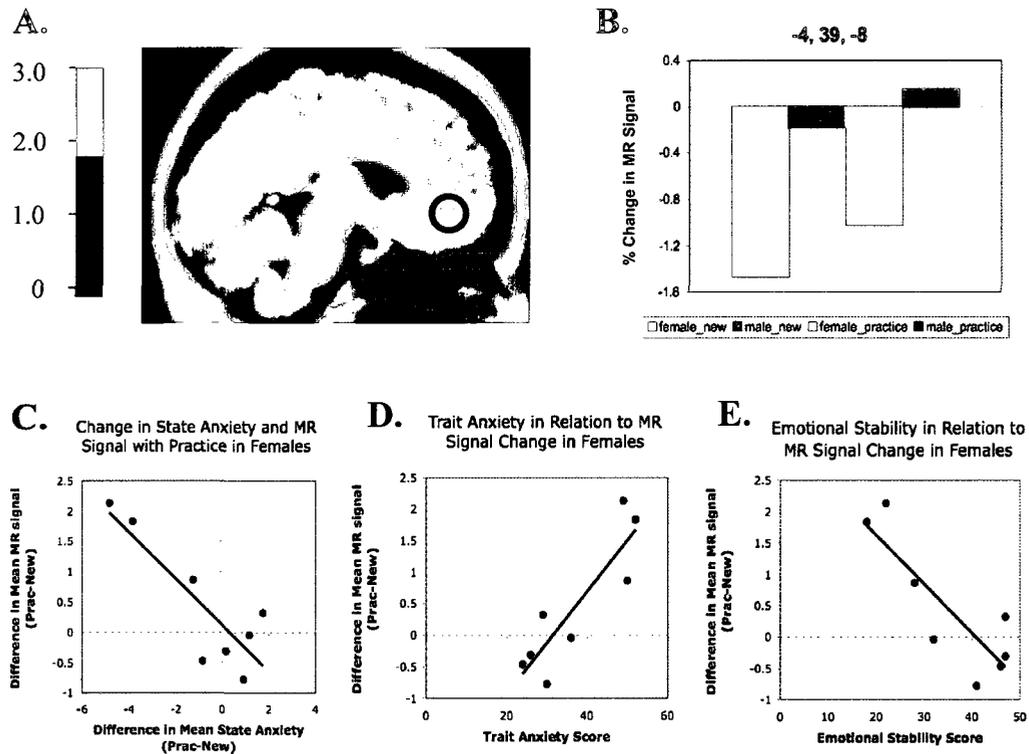
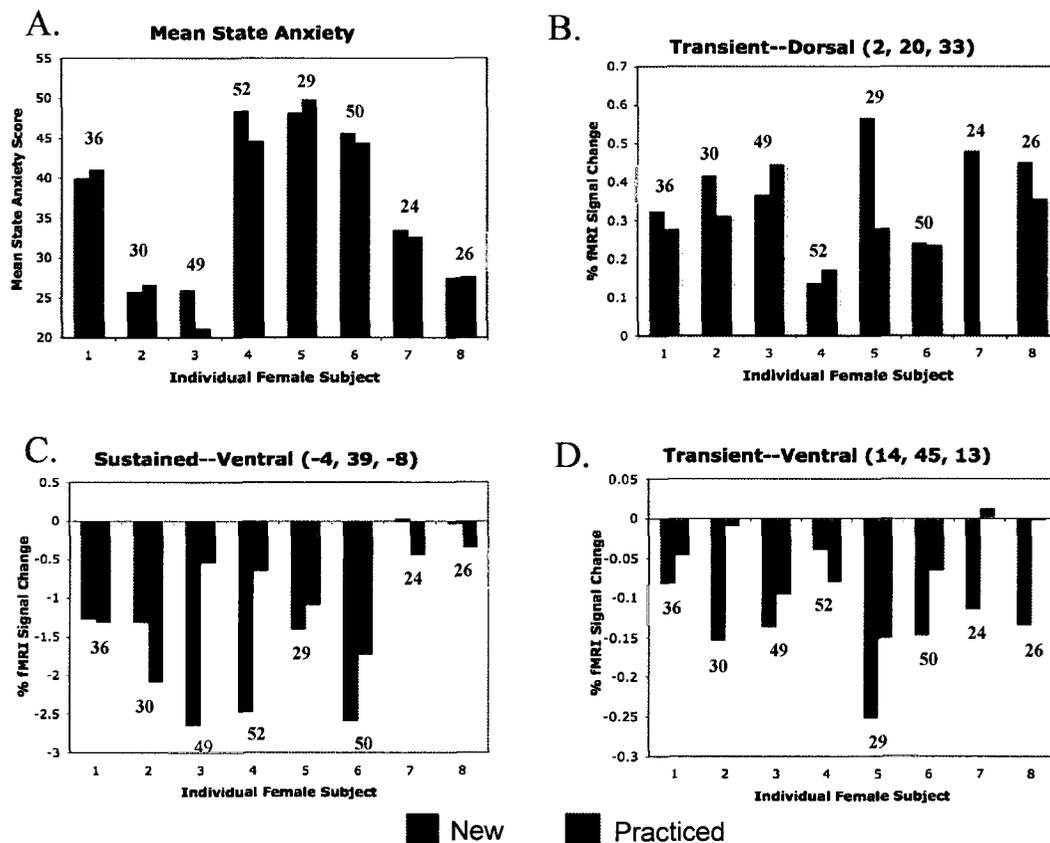


Figure 19. Ventral ACC region exhibiting significant effect of gender in sustained signal. A) Statistical brain map of sustained effect (gender) with region of interest (-4, 39, -8) circled. B) Bar graph of sustained activity for region circled in A. C) Significant correlation in female participants between difference scores (practiced minus new) of region and mean state anxiety. D) Significant correlation in female participants between difference scores of region and trait anxiety. E) Significant correlation in female participants between difference scores of region and emotional stability.

The consistent relationship between trait anxiety, neuroticism and deactivation in the ventral mPFC, which is in a number of cases greater in women than men, might help to explain women's increased vulnerability to the development of affective disorders, such as anxiety and/or depression (Gater et al., 1998). Data from the eight individual

female subjects are displayed in Figure 20 for state anxiety (20A), one ventral (Figure 20B) and one dorsal medial prefrontal region (Figure 20D) exhibiting transient activation that mirror one another, and one ventral ACC region (Figure 20C) exhibiting sustained activation that also exhibits a unique relationship with the transient ventral medial prefrontal regions. This relationship is further described in the discussion section.



Note. Corresponding trait anxiety scores are displayed at the peak of each individual's pair of bars.

Figure 20. Individual data across practice for 8 female participants (x-axis) on A) Mean state anxiety B) Positive transient BOLD activity for time point 3 in dorsal mPFC region 2, 20, 33 C) Negative sustained BOLD activity for ventral ACC region -4, 39, -8 D) Negative transient BOLD activity for negative peak time point 4 in ventral ACC region 14, 45, 13.

