

FUNCTION AND DYSFUNCTION OF THE PREFRONTAL CORTEX: EFFECTS OF
DISTRACTION ON ACTIVE MAINTENANCE IN HEALTHY CONTROLS AND
INDIVIDUALS WITH SCHIZOPHRENIA

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ABSTRACT

SARAH J. HART: Function and Dysfunction of the Prefrontal Cortex: Effects of Distraction on Active Maintenance in Healthy Controls and Individuals with Schizophrenia

(Under the direction of Aysenil Belger, Ph.D.)

The prefrontal cortex (PFC) is thought to be critical for the active maintenance of goal-related information in the face of distraction. Previous studies have demonstrated that schizophrenia is associated with changes in the function of the PFC, and is characterized by difficulties in the active maintenance of information in working memory and in the ability to resist distraction. Two functional neuroimaging experiments were conducted with healthy control participants that examined the effects of distracter demand on working memory by manipulating both voluntary attention to distracters (“executive”) and involuntary capture of attention by emotional distracters. Two additional behavioral experiments were conducted to assess how processing of these types of distracters would be affected in individuals with schizophrenia. It was expected that specific prefrontal subregions would be differentially recruited under conditions of increased distracter demand, and that the group with schizophrenia would be disproportionately affected by executive, but not emotional distraction. The results largely supported the hypotheses, and indicated that the ventrolateral PFC was specifically recruited during both executive and emotional distraction. The dorsolateral PFC was activated during both active maintenance and executive distraction processes, but its activity was significantly disrupted during emotional distraction. The group with

schizophrenia also showed specific impairments in the allocation of attention to executive distracters, but showed similar patterns to controls during emotional distraction. The findings suggest that prefrontal subregions may take on specific roles in resolving interference, and that dysfunction in these regions may underlie changes in distracter processing in schizophrenia.

DEDICATION

This dissertation is dedicated to the memory of my father, Dr. Robert D. Hart.

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CHAPTER I

INTRODUCTION

The prefrontal cortex (PFC) is critical for supporting cognitive control processes that allow for the guidance of behavior according to a goal. Performance of goal-directed behavior requires not only the ability to retain the relevant goal in mind, but also the ability to ignore information that is irrelevant to the primary task at hand. The prefrontal cortex is thought to be important for supporting multiple cognitive processes, such as working memory (WM) (Goldman-Rakic, 1987), selective attention (Banich et al., 2000; Milham, Banich, & Barad, 2003), and inhibition (Fuster, 1980). All of these cognitive processes are thought to rely to some degree on the same prefrontal mechanism, that is, the active maintenance of task-relevant information in the face of interference (Desimone & Duncan, 1995; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). Consistent with a multitude of findings from neuroimaging studies that working memory, selective attention and inhibition share neural substrates in the PFC, behavioral studies have also found these functions to be highly interrelated with one another. Manipulating working memory load, for example, impairs the ability to inhibit inappropriate responses (Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Conway, Tuholski, Shisler, & Engle, 1999; de Fockert, Rees, Frith, & Lavie, 2001; Kim, Kim, & Chun, 2005). Prefrontal mechanisms supporting active maintenance allow for information related to

currently relevant task goals to be maintained, while simultaneously preventing task-irrelevant information from interfering with the task at hand.

The activity of prefrontal neurons during active maintenance is characterized by sustained high rates of firing during delayed-response tasks, where information must be held in working memory across a delay period (Chafee & Goldman-Rakic, 1998; Curtis & D'Esposito, 2003; Ranganath, Cohen, Dam, & D'Esposito, 2004). Functional neuroimaging studies in humans have similarly found sustained high levels of prefrontal activation during working memory performance (Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997; Jha & McCarthy, 2000). Findings from lesion studies have provided complementary evidence supporting the role of the prefrontal cortex in maintenance, as loss of these neurons leads to impaired performance on delayed-response tasks (Curtis & D'Esposito, 2004; Funahashi, Bruce, & Goldman-Rakic, 1993; Mishkin, 1957).

While this sustained activation may reflect processes of keeping information in mind, it may also reflect another crucial function of the PFC, which is keeping information out of mind. Lesioning the PFC leads to increased distractibility to task-irrelevant inputs that interfere with active maintenance processes (Chao & Knight, 1995). A classic study of monkeys with prefrontal lesions performing a delayed-response task showed that despite impaired performance in normal experimental conditions, the lesioned monkeys' accuracy was improved to levels comparable to controls when the lights were turned off during the experiment, which reduced interference from competing visual stimuli (Malmö, 1942). The performance impairment on the original task was,

therefore, largely affected by impaired ability to suppress the effects of task-irrelevant information on information maintained in working memory.

In line with findings that the PFC is important for suppressing interference, neuroimaging studies using task-irrelevant distracters during WM paradigms have found that activation in the PFC is capable of surviving distraction, as opposed to more posterior sensory regions, where sustained activity is disrupted (Constantinidis & Steinmetz, 1996; Miller, Erickson, & Desimone, 1996). Prefrontal sustained activation has also been found to further increase as a function of distraction when compared to maintenance conditions without distraction, suggesting that the PFC may play an active role in protecting memories from interference (Sawaguchi & Yamane, 1999). These findings have therefore supported a role for the PFC in not only active maintenance, but also in the ability to simultaneously protect active memories against distraction (Sakai, Rowe, & Passingham, 2002).

The primary mechanism in the prefrontal cortex that coordinates these processes works by sending bias signals that modulate the activity of more posterior neural pathways. These signals have been found to be critically involved in “top-down” processes of cognitive control, or the ability to guide one’s behavior according to a goal (Miller & Cohen, 2001). This mechanism is thought to be particularly important in conditions where the mappings between stimuli and responses are relatively weak (compared to stimuli with more hardwired or automatic responses), so the task goal must be relied upon to guide behavior. Additionally, when mappings between stimuli and responses must be updated, top-down control allows for the ability to flexibly update the

goal's internal representation and to adjust behavior accordingly (Braver, Barch, & Cohen, 1999).

Miller and Cohen (2001) have argued that these bias signals guide the activity of neural pathways that establish the proper mappings between stimuli, internal states, and responses. While different pathways compete with one another through mutual inhibitory interactions, the pathways that are selected by the PFC reach higher levels of activation (Desimone & Duncan, 1995). Sensory regions processing attended features are biased towards more activation (Giesbrecht & Mangun, 2002; Hopfinger, Buonocore, & Mangun, 2000; Mangun, Buonocore, Girelli, & Jha, 1998), while other regions processing unattended features are suppressed as a consequence of those bias signals (Desimone & Duncan, 1995). These mechanisms have been illustrated, for example, by neuroimaging and electrophysiological studies showing that increasing the amount of attention allocated to a primary task (i.e., bias signal strength) attenuates the neural response to task-irrelevant stimuli (Yucel, Petty, McCarthy, & Belger, 2005a, 2005b). The biasing signals can also be sustained over time, allowing for the active maintenance of attended, task-relevant representations until the goal is achieved.

The following introduction will present a review of the literature that addresses the role of prefrontal mechanisms in normal processes of active maintenance, highlighting the effects of task-relevant and task-irrelevant stimuli on prefrontal function. First, the role of prefrontal mechanisms underlying working memory function and the effects of interference on neural activation will be reviewed. The role of the PFC in active maintenance of abstract rules will also be explored, highlighting the similar cognitive processes and neural substrates that are engaged as during working memory

tasks. Furthermore, this review will address how these mechanisms have been found to be altered in schizophrenia, as evidenced by behavioral and neurophysiological findings.

Prefrontal Cortex Function in Active Maintenance

Working Memory

Working memory is the ability to actively maintain and manipulate information over a short period of time (Baddeley, 1986). Top-down attentional control is thought to play an important role during active maintenance, underlying the ability to keep selected task-relevant goal representations continuously active over time (Awh, Jonides, & Reuter-Lorenz, 1998; Awh et al., 1999; Barnes, Nelson, & Reuter-Lorenz, 2001; Corbetta, Kincade, & Shulman, 2002). Indeed, recent theories have begun to conceptualize working memory as the recruitment of brain systems through attention, as opposed to the operation of specialized systems like the phonological loop, visuospatial sketch pad and central executive in Baddeley's (1986) multiple component model (Postle, 2006). Postle (2006) suggests that rather than reflecting active maintenance of specialized sensory inputs, prefrontal neurons instead support the ability to flexibly adapt behavior according to information that is currently relevant to the task goal (Duncan & Miller, 2002; Fuster, 2002).