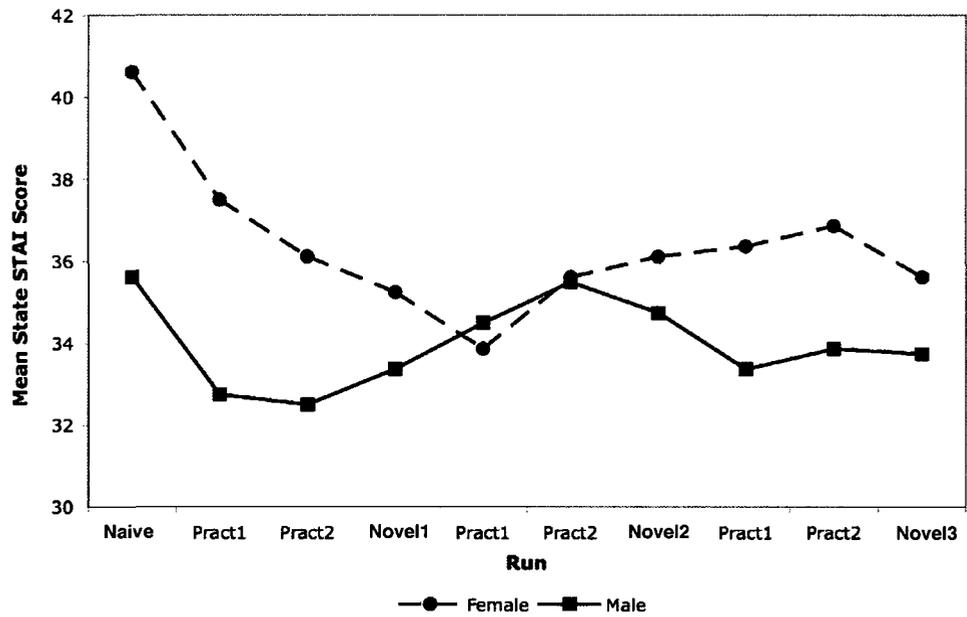
Correlations between behavioral measures and neural signals were the result of two independent analyses (behavioral and fMRI), with mPFC regions defined solely based on functionally significant deflections from baseline, independent of behavior. Behavioral and fMRI data were not examined together until after these independent analyses were complete and difference scores computed. Therefore, these correlations are not subject to the primary criticism posed by Vul and colleagues (2009), in which regions of interest are defined based on significant correlations with the behavioral measure of interest, which can reveal biased results that range from simple inflations to completely spurious correlations between behavioral measures and neural signals. Vul and colleagues also estimated, based on existing literature, that the maximum possible correlation of personality measures with the fMRI BOLD signal should be approximately $r = .74$. This conclusion was based on the reported reliability of the Big Five personality measures (ranging from $r = .73$ to $r = .78$) and fMRI BOLD signals (approximately $r = .70$). A number of correlations reported in the current experiment are greater than the maximum estimated reliability of the measures used, which is difficult to explain. Regions were defined based on the same data set ultimately used to calculate correlational values, which Vul et al. recommends against, but perhaps comparable to the “split half” analysis they propose to compensate for this, data in this experiment were unique in that difference scores were calculated based on data from different runs. Perhaps correlations are inflated due to a small sample size, although some correlations of this magnitude were reported in other experiments and were attributed to “normal sampling variability of the sort found with any kind of imperfect measurement” (p. 285).

Novelty and the ACC

The design of the current fMRI study differs from the 2001 study by Simpson and colleagues in one major respect. The Simpson study began with a “naïve” condition, as we did in the preliminary study, in which both the verb generation task and the list of nouns presented were novel to the participants. Following the naïve run were nine practice runs using the same list of nouns, and then finally subjects were presented with a “novel” run in which the list, but not the task, was new. While for the novel run both anxiety and reaction times increased in comparison to the practice runs, they did not increase to the same level as the naïve run.

In the current fMRI study, a new list was presented every third run, and the “naïve” run was collapsed into the new condition along with the other three “novel” runs. When viewing anxiety levels and reaction times by run, however, as shown in Figure 21A and B, respectively, the naïve run is prominent.

A.



B.

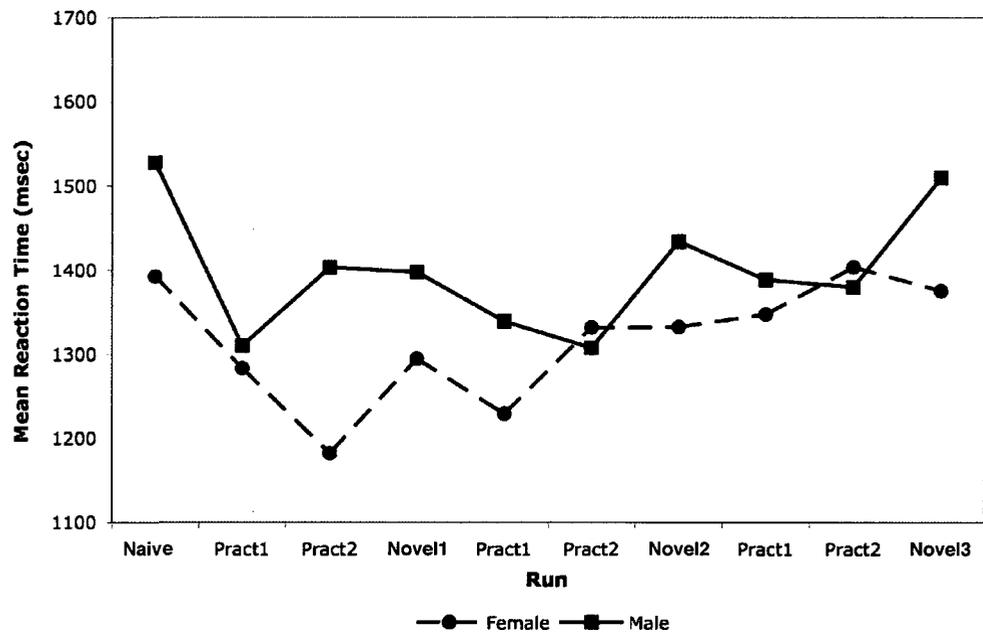


Figure 21. Behavioral results by each of 10 runs for verb generation in 16 fMRI subjects reflecting A) Mean anxiety level. B) Mean reaction time. Note especially high scores on both for naïve (first) run.

A direct comparison between the naïve run and the first novel run revealed marginally significant differences in women's state anxiety, $t(7) = 2.17, p = .067$ and reaction times, $t(7) = 2.12, p = .067$, and a significant difference in men's reaction times, $t(7) = 2.43, p = .045$, but state anxiety did not differ between the naïve and novel runs for men, $t(7) = .76, p = .472$ (all two-tailed). Given these differences between the naïve and novel runs, it seems that the novelty, not only of the list, but also of the task itself, should be an important consideration.

By aggregating ten sessions in the current fMRI experiment we likely measured the trait stress response, which may include contributions of individual personality and coping styles given the extended nature of the exposure to stress (Pruessner et al., 1997). However, novelty might be a dominant situational characteristic that has a profound effect on the state stress response, performance, and level of activation in the ACC (Petersen et al., 1998; Simpson et al., 2001).

Davidson (1998) suggested that not only is the magnitude of an emotional response important to consider when evaluating individual differences, but also the time course of the emotional response should be examined. In fact, several studies have reported that there are differences in how certain individuals or groups respond to emotion, both in reactivity and recovery, based on single or repeated episodes. Certain processes that were once effortful could become automatically emotionally regulated with practice (Davidson, 1998). For example, an EEG study revealed that error related negativity and amplitudes significantly differed between high and low negative affect participants early in the experiment, but those differences decreased with time (Luu, Collins, & Tucker, 2000). In contrast, two other experiments found that low and high