A recent study by Lebedev, Messinger, Kralik, and Wise (2004) directly examined the delay-period activity of prefrontal neurons to separable working memory and attention processes. Monkeys were trained to attend to one stimulus location while simultaneously remembering a different location. The results indicated that the majority of prefrontal neurons responded to the attended locations during the delay period, while a smaller subset represented "hybrid" neurons that responded to both attended and

remembered locations. The smallest subset of recorded neurons responded to remembered locations only. The authors concluded that delay-period activity in prefrontal neurons is primarily accounted for by attentional selection processes, as opposed to memory functions per se. While the findings show that the PFC does support WM functions, they suggest that the delay-period activity in the PFC supports multiple additional cognitive functions, including the guidance of behavior according to currently relevant goals.

The PFC is able to continuously maintain sensory representations for as long as they are relevant to the current task, which usually spans across many other irrelevant, interfering events (Miller & Cohen, 2001). Many studies have therefore examined the effects of different types of task-irrelevant distraction on active maintenance processes. Given the evidence that attention is a primary mechanism supporting active maintenance in the face of concurrent distraction, it is not surprising that diversion of attentional resources to task-irrelevant stimuli impairs active maintenance processes. The following sections will review and compare the effects of several different types of distraction on active maintenance processes.

Effects of Perceptual Interference

One specific paradigm that has been frequently used to examine the effects of interference on WM maintenance involves the presentation of perceptual distracters during a delayed-response task. In a single trial, information to be encoded into working memory is first presented (the “S1” period). The S1 period is followed by a delay interval, during which the encoded information will be maintained in working memory. Finally, a probe is presented (the “S2” period), to which participants indicate whether the

probe stimulus was part of the original memory array. Interference can then be manipulated within trials by presenting distracters during the delay period that are either congruent or incongruent with the domain of the maintained information (e.g., during a face working memory task, presenting pictures of congruent faces and incongruent houses as distracters). According to the attentional rehearsal hypothesis, which posits that attention is the mechanism underlying active maintenance, processing of congruent distracters will be facilitated because the brain areas representing them are already biased due to concurrent active maintenance processes. Under these conditions, prefrontal selection mechanisms should be invoked to prevent distracters from interfering with the primary working memory task (Jha, Fabian, & Aguirre, 2004; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997).

One theory of prefrontal organization posits that this ability to inhibit interference from irrelevant stimuli is represented in more ventral PFC subregions, while more dorsal regions support maintenance processes (Luria & Homskaya, 1970). Alternatively, more recent theories have supported a more general role for ventral prefrontal regions in selecting between competing responses, rather than inhibiting irrelevant information per se (Sakai et al., 2002; Tippet, Gendall, Farah, & Thompson-Schill, 2004). In terms of Miller and Cohen's (2001) model, this differing response competition may be reflected through variations in PFC biasing signals that can account for different activation between prefrontal subregions.

To address the role of prefrontal subregions in WM maintenance and interference resolution, Jha et al. (2004) used a face working memory task to test whether the ventrolateral PFC (vlPFC) subserves processes that select between competing responses,

predicting that delay-period activity in this region would be greater during congruent than incongruent distraction (pictures of faces and shoes, respectively). The results indicated that both dorsal and ventral prefrontal regions showed sustained delay-period activation during the working memory task, but only the ventral PFC was modulated by the congruency of the distracters, with greater activity for the congruent face distracters. In addition, the fusiform face area showed enhanced activation during congruent faces compared to incongruent shoes. These congruency effects were only present during correct trials, suggesting that the interaction between prefrontal selection mechanisms and posterior sensory regions plays an important role in preventing interference during WM.

In contrast to the vlPFC, the dorsolateral PFC (dlPFC) did not respond differently according to distraction, although it showed greater delay-period activation for correct than incorrect trials, suggesting an important role in active maintenance. Jha et al. (2004) suggest that under conditions of difficult, congruent distraction, the selection failures of the vlPFC lead to maintenance failures within the dlPFC, with concomitant decreases in delay-period activation. While these interacting neural mechanisms are still a matter of debate, the results of the study indicate that dorsal and ventral prefrontal subregions may play differential roles in maintenance and interference resolution.

Effects of Proactive Interference

Other studies have approached the manipulation of distraction during working memory by using proactive interference. In this paradigm, a delayed-response design may be used (i.e., S1, followed by a delay, then S2), where a probe item in S2 was a member of S1 in a previous trial but not the current trial (“recent-negative probe”). The

correct response would be to identify the item as a non-match to S1, but interference results from the item being presented previously in the experiment. This type of interference typically leads to slower reaction times and poorer accuracy on recent-negative probe trials compared to other trial types (Goggin & Wickens, 1971; Jha et al., 2004; May, Hasher, & Kane, 1999).

Like studies of perceptual interference, neuroimaging studies of proactive interference have also found increased involvement of the ventrolateral PFC during greater distraction. Several studies have found that the vLPFC is more active on recent-negative probe trials than other trials (Bunge et al., 2001; D'Esposito, Postle, Jonides, & Smith, 1999; Jha et al., 2004; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998). It has been proposed that the vLPFC engages similar selection processes when a probe item is familiar, so that the item must be further evaluated as to whether it is task-relevant or irrelevant (Thompson-Schill, 2003; Tippett et al., 2004). Ventrolateral PFC activation has indeed been found to increase when it is uncertain whether the item is relevant or irrelevant and the need for selection is high (Kan & Thompson-Schill, 2004; Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003; Thompson-Schill et al., 2002). Like studies of perceptual distraction, these findings are consistent with an important role of the vLPFC in representational selection processes that help to resolve interference (Desimone & Duncan, 1995; Jha et al., 2004).

Effects of Attention Allocation

While many studies have examined the effects of perceptual distraction and proactive interference, the effects of distracters requiring active allocation of attention (i.e., “executive” distracters) have remained relatively unexplored. This ability to adjust

the degree of control allocated to a task according to the current goal is an important adaptive function of the PFC. For example, it is important to pay closer attention to the road when driving on a rainy night than during a sunny day (Miller & Cohen, 2001). In the previously described distracter tasks, the primary goal of the task is to maintain information in working memory while allocating as little attention as possible to distracters, as they are irrelevant to the primary task. However, these types of distracters often require some attention to be allocated to them (for example, when pressing a button in response), thus diverting some resources away from the primary working memory task. One question that has remained unanswered is the effect of active allocation of some attentional resources to secondary distracter stimuli, while the bulk of attentional resources are focused on the primary working memory task. Given that attentional mechanisms play an important role in prefrontal active maintenance processes, the active diversion of resources to a secondary task would be expected to similarly impair active maintenance and recruit selection mechanisms to deal with increased competition.

In one study requiring active allocation of attention to distracters, Sakai et al. (2002) used a spatial working memory delayed-response paradigm that included trials with and without distraction. After participants encoded a series of spatial locations, a delay ensued, followed by a probe that tested memory for the spatial order in which the encoded locations were presented. On trials with distraction, a secondary spatial working memory task was introduced, where participants encoded the distracter locations and responded to a probe. This approach required participants to shift spatial attention away from the originally encoded locations and towards the distracter locations, completely disrupting the ability for rehearsal. The results indicated that delay-period activity in

prefrontal regions generally predicted working memory performance. Furthermore, under conditions of distraction, the correlation between activation in prefrontal and posterior sensory regions was found to predict working memory performance. Consistent with findings from perceptual interference paradigms (Jha et al., 2004), these results suggest an important role for interacting prefrontal and posterior sensory regions in protecting active memories from interference, suggesting similar recruitment of prefrontal biasing mechanisms during both active and passive types of distraction.

While the study by Sakai et al. (2002) employed distracters that were actively attended during the delay, it differs notably from the current study (Experiment 1) in that the distracters completely disrupted the ability for active maintenance to occur. The processes underlying executive distraction during simultaneous active maintenance processes have remained unexplored. Furthermore, the study by Sakai et al. (2002) did not distinguish activation patterns between prefrontal subregions. Experiment 1 in this study aimed to directly assess the effects of executive distraction in separate dorsal and ventral prefrontal regions by manipulating the degree to which distracters must be attended, without completely disrupting active maintenance.

Effects of Emotional Interference

An additional type of interference that has been found to impair active maintenance is emotional distraction. Task-irrelevant emotional stimuli can divert attention away from the primary task at hand and impair performance (as for example, when passing the scene of an accident while driving) (Dolcos & McCarthy, 2006; Wang, Labar, & McCarthy, 2006; Wang, McCarthy, Song, & Labar, 2005). Because emotional stimuli are such potent distracters, they can be utilized as a comparison against

emotionally neutral distracters as a modulation of distracter demand during working memory maintenance.

Studies of stress effects, which cause a physiological response and have been conceptualized as an emotional state (Lazarus, 1999), have been found to impair executive ability and prefrontal function. For example, Hartley and Adams (1974) found that presenting loud noise stressors impairs the abilities for selective attention and inhibition during performance of the Stroop task, which requires processing of task-relevant information over competing irrelevant information. Arnsten and Goldman-Rakic (1998) found similar effects in monkeys, where noise stress impaired spatial working memory performance. The authors suggested that emotional stress takes the PFC “off-line”, allowing behavior to be regulated by more habitual responses.

The mechanisms underlying these emotional interference effects have been proposed to rely on an interaction between dorsal and ventral brain systems that differentially support executive and emotional processing (Drevets & Raichle, 1998; Mayberg, 1997; Phillips, Drevets, Rauch, & Lane, 2003). The dorsal executive control system (DECS) includes the dorsolateral PFC and parietal cortex and is critically involved in active maintenance of goal-relevant information. The ventral affective processing system (VAPS) includes the ventrolateral PFC (vlPFC), medial PFC, orbitofrontal PFC, and the amygdala (Davidson & Irwin, 1999; Zald, 2003) (Figure 1). It has been suggested that interactions between these dorsal and ventral systems can account for emotional distraction effects on active maintenance processes (Dolcos & McCarthy, 2006). Integration of information from the VAPS and DECS may depend crucially on the anterior cingulate cortex, which is involved in response inhibition (Mega

& Cummings, 1994), conflict monitoring (C. S. Carter et al., 1998), and evaluating emotional information (Bush, Luu, & Posner, 2000; Vogt, Berger, & Derbyshire, 2003). The vIPFC, in addition, has been proposed to be a site of integration between emotional and executive processes, as it has been found to be activated during both behavioral inhibition (Aron, Robbins, & Poldrack, 2004) and emotional interference (Wang et al., 2005; Yamasaki, LaBar, & McCarthy, 2002).

A study by Dolcos and McCarthy (2006) demonstrated the effects of emotional distraction during working memory maintenance on activation in the DECS and VAPS. Using a delayed-response working memory task for faces, they presented emotional and neutral scenes during the delay period. The results indicated that the emotional distracters elicited activity in the VAPS, including the amygdala and ventrolateral PFC. Simultaneously, the emotional distracters led to deactivation in the DECS, including the dorsolateral PFC and parietal cortex. These changes in activation were also associated with greater behavioral impairment due to emotional distraction compared to equally complex neutral distracters. The study demonstrated that the interactions between these dorsal and ventral systems could explain the detrimental emotional interference effect on active maintenance processes.

A specific region in the VAPS, the orbitofrontal cortex (OFC), has frequently been associated with processing social and affective stimuli (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Price, 1999). The OFC receives extensive projections from the amygdala, and has been found to be critical in aspects of reward processing and emotional evaluation and decision making (Bechara, Damasio, & Damasio, 2000; Schultz, 2002; Tremblay & Schultz, 1999). Miller and Cohen (2001), however, argue

that this region may have a more important role in resolving competition rather than being specialized for emotional information per se, because emotional stimuli are more likely to strongly compete for attention by eliciting reflexive reactions. The orbitofrontal PFC may play an important role in dealing with increased competition, which is reflected under conditions where emotional stimuli lead to greater competition for the focus of attention. While specific prefrontal regions do receive input from areas that process emotion, the increased response competition may account for a significant amount of the activation observed in these regions.

As the role of the PFC in emotional distraction during working memory has only just begun to be examined, the exact mechanisms by which emotional information impairs active maintenance have yet to be delineated. Because emotional stimuli provide a particularly salient form of distraction, they can provide a useful way to manipulate distracter difficulty and to examine how the dorsal and ventral systems interact. Experiment 2 in the current study aimed to expand upon the current findings by assessing how emotional distraction affected the recruitment of prefrontal regions during active maintenance of task goals and rules.

Rule Maintenance

Miller and Cohen (2001) have argued that prefrontal activation during working memory partly reflects the requirement for active maintenance of the goals and rules of the task. Furthermore, the same mechanisms underlying active maintenance of task-relevant information in working memory also allow for flexible shifts in behavior when the task rules change. Miller and Cohen (2001) have argued that selective attention, inhibition, and working memory all depend on the prefrontal representation and updating

of the current task rules. Impairment to these prefrontal mechanisms is associated with difficulty in adapting behavior according to the currently relevant task rule, leading to perseverative behavior.

Evidence from several neuropsychological studies has supported the critical role that prefrontal mechanisms play in rule maintenance and flexible adaptation of behavior. For example, prefrontal damage is associated with perseveration on the Wisconsin card sort task (WCST), which requires participants to sort cards according to a rule that varies periodically (Dias, Robbins, & Roberts, 1997; Milner, 1963). Because no single stimulus-response mapping can be used, behavior must be flexibly adapted when the task goals change. Top-down signals are required to favor the currently task-relevant response (i.e., to sort according to the new rule), which is in competition with the irrelevant but prepotent response (i.e., to sort according to the previously used rule).

The role of the PFC in rule use can be assessed by examining the neural correlates representing specific rules for guiding behavior. Several studies using cellular recording techniques have demonstrated that activity in a large proportion of prefrontal neurons varies according to specific, complex rules (Asaad, Rainer, & Miller, 2000; Hoshi, Shima, & Tanji, 1998). For example, Barone and Joseph (1989) found cells in monkeys that responded to specific light stimuli, but only under conditions where the light was at a particular point in a sequence that the monkey had to imitate. White and Wise (1999) found that in a monkey that was trained to respond according to two different rules, up to half of the recorded lateral prefrontal neurons showed activity that varied according to the specific rule being followed.

Several studies using neuroimaging techniques have found prefrontal activation during abstract rule maintenance in humans. In these studies, participants are typically trained on an arbitrary set of stimulus-response associations before scanning. Neural activity is then recorded while participants hold the currently task-relevant rule in mind in order to guide subsequent responses. Manipulations of demand on rule retrieval and maintenance (e.g., complex versus simple rules) have consistently found greater involvement of the ventrolateral PFC (Brass & von Cramon, 2004; Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Crone, Wendelken, Donohue, & Bunge, 2006). However, the roles of prefrontal subregions in rule maintenance under conditions of interference, such as during task switching, remain controversial.

Effects of Switching

Task switching is considered to be a component of rule implementation, and requires retrieval of the currently relevant task set while ignoring the previously relevant set (Bunge, 2004; Sakai & Passingham, 2006; Swainson et al., 2003). Behavioral studies have consistently found that switching to rules that have two response meanings (i.e., where the response depends on the current rule) is more difficult than switching to rules with single response meanings (Crone et al., 2006; Monsell, 2003). These findings suggest that performance decrements resulting from task switching do not result only from retrieving a new rule, but also result from the need to override the previously relevant rule. Indeed, several neuroimaging studies have demonstrated activation in the same lateral prefrontal regions during both task switching and inhibition (e.g., in proactive interference paradigms) (Brass & von Cramon, 2004; Konishi, Chikazoe, Jimura, Asari, & Miyashita, 2005; Sohn, Ursu, Anderson, Stenger, & Carter, 2000).

While both the vlPFC and dlPFC have been implicated in the ability to flexibly switch behaviors when the task rules change (Shafritz, Kartheiser, & Belger, 2005; Yeung, Nystrom, Aronson, & Cohen, 2006), Crone et al. (2006) found that lateral prefrontal areas may be more important for rule maintenance, while medial prefrontal regions may contribute more to the ability to override the old rule.

Swainson et al. (2003) specifically examined the extent to which a common neural mechanism supports task switching and behavioral inhibition processes using a modified go / no-go paradigm. The task design isolated the processes of inhibiting a motor response and switching between task sets by having subjects switch between two tasks, including a “go” task requiring an immediate response and a “wait” task requiring the response to be withheld until stimulus offset. Within a mixed block of trials, switch and non-switch trial types could be isolated, along with “go” and “wait” trials. The results indicated that lateral prefrontal activation elicited by response inhibition was found only on switch trials, but not non-switch trials. Activation elicited by task switching was, similarly, only apparent on “wait” trials requiring inhibition. The results indicate therefore that lateral prefrontal activation depended on interacting processes of inhibition and task switching. The results are consistent with previous findings suggesting that a common prefrontal inhibitory mechanism may underlie both task switching and behavioral inhibition abilities (Konishi et al., 1999).