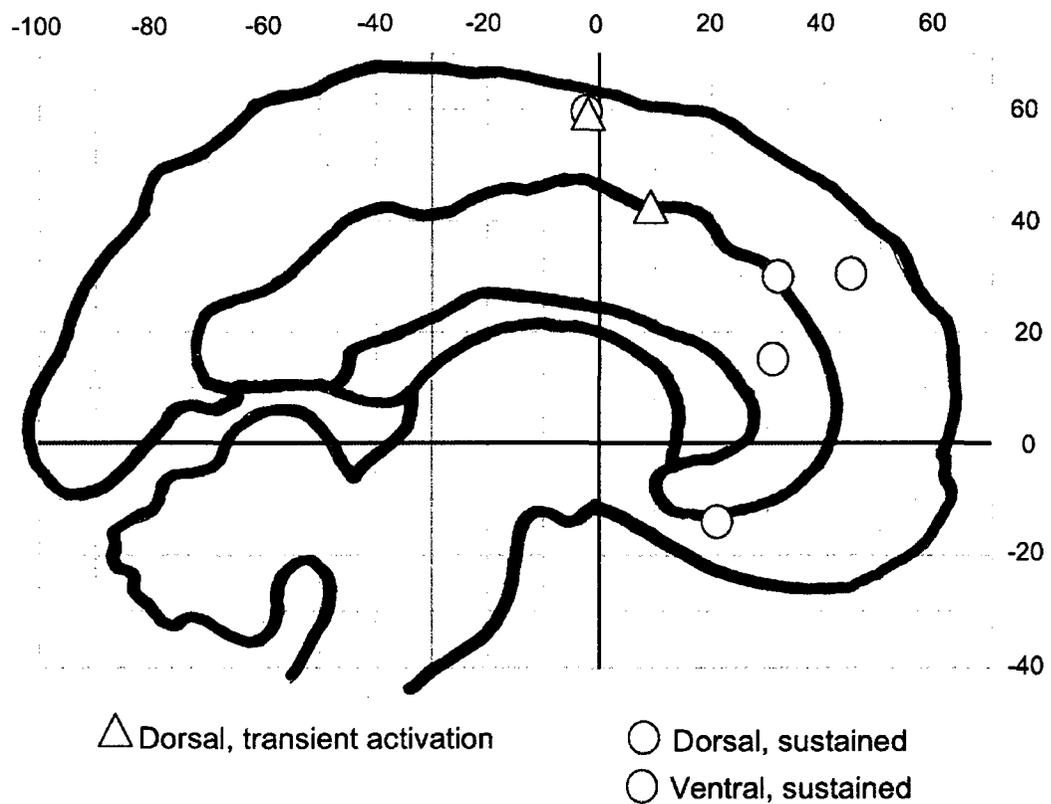
anxiety groups were similar initially but differences emerged with performance on a second and third task (Beidel, Turner, & Dancu, 1985; Eckman & Shean, 1997).

Furthermore, activity in the ACC has been shown to habituate with repeated exposure to emotional material (Phan, Liberzon, Welsh, Britton, & Taylor, 2003). Even in association with a cognitively demanding task, Milham, Banich, Claus, & Cohen (2003) reported that the ventral ACC exhibited a rapid decrease in activity with repetition despite continued need for attentional control, and the drop-off was more dramatic than that seen in other regions. Finally, Wang and colleagues (2005, 2007) reported that activation in certain brain regions, including the ACC, endured beyond completion of the stressful conditions.

While difference scores based on the aggregation of data from all ten runs may explain why we were able to reveal high correlations in emotional adaptation/regulation and personality traits (Pruessner et al., 1997), emotional reactivity and the practice effects in performance could diminish substantially with repeated exposure to the task. This could provide an explanation as to why no regions in the ACC, especially within the dorsal ACC, were correlated with changes in reaction time as was expected. Therefore, correlations computed based only on the first practice “set” (naïve through practice run 2), might reveal different processes in emotion (e.g. reactivity versus regulation/adaptation), performance, and personality (Pruessner et al., 1997).

Using the same procedure outlined above, new regions were defined using data from naïve run 1 and practice run 3. All medial prefrontal regions exhibiting transient or sustained effects were extracted and are displayed, as a schematic, in Figure 22. Using new difference scores calculated by subtracting naïve scores (run 1) from practiced scores

(run 3), new correlations were computed and are shown in Table 14. As expected, correlations between activity in dorsal mPFC (regions 3, 45, 30 and 13, 32, 30) and reaction times were revealed, $r_{female} = -.88, p = .004$ and $r_{male} = .78, p = .022$, respectively.



Note. Brain schematic adapted from “Cognitive and Emotional Influences in Anterior Cingulate Cortex.” *Trends in Cognitive Sciences*, 4, p. 217.

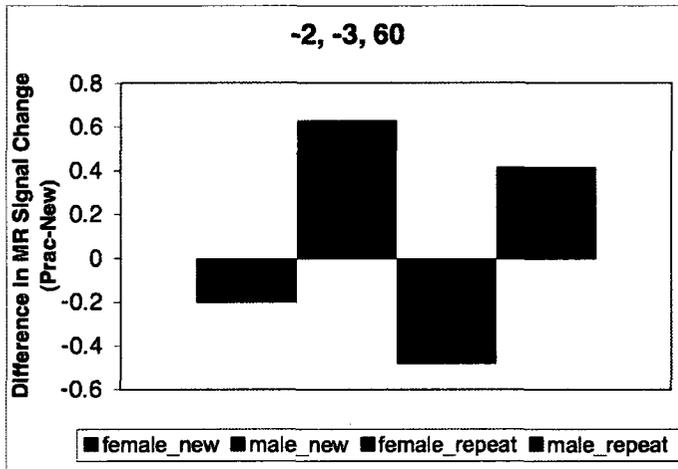
Figure 22. Schematic of medial slice of brain with all medial frontal regions from the first practice set (runs 1-3) *only*, exhibiting either transient or sustained BOLD activation plotted.

Table 14. Significant correlations between peak BOLD signal in mPFC and behavioral measures first practice set

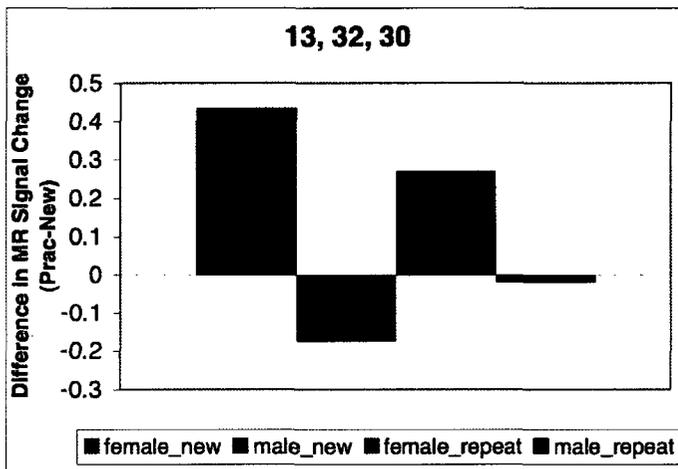
BA	x	y	z	Region	v/d		RT		State		Trait		Extra		Agree		Cons		Emot/Stab		Intell/Imag	
					F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
<i>Transient</i>																						
32	-5	9	42	L Cingulate gyrus	d	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-2	-4	58	L Medial frontal gyrus	d	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
<i>Sustained</i>																						
24	2	31	13	R Anterior cingulate	v	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
25	9	21	-14	R Medial frontal gyrus	v	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	3	45	30	R Medial frontal gyrus	d	-0.88	0.60	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.87
32	13	32	30	R Medial frontal gyrus	d	-0.11	0.78	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-2	-3	60	L Medial frontal gyrus	d	-	-	-0.91	0.05	0.78	-0.32	-	-	-	-	-	-	-	-0.78	0.35	-	-

Note. See notes for Table 11.

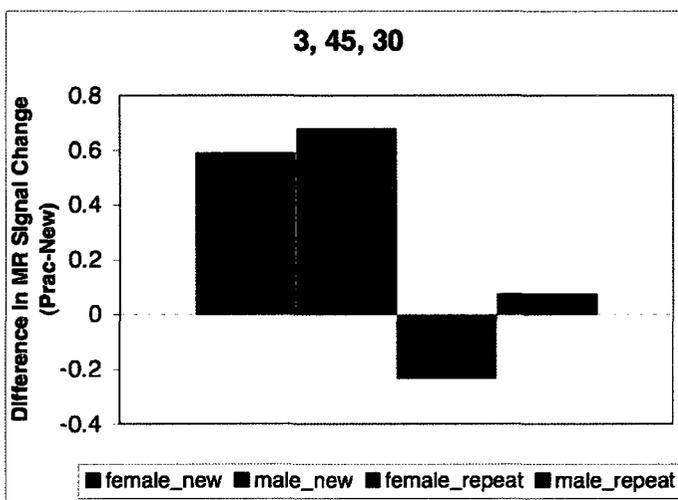
Unexpectedly, however, two of the three dorsal regions exhibited sustained deactivations in either females or males, as shown in Figure 23. Deactivations in dorsal mPFC regions are rarely reported (Paus, Koski, Caramanos, & Westbury, 1998; Bush et al., 2000), with the few exceptions occurring in experiments involving mood induction (Drevets & Raichle, 1998) and anticipation of pain (Drevets et al., 1994). This suggests possible presence of an emotional response which is supported by correlations in one of the dorsal regions exhibiting a deactivation (-2, -3, 60) in women with state anxiety, $r_{female} = -.91, p = .002, r_{male} = .05, p = .906, \chi^2_{c(F)}(1, N = 16) = 6.92, p = .009$, trait anxiety, $r_{female} = .78, p = .022, r_{male} = -.32, p = .440, \chi^2_{c(F)}(1, N = 16) = 5.70, p = .017$, and emotional stability, $r_{female} = -.78, p = .022, r_{male} = .35, p = .395, \chi^2_{c(F)}(1, N = 16) = 5.91, p = .015$. Absent in the data from the first practice set are correlations between affect and ventral medial prefrontal regions, suggesting that the aggregated data set may reveal an element of emotional adaptation in women that is masked by novelty. However, the absence of effects is more difficult to interpret than their presence, especially given the difference in power between the two analyses.