While several studies have examined inhibitory control during task switching using these types of designs, the effects of task-irrelevant perceptual information presented as distracters during rule use are unknown. Although the ability to suppress a previously relevant rule is an integral component of task switching, it is not known

whether the inhibitory mechanisms required for switching are the same as those involved in the ability to ignore irrelevant perceptual inputs. Experiment 2 in the current study addressed the effects of task-irrelevant perceptual information presented during rule use in the form of emotional pictures, in order to examine effects of distracter demand across the period of time that a rule was being maintained.

Effects of Emotional Interference

As described in the working memory section above, distracters with emotional content provide a particularly salient form of interference that allows for the manipulation of distracter difficulty. Few studies have specifically investigated emotional effects on rule maintenance or switching, although several animal studies have examined the interactions between emotion (in the form of associated rewards) and shifting of attentional set (Roberts & Wallis, 2000). Dias, Robbins and Roberts (1996) were able to dissociate attentional and emotional shifts in the prefrontal cortex using lesion methods in monkeys. Monkeys were trained to make visual discriminations between two types of stimuli, one of which was associated with a reward. After receiving lesions to the orbitofrontal cortex and lateral PFC, the monkeys were required to reverse the stimulus-reward association. They found that damage to the OFC, but not the lateral PFC, specifically impaired the ability to switch behaviors according to the emotional significance of the stimuli. In other words, the OFC was necessary to suppress the influence of a previously task-relevant reward association. The lateral PFC, in contrast, was necessary for attentional shifts but not emotional shifts. The results are consistent with the roles of these regions in the DECS and VAPS, which are thought to interact with one another to guide emotional influences on executive processing. Although these

animal studies have dissociated the roles of prefrontal subregions in emotional and executive processing, the effects of emotional information as a perceptual distracter during rule maintenance and switching have remained unexplored. This manipulation was tested in Experiment 2 in the current study.

The final two experiments (3 and 4) in this set of studies addressed distraction effects on active maintenance in individuals with schizophrenia. Like Experiments 1 and 2, these studies addressed the effects of voluntary attention allocation and involuntary diversion of attention on active maintenance processes. The following section will review the effects of schizophrenia on prefrontal mechanisms and the associated changes in active maintenance processes and interference resolution.

Prefrontal Cortex Dysfunction in Schizophrenia

Schizophrenia is a severe and chronic mental illness characterized by behavioral deficits in a multitude of cognitive domains, including working memory, attention, and various executive functions (Braver et al., 1999; Perlstein, Carter, Noll, & Cohen, 2001). A predominant theory of cognitive impairment in schizophrenia posits that these behavioral deficits commonly reflect dysfunction in dopamine transmission in the prefrontal cortex, which leads to dysregulation of behavior due to impaired cognitive control mechanisms (Cohen & Servan-Schreiber, 1992). These dysfunctional control mechanisms are characterized by impaired ability to maintain and update internal representations of task-relevant information while simultaneously ignoring irrelevant information (Braver et al., 1999). These difficulties in distinguishing between task-relevant and irrelevant information have been found in studies using both behavioral and

neurophysiological measurements, including in individuals in the prodromal stage of schizophrenia (Morey et al., 2005; van der Stelt, Lieberman, & Belger, 2005).

Impairments in the ability to selectively attend to relevant stimuli in schizophrenia have been well-documented in the literature, as shown by impaired performance on Stroop tasks, where attention must be allocated to one aspect of a stimulus (the ink color of a printed word) while a prepotent response (reading the word) must be inhibited (Abramczyk, Jordan, & Hegel, 1983; Barch, Carter, & Cohen, 2004; Schooler, Neumann, Caplan, & Roberts, 1997). Individuals with schizophrenia also show impairments on continuous performance tasks like the AX-CPT, where the currently relevant context or goal¹ must be attended to and used to govern a response to a target (Cohen, Barch, Carter, & Servan-Schreiber, 1999; Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989; Nuechterlein & Dawson, 1984). Furthermore, schizophrenia is frequently associated with difficulties on behavioral inhibition tasks that require the suppression of a prepotent response, as shown by impairments on go / no-go tasks (Kiehl, Smith, Hare, & Liddle, 2000; Weisbrod, Kiefer, Marzinzik, & Spitzer, 2000). Impairment to prefrontal mechanisms can therefore influence performance on a multitude of cognitive tasks that require selective attention and inhibition. In addition, individuals with schizophrenia are particularly impaired on tasks that require the active maintenance of selective attention over time, as in working memory.

Working Memory

¹Note that the terms “goal” and “context” are used interchangeably when describing task-relevant information that guides behavior. “Context” refers specifically to information that is directly relevant to the task-appropriate response (Cohen, Braver, & O'Reilly, 1996).

Consistent with the proposed prefrontal dysfunction in schizophrenia, behavioral studies have demonstrated significant impairments in working memory performance, with difficulty in actively maintaining information in the face of distraction (C. Carter et al., 1996; Park & Holzman, 1992). It has been suggested that WM deficits may be a core feature of schizophrenia, underlying many of the disorder's deficits and symptoms (Manoach, 2003). As a result of impairment in the ability to actively keep task-relevant information in mind while resisting interference, individuals with schizophrenia generally have difficulty with goal-directed behavior, leading to behaviors that are guided by stimuli rather than context (MacDonald et al., 2005; Manoach, 2003). This impairment in contextual, goal-directed processing in schizophrenia has been proposed to explain the behavioral difficulties on many different types of working memory tasks that require active maintenance and manipulation of information (Barch, 2006).

A large body of neuroimaging studies have suggested that the WM impairment in schizophrenia is related to hypoactivation in the dorsolateral PFC, where less activation is related to poorer performance (Glahn et al., 2005; Perlstein et al., 2001; Perlstein, Dixit, Carter, Noll, & Cohen, 2003). These prefrontal changes may further influence activation of other posterior brain regions through changes in bias signals. Entire networks of brain regions activated by working memory tasks may therefore be altered in schizophrenia as a result of aberrant activity in prefrontal connections that lead to changes in activity of other regions, or poor integration among regions in the network (Glahn et al., 2005). Indeed, relative decreases in dlPFC activation have been found to be associated with activation increases in other brain regions in schizophrenia (Callicott et al., 2000). The

evidence suggests that working memory deficits in schizophrenia should be considered in terms of network dysfunction, rather than focused exclusively on dlPFC hypoactivation.

While many studies using a variety of paradigms have found evidence of hypofrontality in schizophrenia, several studies have also found equal activation or hyperactivation of prefrontal regions during working memory tasks (Callicott et al., 2000; Honey, Bullmore, & Sharma, 2002). A review by Manoach (2003) addressed these seemingly discrepant findings by examining methodological issues between studies. The review suggests that task difficulty may be an important factor mediating whether prefrontal regions show hyper- or hypoactivation in schizophrenia. Manoach suggests that due to reduced WM capacity in schizophrenia, prefrontal activation as a function of load is shifted so that the dlPFC activates maximally at a lower load relative to controls. Hypofrontality may therefore be largely a result of testing WM loads that exceed the capacity of the individuals with schizophrenia, but not the controls. Findings of hypo- and hyperactivation in the PFC during working memory in schizophrenia may therefore both be informative markers of dysfunction.

Effects of Distraction

Consistent with dysfunction in prefrontal biasing mechanisms, individuals with schizophrenia tend to show the greatest impairment on working memory tasks with some distraction or interference. For example, individuals with schizophrenia have been found to show disproportionately greater errors on recent-negative probe trials in proactive interference manipulations (Goldberg, Patterson, Taqu, & Wilder, 1998; Oltmanns & Neale, 1975; Randolph, Gold, Carpenter, Goldberg, & Weinberger, 1992). Barch (2006) suggests that the impairment in context processing impairs the ability to distinguish

between task-relevant and irrelevant information, increasing the influence of distracting input. Abnormalities in dopamine signaling are thought to dysregulate the ability to gate information in working memory, leading to susceptibility to interference (Braver et al., 1999). Indeed, several studies have found that modulating dopamine levels can improve working memory performance in schizophrenia (Daniel, Berman, & Weinberger, 1989; Daniel et al., 1991).

It has been suggested that a reduction in the amount of available processing resources in schizophrenia leads to impairments on both active maintenance and the ability to resist distraction. The ability to perform and coordinate multiple tasks simultaneously relies on a finite pool of attentional resources that must be allocated according to task demands. The allocation of attentional resources is thought to occur following the detection of conflict, and involves interactions between the PFC and anterior cingulate cortex (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; C. S. Carter et al., 2000). Individuals with schizophrenia have been found to perform poorly across domains under conditions with high processing demands, suggesting that they reach the limit of resources at lower processing loads than controls, an idea which is also consistent with their working memory deficits (Granholm, Asarnow, & Marder, 1996; Nuechterlein & Dawson, 1984; Silver & Feldman, 2005).

However, it has remained a matter of debate whether individuals with schizophrenia have generally intact resource allocation abilities, despite reductions in the amount of available resources. A study by Granholm et al. (1996) used a dual-task paradigm to test the relative degree that amount of resources or allocation of resources was taxed. They asked individuals with schizophrenia and healthy controls to perform a

visual search task simultaneously with a secondary reaction time task requiring a button press in response to an auditory tone, which was either cued by a warning (high demand) or was unwarned (low demand). Allocation of resources was assessed by examining resource tradeoff, that is, the improvement in performance on one task when performance on the other decreases, between the high and low demand tasks in the dual-task condition. The results indicated that that the group with schizophrenia was more impaired on the dual-task condition than controls, suggesting a reduction in the amount of processing resources, but analyses of resource tradeoff indicated that both groups allocated resources similarly. The authors noted, however, that resources may still be allocated improperly when task-irrelevant stimuli are present. Furthermore, it is possible that when competing tasks engage active maintenance processes, rather than only selective attention, the overloading of prefrontal mechanisms would lead to greater distractibility.

Fleming et al. (1995) addressed the effects of task-irrelevant distracters on active maintenance in schizophrenia using a delayed-response paradigm with an “executive” type of distraction, where varying degrees of attention needed to be allocated to a secondary task. The study manipulated distracter demand during a verbal working memory task by comparing the effects of finger-tapping, counting forwards, and counting backwards from 100 by threes during active maintenance. As the combination of working memory requirements and need to resist distraction necessitates the simultaneous activation of competing processes, the authors hypothesized that decreased resource capacity in schizophrenia might be overwhelmed by the coordination and implementation of the two tasks. The results indicated that, contrary to other findings of intact resource allocation (Granholm et al., 1996), recall ability in the group with

schizophrenia was disproportionately impaired by greater distracter demand relative to controls. Even distracters that required relatively little attentional resources, like forward counting, resulted in significant disruption to the primary working memory task, supporting the possibility that overloading prefrontal mechanisms leads to greater distractibility.

The study by Fleming et al. (1995) was limited in that it did not directly measure the degree of attention allocated to the distracter tasks (for example, by measuring speed or accuracy when counting backwards). Furthermore, the study averaged only 5 trials to assess the effect of each distracter condition. Experiment 3 in the current study aimed to improve upon the design of Fleming et al. (1995) by measuring behavioral responses at both WM retrieval and during the secondary distracter task itself, and included 24 trials per condition. Furthermore, it was able to control for perceptual and motor requirements across the distracter conditions in order to better isolate the effects of attentional allocation. This allowed for the examination of whether increased attention allocation to distracters could account for impaired working memory performance in schizophrenia.

Attention-Emotion Interactions

While Experiment 3 assessed the effects of distracter demand in schizophrenia by degree of attention allocated, Experiment 4 manipulated it according to emotional salience. While many studies have found changes in attention and emotional processes in schizophrenia, few have directly examined their interactions. While findings in healthy controls have indicated that emotional distracters impair active maintenance by capturing attentional resources (Dolcos & McCarthy, 2006), it is currently unknown whether

schizophrenia is characterized by proportionately greater distractibility to emotional stimuli.

Schizophrenia is characterized by changes in social and emotional processing, which have been linked to impaired prefrontal function (Andreasen et al., 1992). The negative symptoms of schizophrenia are associated with abnormalities in affect and motivation, including emotional blunting, apathy, lack of spontaneity, social withdrawal, and anhedonia (Andreasen et al., 1992; C. Carter et al., 1996). It has been furthermore suggested that positive symptoms, such as hallucinations and delusions, may directly reflect the interplay between executive and emotional processes (Freeman, Garety, Kuipers, Fowler, & Bebbington, 2002).

These executive-emotional interactions have been found to be abnormal in schizophrenia in several types of cognitive paradigms, and have been associated with abnormal attentional biases for affective information (Waters, Badcock, & Maybery, 2006). It has been argued that affective information provides context for directing behavior and directs attention toward relevant stimuli, a process which relies on the PFC (Park, Gibson, & McMichael, 2006). Emotional and motivational processes are therefore necessary for goal-directed behavior to occur. Impaired affective processing may therefore impair the abilities for active attention and working memory, or conversely, WM deficits may disrupt socio-affective functioning. It is also possible that the deficits in schizophrenia may generally reflect impaired goal-directed behavior, whether it is guided by cognitive, affective or social information (Park et al., 2006).

A multitude of studies have indicated that individuals with schizophrenia show abnormal processing of emotional stimuli, particularly in recognizing facial expressions

and speech affect (Edwards, Jackson, & Pattison, 2002; Gooding & Tallent, 2002; Martin, Baudouin, Tiberghien, & Franck, 2005; Schneider et al., 2006). In particular, individuals with schizophrenia have been found to have deficits in recognizing fearful facial expressions, which has been linked to dysfunctional activation in the amygdala (a region in the VAPS) (Edwards, Pattison, Jackson, & Wales, 2001; Evangelii & Broks, 2000). Several studies have also found that schizophrenia is associated with memory biases for negative information (Calev & Edelist, 1993; Corcoran & Frith, 2003), however, other findings have instead indicated better memory for positive stimuli (Neumann, Blairy, Lecompte, & Philippot, 2006).

Other studies have found that a greater degree of emotional interference impairs selective attention and inhibitory processes in schizotypy, or individuals with a predisposition for developing schizophrenia. These individuals have been found to show increased behavioral interference to threat-related words on an emotional Stroop task, which requires selective attention to the task-relevant ink color while ignoring the emotional meaning of the word (Epstein, Stern, & Silbersweig, 1999). Mohanty et al. (2005) similarly used fMRI to examine the neural underpinnings of the emotional Stroop task in schizotypy. Their results indicated abnormal dlPFC activation patterns, which the authors interpreted as reflecting impaired ability for active maintenance of attentional set in the presence of emotional distraction. The group with schizotypy also showed abnormal activity in ventral limbic areas (i.e., part of the VAPS) such as the nucleus accumbens, hippocampus and amygdala.

Given the contradictory findings about whether attentional bias is increased (as in the emotional Stroop) or decreased (as in facial expressions) towards emotional stimuli, it

is clear that further research is needed to elucidate the neural mechanisms of executive-emotional interactions in schizophrenia. It may be that the social aspects of the emotional stimuli may play an important role in determining attentional bias. For example, it is possible that pictures of negative emotional social interactions or facial expressions may be attended less as a result of specific impairments in social cognitive processing and amygdala dysfunction. In contrast, stimuli that consist of negative emotional words may lead to greater attentional bias in schizophrenia, as suggested by studies using the emotional Stroop paradigm (Epstein et al., 1999). Experiment 4 in the current study assessed the effects of social-emotional distracters on active maintenance. Due to the social nature of these stimuli, it was hypothesized that while distracting pictures would impair active maintenance in general, negative emotional pictures would be processed less in individuals with schizophrenia than in healthy controls, leading to relatively less interference.

Rule Maintenance

Consistent with a general impairment in active maintenance of task-relevant information, schizophrenia has also been associated with deficits in tasks that require active rule maintenance and task switching. These tasks are thought to similarly rely on the integrity of prefrontal, dopamine-mediated mechanisms, requiring the ability to exert control over thoughts and actions, guided by the ability to maintain and update internal representations of tasks goals or context (Braver et al., 1999). These impairments in prefrontal function in schizophrenia are thought to underlie behavioral impairments on multiple tasks that require keeping task rules in mind and the flexible updating of behavior when rules change.