Main Effect of Gender
 $F(1, 14) = 16.14, p = 0.001$



Main Effect of Gender
 $F(1, 14) = 27.80, p < 0.001$



Main Effect of Practice
 $F(1, 14) = 21.03, p < 0.001$

Figure 23. Bar graphs of sustained activity for three dorsal mPFC regions from first practice set *only*. Note deactivations in regions -2, -3, 60 and 13, 32, 30 in females and males, respectively.

General Discussion

The present study was designed to assess whether or not ventral and dorsal subdivisions of the ACC have distinct functional roles in emotional and cognitive processes, respectively. Of the three ACC regions examined, the ventral ACC region exhibited transient deactivation and the dorsal ACC regions exhibited positive transient activation, with the activity of both subdivisions shifting back towards baseline with practice, as was expected. However, no significant correlations were observed between changes in neural activation and our behavioral measures of emotion and cognition, state anxiety and reaction times, when collapsed across gender. Therefore, the experiment, as it was originally designed, failed to yield data that could be used to address the original question. By contrast, exploratory analyses that examined additional factors such as gender, trait anxiety, and the Big 5 IPIP Personality Inventory, proved to be more fruitful in addressing the possible specializations of the ventral and dorsal subdivisions of the more expansive, medial prefrontal cortex. Although some of these correlations are unexpectedly high, as previously discussed, results are not believed to have resulted from nonindependence errors (Vul et al., 2009).

On one hand, the current results are consistent with a ventral/dorsal functional division within the mPFC. Albeit in different individual regions, in both women and men (regions 3, 45, 30 and 13, 32, 30, respectively), a correlation between cognition, as measured by response time, and sustained activation in the dorsal mPFC was revealed in the analysis of the first practice set, although the aggregated data set failed to reveal such correlations between response time and activity in any mPFC region. In addition, in the aggregated data set, a consistent pattern emerged, primarily in women, revealing an association between

negative affect, as measured by state and trait anxiety and emotional stability/neuroticism, and both transient and sustained deactivation in the ventral mPFC. This correlation was significantly greater in women than men between state anxiety and deactivation in transient region -15, 47, 5 and sustained region -4, 39, -8, and between both trait anxiety and emotional stability and deactivation in transient region 16, 36, 14.

On the other hand, some results challenge the proposed concept of a ventral/dorsal distinction within the mPFC. In women, change in one dorsal ACC region exhibiting transient activation in the aggregated data set (region 2, 20, 33), and change in one dorsal mPFC region exhibiting sustained deactivation in the first practice set (region -2, -3, 60), revealed a correlation with state and trait anxiety and neuroticism. This relationship with negative affect in the dorsal portion of the mPFC, which was significantly larger in women than men, should not have existed if activity in the dorsal mPFC were specific only to cognition. In addition, few ventral/dorsal pairs of regions exhibiting transient activation in the mPFC exhibited an inverse correlation, or reciprocal suppression, and no sustained regions did, suggesting that activation in a region from one subdivision of the mPFC does not necessarily drive inverse activity in another.

Although results suggest that there might be a great deal of functional specialization in ventral and dorsal regions of the mPFC for emotion and cognition, respectively, the interaction is likely to be much more complex, especially when concurrently considering both transient and sustained signals in the brain between both women and men. Emotion and cognition are closely intertwined (Mohanty et al., 2007), and anxiety, in particular, is a negative emotion that might involve secondary cognitive processing and evaluation before a response is generated (Pruessner et al., 2008). Therefore, it is more likely that there is an

integration of emotion and cognition within and between subdivisions of the mPFC and the rest of the brain (Mesulam, 1998). This conclusion is supported by recent publications examining the brain's default mode network, a concept that will be further explored in the following paragraphs.

Perhaps the most intriguing results of the experiment, however, involved differences between the genders that were readily apparent in the fMRI data but not in the behavioral data, confirming previous reports (Butler et al., 2005; McRae, Oschner, Mauss, Gabriele, & Gross, 2008; Koch et al., 2007; Bell, Wilson, Wilman, Dave, & Silverstone, 2006). According to Esposito and colleagues (1996), functional differences between women and men are unlikely to be a result of differences in brain size, neuronal packing, or other technical differences given that in their study they examined a range of cognitive tasks within a single session and functional differences existed only in some.

Importantly, different emotional or cognitive processes or strategies can produce similar behavioral output patterns yet have distinctive underlying neural activation patterns (Wilkinson & Halligan, 2004). For example, changes in stimulus information or task instruction have been shown to have no effect on task performance yet be associated with changes in brain activation. Despite women and men performing equally well *on average* on the verb generation task, reporting similar levels of state and trait anxiety and emotional stability, and meeting the same stringent mental health exclusion criteria, the fMRI data in the current experiment revealed distinctly different neural patterns between genders that could reflect gender differences in emotional or cognitive processes that are simply too subtle to be detected overtly.

Therefore, the remainder of the discussion will speculate on what possible processes could account for the striking neurofunctional differences revealed between healthy women and men specifically in the ventral mPFC, in which only women consistently exhibited the expected pattern of sustained deactivations. It should be emphasized that this subsequent discussion is based on the analyses reported above involving gender and on supporting studies in the literature. *This discussion is clearly meant to be speculative*; replication on a larger sample would ideally be required to support this speculation.

The Default Mode, Gender, and the Self

There are a number of regions in the brain, including the medial prefrontal cortex, the posterior cingulate/precuneus, and the inferior parietal cortex that are highly active at rest or during passive or low demand tasks (Raichle et al., 2001). This organized network of regions, originally only of interest for its role as a baseline condition, has been identified as the default mode network. More recently, the function of the default mode has drawn attention on its own merit. It is believed that the resting brain engages in ongoing, internally cued processes, such as production of a representation of the external environment (Vogt et al., 1992), attention to one's visceral and emotional state (Gusnard & Raichle, 2001), recollection of the past in preparation for the future (Binder, et al., 1999), and integration of emotional and cognitive processes (Griecius, Krasnow, Reiss, & Menon, 2003).

Although the function of the default mode network activity is not fully understood, activity in these regions consistently decreases during performance of a wide array of cognitively demanding tasks (Mazoyer et al., 2001; Binder et al., 1999; Shulman,

Fiez, Corbetta, & Buckner, 1997), as was revealed in the current experiment.

Deactivations are believed to result when self-focused attentional resources are suspended, interrupted, or reallocated to other regions of the brain required to meet the demands of externally cued cognitive tasks (Gusnard, Akbudak, Shulman, & Raichle, 2001; Gusnard & Raichle, 2001; Raichle et al., 2001). This explanation is supported by evidence that optimal performance and accuracy are correlated with the magnitude of task-induced deactivation in these regions, and these deactivations increase in magnitude with task difficulty by increasing factors such as stimulus presentation rate or cognitive load (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). According to Greicius and Menon (2004), the degree to which an individual attends to external stimuli over default mode processing during performance of a cognitive task is highly variable, but generally as a task progresses, participants tend to shift back from task-specific processing to default mode processing.