For example, Posada and Franck (2002) found that individuals with schizophrenia had proportionally longer reaction times than controls when performing a task requiring rule use, compared to a task that required simple discrimination. A more recent study by the same group examined neural activity during the same rule use task using event-related potentials (ERPs) (Posada, Zalla, Vianin, Georgieff, & Franck, 2005). The results indicated that while controls showed a frontal negativity wave that was modulated by rule use, the ERPs in the group with schizophrenia were not modulated by the rule use task. The results suggest that impaired ability to acquire and actively maintain rules in schizophrenia may be associated with impaired prefrontal function.

Effects of Switching

The Wisconsin card sort task has been used in many studies of schizophrenia in order to assess the ability for rule use and task switching. Individuals with schizophrenia show similar perseverative deficits on the WCST as patients with prefrontal lesions, in that they continually sort the cards according to the same rule despite negative feedback (Everett, Lavoie, Gagnon, & Gosselin, 2001; Goldberg et al., 1988). Functional neuroimaging studies have found that during WCST performance, individuals with schizophrenia show reductions in prefrontal activation relative to controls, particularly in the dlPFC (Meyer-Lindenberg et al., 2002; Riehemann et al., 2001; Volz et al., 1997).

Other studies have further suggested that task switching itself is actually intact in schizophrenia (Kieffaber et al., 2006), and that impairments in other cognitive functions like attention, inhibition and working memory can fully explain the WCST performance deficits (Barton et al., 2002; Manoach et al., 2002). Manoach et al. (2002) dissociated task switching from inhibition in a paradigm that compared 1) WCST performance, 2)

performance on prosaccades, where participants looked at a target, and 3) anti-saccades, where participants looked in the opposite direction of a target. Prosaccade and anti-saccade trials were presented in a random sequence so that individual trials could be preceded by the same task or the other task (i.e., switched). The results indicated that individuals with schizophrenia were impaired on both WCST and anti-saccade performance, but showed normal task switching ability, suggesting that the WCST impairments in schizophrenia primarily reflect impairment in attentional functions.

However, findings of intact task switching in schizophrenia seem to be at odds with findings of prefrontal impairment. If a major function of the PFC is the flexible guidance of behavior in the face of interference, it would be expected that prefrontal impairment would affect task switching abilities in addition to attention and working memory. It has been suggested that the requirement to actively maintain context may explain the discrepancies between task switching studies (Birkett, Brindley, Norman, Harrison, & Baddeley, 2005; Meiran, Levine, & Henik, 2000). When the ability to keep contextual information in mind confers an advantage in task switching such as in the WCST, individuals with schizophrenia are disproportionately impaired relative to controls. The anti-saccade task by Manoach et al. (2002), however, provided contextual cues so that the task switching condition would have no greater demands on ability to maintain context than the control condition. Task switching impairments in schizophrenia therefore appear to most likely reflect the inability to sustain and update goal-related contextual information, rather than a deficit in the isolated switching process itself.

An additional potential explanation for the discrepancy between task switching studies could be the degree to which previously relevant rules must be inhibited on switch trials. If individuals with schizophrenia have particular difficulty in inhibiting irrelevant information, it would be expected that tasks with little interference might lead to performance comparable to controls. According to Bunge (2004), rules that are univalent or bivalent have differing requirements for inhibitory control due to differing amounts of response competition. For example, a univalent rule would require a single response for different stimuli (e.g., press the left button for houses, and press the right button for trees). Bivalent rules require responses dependent on the current rule (e.g., if preceded by triangle, press left for houses and right for trees, but if preceded by circle, press right for houses and left for trees) (Crone et al., 2006). Indeed, the study by Manoach (2002) examined the effects of univalent rule switching in schizophrenia, which may not have required significant inhibition of previously relevant rules, in addition to having reduced requirements for working memory and contextual updating.

Experiment 4 in the current study assessed the effects of interference on rule use in schizophrenia while taking into account the methodological considerations discussed above. The experiment assessed processes underlying active maintenance of task rules where the currently relevant context needed to be utilized in order to respond correctly. It also used a bivalent rule design, therefore requiring significant inhibitory processing during switch trials. This design allowed the assessment of interference effects on active maintenance and updating of contextual information in schizophrenia, rather than on isolated switching processes.

Effects of Emotional Interference

The effects of emotional interference on rule maintenance and switching in schizophrenia have remained relatively unexplored in the literature. Although it has been found that individuals with schizophrenia show abnormal attentional biases to negative emotional stimuli, it is unclear whether these biases interfere with rule maintenance or switching. One particular task that was developed in order to assess emotional effects on interference is the Affective Shifting Task (AST), which independently assesses selective attention for emotional valence information and task switching abilities (Murphy et al., 1999). In the AST, participants respond to emotional target words of one type (positive or negative) while inhibiting responses to words of the opposite emotional valence. Shifting is addressed by periodically varying the rule for responding to the target, that is, whether the goal is to respond to positive or negative words. Participants must therefore shift attention to a new, relevant emotional target, while ignoring the irrelevant emotional words.

Waters et al. (2006) applied this paradigm to a study of executive and emotional processing in individuals with schizophrenia. Contrary to previous findings, the results did not indicate that the group with schizophrenia overall had a greater attentional bias to negative than positive words. However, when the group with schizophrenia was divided into subgroups with high and low depression scores, those with high levels of depression did show a significant attentional bias to the negative words. The findings also indicated that the group with schizophrenia, as a whole, had impaired interference control as evidenced by overall slowing of reaction times on the task, but was not disproportionately impaired on switch trials compared to non-switch trials. These findings of intact switching may be influenced by the task's relatively low requirements for working

memory and context updating as well as the univalent rule design, as discussed above. The results also highlight the importance of assessing specific symptoms in studies of schizophrenia in terms of their contribution to measurements on executive control tasks.

Remaining Questions

In summary, the current literature indicates that several questions remain to be answered regarding the effects of voluntary attention allocation and involuntary diversion of attention to task-irrelevant stimuli during concurrent active maintenance processes. While the mechanisms of the PFC in active maintenance have been characterized in the normal brain, it is unknown how the mechanisms respond, particularly within specific subregions, to these variations in distracter demand. The majority of studies examining distraction effects have typically examined effects of task-irrelevant sensory distracters that cause interference by overlapping with the working memory task's domain (e.g., face distracters during a face working memory task). It is unknown whether distracters that interfere by diverting attentional resources recruit similar prefrontal regions that are involved in suppressing sensory interference. Manipulating distracter difficulty through attention requirements should help to elucidate which prefrontal regions primarily support active maintenance compared to those more involved in coping with attentional resource demands from competing stimuli.

Finally, it is unknown precisely how prefrontal dysfunction affects the processes of active maintenance and interference resolution in schizophrenia. While behavioral studies of schizophrenia have indicated impairments in both working memory and resisting distraction, it is likely that these processes interact, so that the working memory difficulties in schizophrenia can be partly explained by the simultaneous diversion of

attention toward irrelevant thoughts or stimuli. However, few studies have assessed the effects of simultaneous active maintenance and attention allocation to competing distracters in schizophrenia. It might be expected that greater attentional demand from distracters would lead to proportionately greater active maintenance impairments in schizophrenia. However, it is also possible that if attentional resource allocation processes are intact in schizophrenia despite reductions in the amount of resources (Granholm et al., 1996), individuals with schizophrenia may show similar trade offs in performance to controls, with similar effects of distracter load on the working memory task despite an overall decrease in performance.

The following four experiments aimed at addressing these questions by elucidating the neural regions recruited in the normal brain and by behaviorally testing the integrity of these processes in individuals with schizophrenia. In order to investigate the prefrontal mechanisms underlying active maintenance and processing of distracter demands, two functional neuroimaging experiments were conducted with healthy control participants that examined the effects of both actively attended and attention-capturing emotional distraction on active maintenance processes. To assess the impairments in individuals with schizophrenia, two additional behavioral experiments were conducted that compared performance between patients and controls on paradigms similar to the neuroimaging experiments. The set of studies specifically aimed to characterize the functional neuroanatomy underlying active maintenance and resolution of attention-demanding distracters in the normal brain, and to behaviorally assess the specific effects of distracter demand on concurrent active maintenance processes in individuals with schizophrenia. It was expected that specific prefrontal subregions would be recruited

under conditions of increased distracter demand, and that these mechanisms would be disproportionately impaired in schizophrenia, leading to greater impairments in active maintenance.

The specific aim of Experiment 1 was to assess the effects of “executive” distraction on normal prefrontal working memory processes using functional magnetic resonance imaging (fMRI). In this experiment, degree of distraction was manipulated according to the amount of attention that needed to be actively allocated to each distracter stimulus that appeared during the maintenance phase of a delayed-response spatial working memory task. Given that attentional mechanisms play an important role in prefrontal active maintenance processes, the diversion of more resources to a secondary task was expected to impair active maintenance due to reduced available resources for working memory (Posner & Rossman, 1965). Furthermore, it was expected that selection mechanisms would be recruited in order to deal with the increased competition. Given the postulated role of the ventrolateral PFC in inhibition and selection among competing responses, it was expected that this region would be recruited to a greater degree under conditions of greater “executive” distraction. The dorsolateral PFC, in contrast, was expected to be primarily recruited during the active maintenance requirements of the primary working memory task.

The specific aim of Experiment 2 was to assess the effects of attention-capturing distraction on active maintenance of rule information. While Experiment 1 manipulated voluntary attention allocation to distracters, Experiment 2 manipulated degree of distraction through the involuntary diversion of attention by using distracters with emotional content. The use of emotionally salient distracters was expected to similarly

divert attentional resources away from the primary active maintenance task (Dolcos & McCarthy, 2006). The primary task required the active maintenance of rule information across a delay period in order to guide a subsequent behavioral response. It was expected that through the interactions of dorsal and ventral prefrontal regions, emotional distraction would impair the ability to actively maintain the currently relevant rule, and would lead to further impairment when behavior needed to be flexibly switched after the rules changed. Furthermore, it was hypothesized that activation of more ventral prefrontal regions in response to emotional distraction would be associated with decreased dorsolateral PFC activation, with concomitant impairment on active maintenance abilities.

The primary aim of Experiment 3 was to assess the effects of executive distraction on active maintenance processes in schizophrenia. Using the same delayed-response primary working memory task and executive distracter paradigm as Experiment 1, Experiment 3 assessed whether greater attentional allocation to distracters impaired active maintenance ability in schizophrenia more than controls. If resource allocation was intact in schizophrenia (as suggested by Granholm et al., 1996), it was expected that performance on the active maintenance task would be reduced as a result of distracter difficulty, but to the same degree as in control participants (despite an overall decrease in performance). If individuals with schizophrenia had impairments in resource allocation during working memory, it was expected that active maintenance in the group with schizophrenia would be disproportionately impaired by the distracter condition. The hypothesis for the current study favored the latter possibility, as previous findings have suggested that individuals with schizophrenia are more vulnerable to attention-

demanding distracters during simultaneous working memory performance (Fleming, Goldberg, Gold, & Weinberger, 1995).

The aim of Experiment 4 was to assess the effects of emotional distraction on rule maintenance in schizophrenia. Similar to Experiment 2, the use of emotional distracters in Experiment 4 manipulated distracter degree by providing a salient, attention-capturing stimulus that diverted resources from the active maintenance task. Because individuals with schizophrenia have been proposed to process social-emotional stimuli differently (Schneider et al., 2006), it was expected that decreased attentional bias to negative social-emotional distracters would lead to similar impairments in active maintenance for both emotional and neutral distracter conditions. Furthermore, it was expected that the group with schizophrenia would be impaired overall on the primary rule use task, which required the active maintenance of currently relevant context information to guide behavior. Finally, it was expected that performance in the group with schizophrenia would be disproportionately impaired following rule switches, which required the flexible updating of task-relevant information.

CHAPTER II

EXPERIMENT 1

Experiment 1 used fMRI to assess the effects of “executive” distraction on active maintenance processes using a spatial working memory task in healthy controls. The degree of distracter demand was manipulated according to the amount of attention that needed to be actively allocated to competing stimuli that appeared during maintenance.

Method

Participants

Fifteen healthy volunteers were recruited for the functional neuroimaging task. Participants were recruited through the database at the Duke-UNC Brain Imaging and Analysis Center and from advertisements on the campus of the University of North Carolina at Chapel Hill. Eligible participants included both males and females between the ages of 18 and 35. Exclusion criteria included presence of a neurological, psychiatric, or substance abuse disorder, presence of metal in the body, and pregnancy. The sample of participants had a mean age of 23.33 years (range 18-30 years).

Imaging Task

Experiment 1 examined the effects of active attention allocation to distracters during a spatial working memory task on brain activation patterns using event-related fMRI. The study used a delayed-response working memory design where information was encoded (S1 phase), maintained over a delay period, and retrieved (S2 phase).

During the S1 phase, participants encoded the spatial locations of four red squares that each appeared randomly (for 1 second) in one of 12 possible locations. A delay period of 17 seconds ensued, during which 9 distracter shapes were presented in randomly chosen locations. During the S2 phase, a green probe square appeared (for 4 seconds), and participants were asked to respond by button press as to whether its location matched one of the 4 previously presented red squares (Figure 2). Participants pressed a “target” button when the location matched, and pressed a “non-target” button when it did not match. Intertrial intervals of 17 seconds were presented displaying a central crosshair. The advantage of this design was that activity related to each temporal phase of the working memory task could be isolated because the hemodynamic response would return to baseline levels if no sustained activity occurred (Hart, Davenport, Hooper, & Belger, 2006; Jha et al., 2004). Sustained activity related to active maintenance and distracter resolution was therefore able to be assessed without contamination from encoding effects.

Distracter difficulty was manipulated according to the amount of attention that needed to be allocated to the 9 shapes presented during the delay period. The low distraction condition assessed the effects of perceptual interference on active maintenance. Participants were presented with a series of circles and triangles in different locations, and were asked to simply press a button when any distracter shape was presented. Participants were therefore pressing a button to each distracting stimulus, which controlled for sensory interference and motor requirements across the delay period. During the high distraction condition, circles and triangles were similarly presented in varying locations throughout the delay phase, but participants were required to perform a modified 1-back task on the distracters, that is, by pressing one button when a triangle

was preceded by another triangle and pressing another button for all other distracters. The high distraction condition required the same sensory and motor requirements as the low distraction condition, but differed only in the amount of attention that needed to be allocated to the shapes in order to discriminate the repeated triangles.

The task was designed so that the low and high distraction conditions were grouped together in a series of runs, to prevent confusion on the task instructions. In half of the participants, the low distraction condition was presented in the first 3 runs, followed by the high distraction conditions in the last 3 runs. The other half of the group was presented with the conditions in the opposite order. Additionally, all locations in the low and high distraction conditions were equated by presenting mirror images of the same spatial patterns between conditions. This ensured that the primary working memory task did not differ in difficulty between conditions, in order to isolate the effects of distracter demand. There were 24 trials presented per condition (where one trial includes S1, the delay period, and S2), with 8 trials presented per run and a total of 6 functional runs.

Image Acquisition

During performance of the task, participants were scanned on a General Electric 3.0 Tesla MRI scanner using a spiral acquisition sequence sensitive to blood oxygenation level dependent (BOLD) contrast (TR: 1500 msec; TE: 27 msec; FOV: 24 cm; image matrix: 64 x 64; Flip Angle: 60; voxel size: 3.75 x 3.75 x 5 mm; 27 axial slices) that allowed for whole brain coverage. Functional runs consisted of 244 time points, and head movement was minimized by using a vacuum cushion. Preceding the functional image acquisition, structural MRIs were acquired to obtain 3D high resolution anatomical

T1 images using a spoiled gradient-recalled acquisition (SPGR) pulse sequence (TR: 22 msec; TE: 3 msec; FOV: 24 cm; image matrix: 256 x 256; Flip Angle: 20; voxel size: 1 x 1 x 2.5 mm; 54 axial slices).

Analyses

Imaging Data

Preprocessing

Image preprocessing was performed with automated scripts using SPM software (Wellcome Department of Cognitive Neurology, UK). Standard quality assurance assessments provided information on temporal signal-to-noise measurements, and epochs with detected artifacts were eliminated from further analysis. Functional images were adjusted for interleaved slice acquisition and corrected for head motion, and were co-registered with the anatomical images. The realigned scans were then normalized to the Montreal Neurologic Institute Template.

Voxel-Based Analyses

Epochs synchronized to the onsets of each trial were excised containing 4 images preceding and 29 images following the onset of the encoding period, to cover the encoding, delay, and probe periods of each trial. Epochs for the low distraction and high distraction trials were separated and averaged. Using custom Matlab-based scripts, the average BOLD-intensity signal values were converted to percent signal change relative to the prestimulus baseline. Voxel-based statistical analyses were performed with a hemodynamic response template, in order to identify voxels whose time courses significantly correlate with the template as “active” using *t*-statistics. This process provided *t*-maps of voxels that significantly activated to each condition for each subject.