Fair and colleagues (2007) concluded that activity during the resting state of blocked or mixed blocked/event-related fMRI designs is comparable to and can be extracted to examine continuous resting state activity. Other studies have also confirmed the existence of two anti-correlated networks (Greicius et al., 2003; Fox et al., 2005), a default mode network and an attentional network, which are associated with task-induced deactivations, and task-induced activations, respectively. Therefore, with regard to the present experiment, conclusions have been drawn regarding default mode activity based on the theory that deactivations observed, while participants performed the cognitively demanding verb generation task, represent suspended or suppressed default mode activity. This argument is particularly compelling when considering the fact that the

ventral mPFC is one of two major hubs of the default mode network (Buckner et al., 2008), and the two previously published ventral mPFC nodes of the default mode network (regions 1, 54, 21, and -3, 39, -2) (Fair et al., 2007; Fox et al., 2005; Greicius et al., 2003) are particularly close to two of the ventral mPFC regions exhibiting significantly greater sustained deactivations in women, as compared to men, in the current experiment (region 3, 51, 15, as shown in Figure 24A and region -4, 39, -8, as shown in Figure 24B).

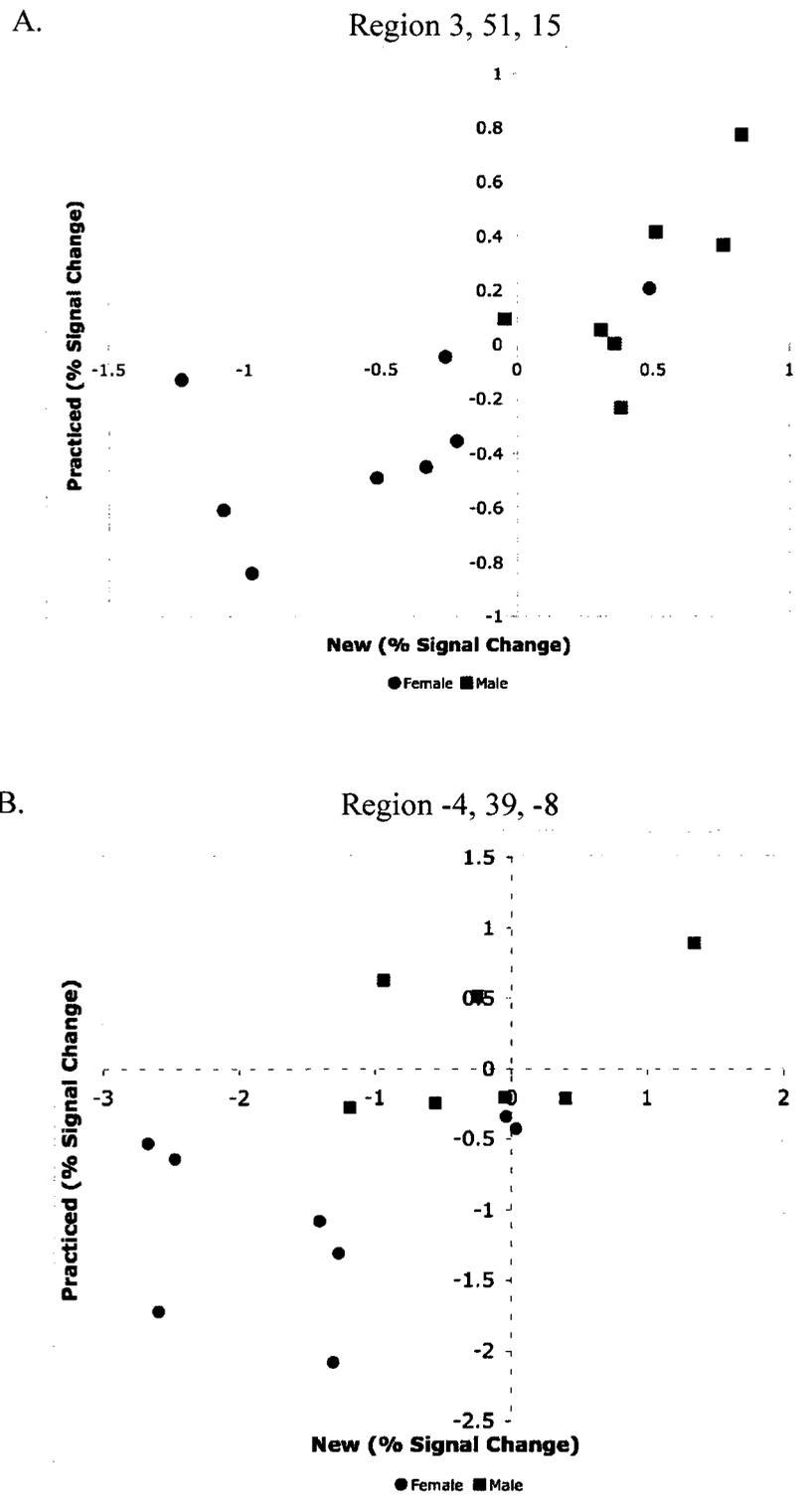


Figure 24. Individual activation in the two regions of the ventral mPFC exhibiting striking gender differences in sustained activation/deactivation.

While the processes that occur during the unconstrained “rest” period associated with default mode activity are the focus of much debate (Raichle & Snyder, 2007), many claim that these processes are self-referential or introspective in nature and are associated with preferential activation in the mPFC (Buckner & Carroll, 2007; D’Argemba et al., 2005; Frith & Frith, 1999; Gusnard et al., 2001; Mason et al., 2007; Northoff et al., 2006). These claims are supported by self-referential and social cognition experiments that generally exhibit positive activation in the same ventral mPFC regions during self-focused processing (Amodio & Frith, 2006), that are deactivated during the performance of cognitively demanding tasks (Bush et al., 2000; Drevets & Raichle, 1998). Indeed, the mPFC, in particular, might be responsible for integrating all of the information produced by the default mode network to create an integrated image of the “self” (Ingvar, 1985; Damasio, 1999).

Self-referential thought and emotions are closely intertwined. Given the importance of self-referential processing to one’s own person, it is inherently more affective than non-referential processing (Northoff et al., 2006). Self-referential thought allows humans to feel emotions based on past and future self-representations and on their own beliefs about themselves and their perceptions of others’ beliefs about them (Leary, 2007). By contrasting detailed, self-relevant mental simulations of imagined scenarios, people are better able to interact with others in social settings (Buckner & Carroll, 2007). Examples of self-referential or social cognition tasks associated with activity in the mPFC, which require self-knowledge, person knowledge, or mentalizing, include the following: evaluation of self-related traits (Kelley et al., 2002; Heatherton et al. 2006); monitoring or reflecting on one’s own emotional state (Gusnard et al., 2001); thinking

about the mental states of others (Mitchell, Banaji, & Macrae, 2005); reading about communicative as compared to private intentions of others (Walter et al., 2004); and judging trust and reciprocity with others (McCabe, Houser, Ryan, Smith & Trouard, 2001).

The complex self-system is a significant contributor to motivating and regulating thoughts, feelings, perceptions, and behaviors, so that a person can achieve, protect, enhance, or simply maintain a positive and accepted social self (Leary, 2007). Self-conscious emotions, such as guilt, shame, embarrassment, social anxiety, and pride, develop from complex cognitions based on a person's inferences about how other people evaluate or perceive them. These emotions can be particularly powerful when in evaluative situations that can potentially harm a person's social self by questioning his or her abilities, character, or social acceptance (Dickerson, 2008; Gruenewald, Kemeny, Aziz, & Fahey, 2004).

What is absent from previous work in social neuroscience and resting state experiments is an assessment of the influence of gender in self-referential and/or default mode neural activity. This is especially important given that for well over a decade social psychologists have reported gender differences in how one defines his or her own self (Cross & Madson, 1997). Furthermore, D'Argembeau and colleagues (2005) proposed that resting state activity in the ventral mPFC is associated with trait-like representations of the self and an individual's ability to infer the mental states of others by imagining his or her own mental state in a similar situation. Therefore, gender differences in models of the self may account for the neurofunctional differences in the anterior portion of the default mode network, the ventral mPFC, commonly believed to play a significant role in

self-referential processing and social navigation (Buckner, Andrews-Hanna, & Schacter, 2008).

Given that the self, and the degree to which others are incorporated into it, affects emotion, motivation, and cognition, gender differences in many domains may be largely accounted for by differences in self-construal (Markus & Oyserman, 1989). Two types of self-construals have been defined (Cross & Madson, 1997). The *interdependent* self-construal emphasizes the importance of social relationships, harmony, interconnectedness, and an obligation and closeness to others (Markus & Kitayama, 1994). The *independent* self-construal, by contrast, refers to a self-definition that emphasizes individuality and uniqueness, independence and autonomy, and the importance of distinguishing and separating oneself from the rest of the world (Markus & Kitayama, 1994). Generally in the United States, self-representations are distinctly different between women and men, with women more often characterized as having interdependent, collective, or communal self-schemas, and men best described as having independent, individualist, or autonomous self-schemas (Gilligan, 1982; Markus & Oyserman, 1989).

Potential differences in self-representations between women and men may lead to differences in how they attend to, process, and remember stimuli (Markus & Wurf, 1987). Presumably because of women's greater interest in relationships, women attend more to others, have greater nonverbal skills (DePaulo, 1994) and attempt to "mind read" or take the perspective of others in an effort to adjust their own behavior (Cross & Madson, 1997). Women also think and remember more about others, especially those close to them, than men do. Women's self-esteem is far more influenced by both positive

and negative feedback from others and from perceived evaluation even in the absence of explicit feedback (Roberts & Nolen-Hoeksema, 1994), because it influences their sense of belongingness (Cross & Madson, 1997). Men, on the contrary, thrive on being unique and independent regardless of feedback (Roberts & Nolen-Hoeksema, 1994).

Just as perspective taking often requires some degree of self-referential processing, self-referential processing may involve a perspective-taking component (D'Argembeau et al., 2007). Certainly, people's behavior is driven not only by their own values and how they perceive themselves, but also by others' values and how they want others to perceive them—their reputations (Amodio & Frith, 2006). Understanding one's own reputation requires an understanding about how others think of oneself. Oschner and colleagues (2005) refer to this as reflected self-knowledge. Using a repetition suppression technique, Jenkins, Macrae and Mitchell (2008) recently confirmed that activity in the same ventral medial prefrontal region was associated not only with accessing the self, but also with spontaneously accessing the self when inferring the mental states of others deemed to be similar to oneself. The intimate connection between understanding one's own self, and in understanding others, may help to explain why thinking about either one is associated with activity in the same ventral mPFC region.

Although it is not yet clear how a person assesses the degree of similarity between oneself and another, there could be gender differences in the degree to which others are perceived to be similar to oneself, especially given that women more frequently than men spontaneously take the perspective of another in an attempt to “mind read” and anticipate the potential thoughts, feelings, and actions of another (Cross & Madson, 1997). Women generally consider themselves in relation to others, while men generally consider

themselves in comparison to others. Women, therefore, are especially attuned to their social environments, and are naturally driven to attain knowledge and understanding of others because acceptance in their relations with others is an integral part of how they define themselves. A woman's experience generally revolves around understanding the experiences of others because it is considered self-relevant, and she may even be responsive to and concerned about others without any explicit intentions (Markus & Oyserman, 1989). It should not be surprising, then, that the ongoing neural activity proposed to be occurring during the default mode state reflects these fundamental differences in individual experiences.

The anterior medial prefrontal area of the default mode network, which includes the ventral mPFC region that exhibited sustained deactivation in women but positive activation in men (3, 51, 15), is most frequently cited in social cognition experiments (Amodio & Frith, 2006). Activity in this region is associated with experiments manipulating communicative intentions and might reflect one's wishes to create with others a shared reality, although this intention may be an unconscious one. This region is also active when people make moral judgments potentially affecting their reputations and when they participate in economic games involving trust and reciprocity. Finally, activity in this region has been associated with reflection about participants' own feelings and reflections of others' feelings about them.

Perhaps, it is a woman's pervasive tendency to include herself in her representation of others, and others in her representation of herself, that renders her more vulnerable than men to ruminative styles of thinking (Markus & Oyserman, 1989). The object of ruminative thought is often oneself, oneself as evaluated or treated by others, or

one's negative mood. Women have a greater tendency to be inquisitive about and wish to understand themselves and stay attuned to their emotional states, as well as develop expertise in interpersonal domains (Butler & Nolen-Hoeksema, 1994; Markus & Oyserman, 1989). So to a certain extent, rumination can facilitate the development and maintenance of social bonds with others (Butler & Nolen-Hoeksema, 1994).

Ray and colleagues (2005) reported that neural activity in the ventral mPFC was associated with individual ruminative tendencies. When participants were instructed to process emotional stimuli in less emotional terms, surprisingly, high trait ruminators were as successful as controls in down-regulating negative affect and activity in the ventral mPFC by interrupting their focus on the self and emotions. When distracted by performance of a difficult cognitive task, deactivations in the ventral mPFC were also associated specifically with decreases in emotional processing (Erk, Abler, & Walter, 2006). Thus, while ruminators were equally able to down-regulate negative affect when explicitly instructed to do so, when unconstrained, ruminators likely return to self-focused attention and may chronically activate regions in the mPFC associated with negative self-referential processing (Ray et al., 2005).

Although rumination was not measured in the current experiment, it is plausible that women were ruminating during passive fixation, but performing the cognitively demanding task served as a distraction from their repetitive, self-referential thought. Sustained deactivation in the ventral mPFC in the current experiment could reflect suppression of women's automatic and ongoing attempts to understand themselves and those around them, their need to feel positively evaluated and accepted, their vicarious internalization of others' emotions, and subsequent feelings of uncontrollability,

processing that very well may be ongoing during the default mode when thoughts are unconstrained.

While not all forms of ruminative thinking are maladaptive (Watkins, 2008), such self-reflection as a means of coping with stress or negative mood (Nolen-Hoeksema, Morrow, & Fredrickson, 1993), or among individuals with negative self views (Sedikides, 1992), could make them more susceptible to negative self-referential processing and the development of affective disorders (Simpson & Papageorgiou, 2003). Indeed, rumination is a risk factor for depression (Butler & Nolen-Hoeksama, 1994), and women are more likely to ruminate than men (Nolen-Hoeksema & Jackson, 2001). This tendency to respond to and cope with depressed mood by self-focused attention to emotion leads to greater duration and recurrence of depressed mood (Butler & Nolen-Hoeksama, 1994) and intrusive thoughts (Watkins & Brown, 2002).

In those suffering from depression, activity in the ventral ACC, specifically, has been identified as a possible region in which self-referential processing is “recast” or re-interpreted in more unfavorable terms (Moran, Macrae, Heatherton, Wyland, & Kelly, 2006). Indeed, abnormal activation in the ventral ACC has been affiliated with dysregulation of emotion and over-activation of self-referential processes, particularly in the form of ruminations (Sheline, 2009). Further, in depression, the ventral mPFC has been shown to contribute excessively to functional connectivity in the default mode network. Given the convergence of correlations between *healthy* women’s state and trait anxiety and neuroticism scores in the ventral mPFC, correlations that were in some cases significantly greater in women than men, and much greater sustained deactivation in women in the ventral ACC region (-4, 39, -8) that is close to the previously identified

default mode node (-3, 39, -2) (Fair et al., 2008; Fox et al., 2005; Grecius et al., 2003), the current data provide a possible neural mechanism for women's greater vulnerability to the development of anxiety or depression (Bar-Haim, Lamy, & Glickman, 2005).

Because difference scores were calculated based on both changes in deactivations and positive activations, interpreting the significance of the direction of the correlations is complicated. However, the data suggest opposite roles for sustained versus transient signals within the ventral mPFC in women. In looking back at ventral medial prefrontal regions in 21 C and D and Tables 12 and 13, both transient and sustained signals are deactivated in women, but they seem to reflect uniquely different roles with regard to negative affect. Across the three regions in the ventral mPFC exhibiting transient deactivation, the *smallest* difference scores with practice are correlated with the *highest* levels of trait anxiety and neuroticism. Incidentally, the dorsal region, exhibiting a positive transient activation, displayed a similar relationship with negative affect. By contrast, the ventral ACC region exhibiting sustained deactivation showed an unexpected relationship, in which the *largest* changes in deactivation with practice were associated with the *highest* levels of trait anxiety and neuroticism.

This complimentary relationship between transient and sustained activation in women was echoed in their functional imaging data, with the ventral ACC region exhibiting sustained deactivation (-4, 39, -8) inversely correlating with all three regions exhibiting transient deactivations in the ventral mPFC (region -15, 47, 5, $r_{female} = -.77, p = .025$; region 14, 45, 13, $r_{female} = -.79, p = .020$; region 16, 36, 14, $r_{female} = -.69, p = .058$). Although men, on average, exhibited transient deactivations in two of the same three ventral mPFC regions (14, 45, 13 and 16, 36, 14), with a similar correlation with state

anxiety in one of them, and they also exhibited modest sustained deactivations in the ventral ACC region (-4, 39 -8), this complimentary relationship between types of neural signals was not apparent in men. In fact, in men there was no relationship between activation in one of these pairs (14, 45, 13 and -4, 39, -8), $r_{male} = -.02, p = .963$, which was marginally different from that in women, $\chi^2_{c(F)}(1, N = 16) = 3.72, p = .054$, and a trend towards a positive relationship in the other pair that was significantly different from women (16, 36, 14 and -4, 39, -8, $r_{male} = .64, p = .087, \chi^2_{c(F)}(1, N = 16) = 7.09, p = .008$).

Eysenck and Calvo (1992) proposed that high trait anxious individuals may have high performance *effectiveness*, in that in low cognitive load conditions participants are able to compensate with greater mental effort to perform at a level similar to that of low anxious participants, but their performance *efficiency* is noticeably impaired during conditions of high cognitive load. A slightly different perspective was recently proposed by Fales and colleagues (2008), in which they suggested that the differences between transient and sustained neural activation between individuals with high and low trait anxiety during the performance of a high load working memory task may simply reflect alternate, yet equally efficient, routes to the same behavioral outcome. They revealed that trait anxiety is inversely correlated with sustained activation and positively correlated with transient activation, results that are consistent with ours, suggesting that the degree to which an individual employs sustained versus transient neural activation may vary depending on his or her level of trait anxiety. If we presume that sustained activity reflects a neural “state” of control, then perhaps participants with higher anxiety levels generally require greater control, or greater sustained ventral mPFC deactivation, to

achieve the same degree of performance on the task, possibly as compensation for more frequent interruptions in transient deactivations.

However, our data suggest that gender is another important factor associated with the balance of transient and sustained activation employed in response to an anxiety-provoking task. Both transient and sustained task-induced deactivations have been associated with the default mode of brain function (Buckner et al., 2008). However, in comparing men to women in this experiment, men exhibited a comparable degree of transient deactivation in two of the three ventral mPFC regions but minimal sustained deactivation in the ventral ACC region (-4, 39, -8). By contrast, the majority of women exhibited marked sustained deactivations in the ventral ACC region with magnitudes that far exceeded the minimum .1% signal change criterion used for this study (Figure 24B).

If default mode activity is actually a reflection of ongoing, self-referential and/or affective processing (Northoff et al., 2006), and deactivations generally represent a reduction in that default mode activity during the performance of cognitively demanding tasks, maybe there is some distinction to be made between reductions that are associated with transient versus sustained deactivations. Perhaps transient deactivation in ventral mPFC represents a mere suspension of default mode activity, whereas sustained deactivation is an active suppression of the self-referential and ruminative thought of the default mode (Greicius & Menon, 2004). The potential cognitive demand from active suppression in the ventral mPFC in women, in turn, may also explain the transient increases they exhibited in cognitive control regions, such as the dorsal mPFC (Fales et al., 2008). Finally, an extension of this notion may help to account for previously reported behavioral and neurofunctional gender differences in overall emotional

responding, which includes both a reactive and a regulatory component (McRae et al., 2008) and the gender differences in baseline state anxiety revealed in the current experiment, prior to the collection of neuroimaging data (Figure 25).

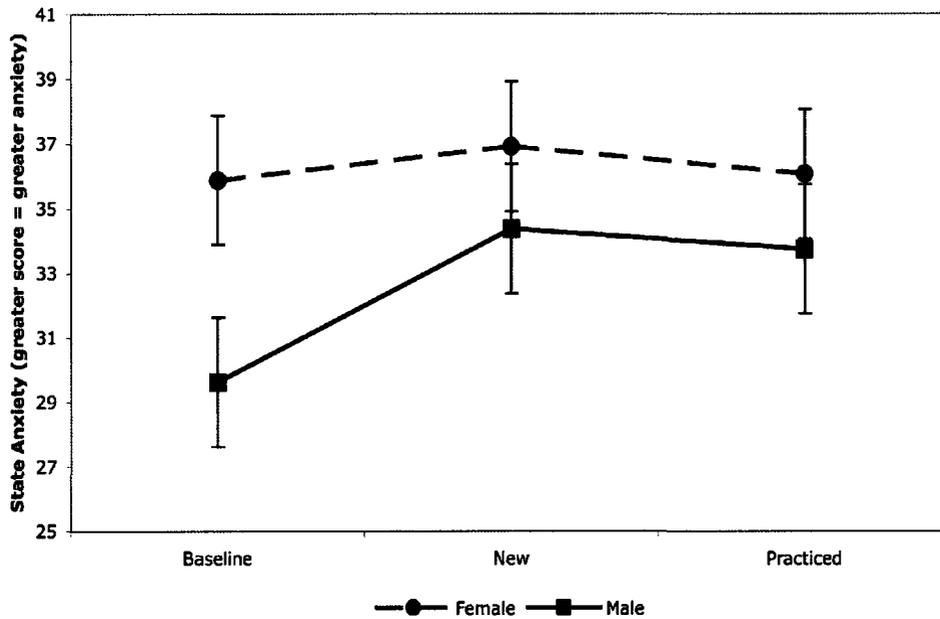


Figure 25. Comparison of baseline, new, and practiced state STAI scores showing a significant difference between baseline and new in men but not women.

Differences between self-construals may affect how a person perceives and responds to emotional experiences (Cross & Madson, 1997) and social evaluative threat (Dickerson, 2008). While the emotions of those with interdependent self-construals, who frequently include other people in their self-concept, may be more sensitive to the social environment and the emotions of others, those with independent self-construals may be more influenced by their own personal experiences (Cross & Madson, 1997). A failure to regulate, adapt, or recover from individual negative emotional or cognitive responses can render a person vulnerable to various diseases (Dickerson, 2008). One may speculate,

therefore, that should the ability to appropriately regulate or suppress default mode activity become compromised, especially in those who rely more heavily on sustained than transient deactivations of the default mode network, a person may be more vulnerable to the development of affective disorders.

Interpretation and Implications

Those with an interconnected self-schema automatically incorporate others into their self-schemas and likely develop expertise in interpersonal domains (Markus & Oyserman, 1989). Just as those with panic disorder engage in extensive processing of threat-related words (Maddock, Buonocore, Kile, Garrett, 2003), perhaps when thoughts are unconstrained, women engage in more extensive processing of their social environment and the meaning of their interpersonal interactions with others. This might involve repetitive reframing of the same information in self-relevant and sometimes negative terms. Although it seems counterintuitive, Ray and colleagues (2005) proposed that, “by repeatedly turning over interpretations of events in their minds, those who tend to ruminate may have developed a cognitive skill of representing information flexibly” (p.166). This cognitive flexibility, in turn, could enable a woman to suppress self-reflection and self-conscious emotions when confronted with a difficult task, and thus exhibit significant sustained deactivation in ventral mPFC. Perhaps the greater the extent of thought suppression required, the greater the absolute magnitude of sustained deactivations in the ventral mPFC during cognitive task performance. As the task becomes easier and less stressful with practice, however, participants gradually gravitate back to the ruminative thought of the default mode (Mason et al., 2007).

As Markus and Oyserman (1989) have argued, “there may be subtle but powerful differences in the nature of the self-concepts that are constructed by women and men because of the relatively greater tendencies of women to automatically focus on and incorporate *others* into their self structure” (p. 108). These differences in models of the self may account not only for gender differences in personality and behavior (Sherif, 1982), but also for fundamental differences in functional brain activity and vulnerability to disease.

Although developmental experiments of default mode activity have not examined gender, these studies reveal that default mode function and connectivity in infants and school-age children differ substantially from adults; so default mode function and efficiency in skills of introspection and mentalizing about others might develop through young adulthood (Fair et al., 2007; Fransson et al., 2007). Therefore, the possibility exists that gender differences in default mode activity could be influenced by early socialization and the development of individual self-construals.

Limitations

Self-Reports and Physiological Measures. Other than functional imaging, no physiological measures such as heart rate, cortisol levels, or skin conductance, were collected in the current experiment. There is much inconsistency in the literature regarding the association between physiological responses and psychological stress (Cacioppo & Tassinary, 1990). Perhaps this is because physiological measures cannot distinguish between types of emotions experienced, only overall arousal level, and are likely a combination of biological systems that vary in time and magnitude (Wang, et al., 2007).

Mauss, Wilhelm, and Gross (2004) reported that participants high in trait anxiety reported greater levels of stress than those with lower anxiety, and they exhibited greater anxious behavior, but there were no differences revealed between the two groups in physiological measures. There are a few possible explanations. There is likely just as much individual variability in physiological reactivity as there is in emotional experiences, and these differences may not be simply across individuals, but also across different kinds of emotional, behavioral, and physiological responses within individuals (Mauss, Levenson, McCarter, Wilhelm, & Gross 2005; Davidson, 2003). Given that there was greater correspondence between self-report and behavior than there was between self-report and physiological responses also suggests that participants might be influenced by socialization, especially with regard to negative emotions because they are often more controlled in social situations (Mauss, Evers, Wilhelm, & Gross, 2006).

Furthermore, some participants may be more willing than others to report emotions (Egloff, Wilhelm, Neubauer, Mauss, & Gross, 2002). Self-reports are particularly vulnerable to gender stereotypes that may lead women to over report their emotions and men to under-report them (Wager & Oschner, 2005). Women might have been more willing to disclose their feelings than men, perhaps because to do so facilitates intimacy in relationships with others (Cross & Madson, 1997), while men might have been less willing to report negative emotions (Snell, Miller, Belk, Garcia-Falconi, & Hernandez-Sanchez, 1989) perhaps because it threatens their sense of autonomy (Cross & Madson, 1997). Finally, some individuals could be better able to perceive autonomic responses than others, and in some cases, because emotions are often automatic and may

not be available at a conscious level, they simply do not lend themselves to self-report at all (Davidson, 2003).

Because anxiety is such a complex construct, collecting more than just a behavioral measure of anxiety would have provided us with a more comprehensive assessment of anxiety within and across individuals. An additional physiological measure, in particular, could have provided us with a more objective, unbiased measure of anxiety (Egloff et al., 2002). Further, because we used self-report, anxiety was only collected retrospectively. Having a physiological measure would have allowed continuous data collection that could have been examined along with stimulus presentation, as we were able to do with the reaction time data. Another consideration is that participants completed the state STAI as soon as they were placed in the scanner, and between runs throughout the session, so they might have either been more attuned to any anxiety symptoms or anxiety might have even increased as a result of completing the inventory (Quirk, Letendre, Ciottone, & Lingley, 1989).

Finally, degree of perceived social threat could explain why overall levels of anxiety were greater for the preliminary experiment (see Figure 4), in which the experimenter was in the same room recording the participant's responses, than in the fMRI experiment (see Figure 12A), in which the experimenter was in a separate room from the participants. In the fMRI experiment, although experimenters did not address whether or not participant responses were being listened to and scored in real time, spontaneous confessions to the experimenters by some of the participants regarding the quality of their responses suggested that many assumed they were. This also suggests

that at least some participants were thinking about their performance during the control periods.

Anxiety Manipulation. No explicit attempts were made to increase anxiety levels in this experiment, as was our intention. Any anxiety that was experienced was naturally occurring as participants performed a difficult cognitive task. However, to increase the anxiety manipulation, we might have benefited from at least emphasizing the presence of an evaluative audience, especially during the fMRI experiment. In a study by Rohelder, Beulen, Chen, Wolf, & Kirschbaum (2007), professional dancers only showed a significant increase in cortisol levels when performing in front of an audience, as compared to during practice sessions. Therefore, subtle manipulations, for example videotaping the subjects' experimental sessions and informing them that a group of peers would score their tapes, or simply providing negative feedback to the participants regarding their performance, might have facilitated a stronger anxiety response.

Controlling Words. This experiment did not control for low versus high constraint nouns, nor was the quality of participant responses, as weak or strong associates, taken into account. Furthermore, errors were few and were therefore excluded from all analyses, so the ACC's role in response selection, conflict monitoring, and error detection was not explored in this experiment (Barch, Braver, Sabb, & Noll, 2000).

Generalizability. Because participants were recruited from the Rice University community, participants were primarily undergraduate and graduate students under the age of 35 years. Therefore, it is unknown whether or not results are representative of the general population.

Statistical Thresholding and Corrections for fMRI Data. The sample size was particularly small, with only 8 females and 8 males, the threshold used to define regions was low (0.01 for transient and 0.05 for sustained effects) yet still significant, and while fMRI data were sphericity corrected, data were not corrected for multiple comparisons. To compensate, strict criteria were set to determine regions exhibiting “true” activation, possibly excluding some legitimate regions from further analyses.

Control Signal. If, indeed, there are gender differences in default mode activity (unconstrained rest), using passive fixation as the control signal in the current fMRI experiment could be particularly problematic. Because medial frontal regions, in particular, exhibit activation that is often associated with social tasks, an additional simple comparison task, such as reading words, could have helped to distinguish better between task related activity and default mode activity between genders (Meltzer et al., 2008). In the future, some effort should also be made to discover what individual processes are occurring at rest (Oschner et al., 2004).

Hormones. Information regarding the phase of the female participants’ menstrual cycles was not collected for the current study. Phase of menstrual cycle has been shown to affect emotional responding (Amin, Epperson, Constable, & Canli, 2006), cognitive processes (Hampson & Kimura, 1992), magnitude of BOLD signal (Dietrich et al., 2001), and location of functional activation (Berman et al., 1997; Shaywitz et al., 1999).

Future Direction

Results from the current experiment raise as many questions as they answer. Of most interest in future research is to further explore the influence of gender in default mode activity, particularly in the ventral mPFC. It will also be important to examine

potential factors that could account for gender differences in neural activity, including differences in self-construal and self-referential thought during the resting state, innate versus socialization effects, and trait versus state factors. This may be accomplished, in part, by using the recently developed mixed-blocked event-related fMRI design to concurrently examine the contributions of both transient and sustained neural signals to default mode and attentional networks. Also, inclusion of additional physiological measures of affect could help to remove social bias in self-reports between genders, and consideration of hormonal phase may help to further explain variability between individual female participants. There are also a lot of interesting prospects worth exploring with regard to the neural underpinnings of personality. Finally, correlational analyses and manipulations of task difficulty (computation of difference scores) seem to be successful methods of assessing individual variability in affective and cognitive regulation and adaptability.

It is important to emphasize that in this experiment, the sample size was small and the thresholds were low. Therefore, until future experiments can be conducted with a larger sample size and greater statistical power, results should be considered tentative and interpretations speculative.

Conclusions

Exploratory analyses suggest that while the ventral and dorsal subdivisions of the mPFC make highly specialized contributions to the processing of emotion and cognition, respectively, there appears to be a complex interaction between the two subdivisions. More intriguing, perhaps, are results suggesting that there may be a fundamental, neurofunctional difference between the way in which women and men balance the

competing demands of emotion and cognition that may be related to differences in self-concept and neural activity in the default mode. Future research on gender differences in self-schemas in relation to neural functioning in the default mode, specifically within the ventral mPFC using the mixed-blocked event-related fMRI design, may help to elucidate gender differences in affect, cognition, and psychopathology.

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