Additionally, second level group-average activation maps were generated along with random effects analyses to create between-condition contrast maps. This allowed for the examination of which regions significantly activated during low and high distraction, and which regions activated differentially according to the degree of distraction present during the working memory task.

Region of Interest (ROI) Analyses

Finally, the percent signal change during each condition was characterized within specific, hypothesis-based brain regions of interest. The BOLD response was specifically examined within functionally activated clusters in the dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC), anterior cingulate gyrus (ACG), and intraparietal sulcus (IPS), regions which have been found to be specifically recruited during executive function and spatial working memory processing (Belger et al., 1998). After the ROIs were selected according to group-average activation clusters, intensity changes that were time-locked to stimulus events were interrogated within each ROI in each individual subject. The average hemodynamic responses were measured in each region, so that the amplitudes of percent signal change at S1, S2, and the delay period could be compared across conditions for each ROI and subject. A series of ANOVAs were then conducted to test differences in activation as a function of stimulus condition.

Behavioral Data

Behavioral measurements of accuracy and reaction time (RT)² for the working memory retrieval responses at S2 and for the distracter task responses (i.e., low distraction control and high distraction 1-back performance) were analyzed using

²Reaction time analyses reported in all studies are for correct trials only.

repeated measures ANOVAs. This allowed for the examination of whether distracter demand significantly impaired performance on the working memory task, and whether performance on the distracter task itself differed according to the low or high distraction demands. Further exploratory analyses correlated the behavioral measurements with the percent signal change data in order to assess whether the activation patterns were related to working memory performance.

Results

Behavioral Performance

Behavioral measures of accuracy and reaction time were examined to test the hypothesis that the diversion of more resources to a secondary task would impair active maintenance due to reduced available resources for working memory. However, contrary to the hypothesis, a repeated-measures ANOVA on accuracy during the working memory task showed no significant differences between the control and one-back conditions ($F(1,14)=2.39, p=.144$) (Figure 3A). Participants performed at 82.64% accuracy ($SD=.13$) during the control condition, and at 77.64% ($SD=.09$) during the one-back condition. Reaction times at working memory retrieval, similarly, did not differ between conditions ($F(1,14)=1.94, p=.185$). Average RTs were 1337.34 msec ($SD=417.58$) for the control condition and 1448.84 msec ($SD=443.33$) for the one-back condition. These results indicated that active maintenance processes were not significantly differentially disrupted by the distracter manipulation.

Performance on the secondary distracter task, that is, the percent correct of control and one-back targets identified during the delay period, was also assessed with repeated-measures ANOVA. In contrast to the working memory task, performance was

significantly impaired for the one-back relative to control condition ($F(1,14)=5.48$, $p=.035$) (Figure 3B). Participants correctly pressed a button for 95.86% of control distracters ($SD=.07$) and for 88.42% of one-back targets ($SD=.14$). These results suggest that while active maintenance processes were not significantly disrupted, fewer resources were available for allocation to the more difficult distraction task. Additionally, no significant interactions were found between working memory and distracter performance for the two conditions ($F(1,14)=.39$, $p=.543$). That is, working memory performance on each condition was not differentially affected by distracter performance.

Imaging Data

Effects of Executive Distraction

Activation patterns were assessed to test the hypothesis that the ventrolateral PFC would be recruited to a greater degree under conditions of “executive” distraction (i.e., the one-back condition). Furthermore, activation patterns in the dorsolateral PFC were examined to test the hypothesis that it is primarily recruited during active maintenance in working memory. The voxel-wise group average analyses indicated that both distraction tasks activated similar regions in a network of prefrontal (middle frontal gyrus), parietal, and subcortical regions (Table 1). Random effects difference maps were calculated for trials where the working memory probes were correctly identified (i.e., active maintenance was not disrupted). Consistent with the predicted role of the vlPFC in resolving distraction, difference maps on correct trials indicated that the vlPFC was recruited to a greater degree during the one-back than the control condition. However, these maps also indicated a role for the dlPFC in resolving executive distraction. The random-effects contrasts maps indicated that under conditions of greater executive

distraction, clusters of voxels in regions such as the ventrolateral PFC (inferior frontal gyrus), dorsolateral PFC (middle frontal gyrus), cingulate gyrus, and inferior parietal lobule were more active during the one-back than the control condition (Table 2). During the control condition, areas that were more active relative to the one-back task included clusters within the anterior and posterior cingulate and the parietal lobule (Table 3).

To probe the activity within regions of interest, repeated-measures ANOVAs were performed on selected time points during the delay period to assess the percent signal change during each condition. These analyses were carried out on time points within 16-18 seconds after the beginning of each correct trial, and provided a sampling of activity near the end of the working memory delay and distraction period. In the vlPFC, the results showed a pattern consistent with its proposed role in resolving interference, where delay-period activity was significantly sustained above baseline during the one-back ($F(1,14)=9.22, p=.009$), but not the control ($F(1,14)=2.09, p=.17$) conditions (Figure 4). The dlPFC, in contrast, showed a pattern consistent with a role in active maintenance, where activity was significantly sustained above baseline for both the control ($F(1,14)=4.86, p=.045$) and one-back ($F(1,14)=28.37, p=.0001$) conditions (Figure 5). Repeated-measures ANOVAs indicated a trend towards a significant effect of distracter demand ($F(1,14)=3.78, p=.072$), suggesting potential roles in both active maintenance and interference resolution for the dlPFC.

In the anterior cingulate gyrus and intraparietal sulcus, delay-period activity was not differentially modulated by distracter demand. The ACG showed activity that was significantly sustained for both the control ($F(1,14)=7.94, p=.014$) and one-back conditions ($F(1,14)=15.36, p=.002$), with no significant overall effect of distracter

demand ($F(1,14)=1.82, p=.199$). Similarly, the IPS did not show a differential effect of distracter demand ($F(1,14)=1, p=.334$), and showed significantly sustained delay-period activity for both the control ($F(1,14)=6.96, p=.019$) and one-back ($F(1,14)=13.75, p=.002$) conditions. These patterns suggest that these regions are sensitive to active maintenance requirements, but are not differentially recruited under conditions of executive distracter demand.

Laterality Effects

In order to assess whether the hemispheres differed in their response to executive distraction, interactions between hemisphere and distracter type were assessed in each ROI. Only the vlPFC showed a trend towards a significant interaction between hemisphere and distraction ($F(1,14)=3.99, p=.066$), where the left vlPFC showed greater sustained activity during one-back condition. No other significant laterality differences were found.

Brain-Behavior Correlations

To assess whether activity in the regions of interest predicted working memory performance, correlations were performed between the delay-period activation and subsequent WM performance. In addition, activity in each ROI was correlated with performance on the secondary distracter task performance. Activity in the vlPFC was significantly correlated with accuracy at retrieval on the one-back ($r=-.56, p=.029$), but not with the control condition. That is, during difficult distraction, better performers had less sustained delay-period activity. Activity in the vlPFC was also found to be correlated with performance on the secondary one-back distracter task ($r=-.64, p=.014$),

but not with the control task. Better identification of one-back targets through active attention allocation was associated with less vIPFC delay activity.

The dlPFC activity showed a similar relationship to working memory performance, but there was only a trend towards a significant correlation between the two measures on the one-back task ($r=-.44$, $p=.1$) and no significant relationship on the control task ($r=.34$, $p=.215$). The direction of the relationship was similar to the vIPFC, where better WM performance was associated with less activation during one-back distraction. No significant relationship was found between dlPFC activation and distracter task performance.

The ACG did not show a significant relationship between activity and performance on the working memory task. However, there was a trend toward a significant correlation between activity and performance on the one-back distracter task ($r=-.47$, $p=.09$). Again, this trend was in a similar direction as found in the prefrontal regions, where better performance was associated with less activity.

The IPS, in contrast, showed a near-significant relationship between delay-period activity and WM performance on the control ($r=.49$, $p=.064$), but not the one-back task ($r=.05$, $p=.858$). While the prefrontal regions showed a negative relationship between activity and performance, greater IPS activity during the control task was associated with better performance. In addition, the degree of functional coupling between the dlPFC and IPS was assessed to determine whether it predicted WM performance, as found by Sakai et al. (2002). During correct trials, the dlPFC and IPS delay activity was indeed found to be significantly correlated during the control ($r=.76$, $p=.0009$), but not in the one-back condition ($r=.21$, $p=.44$). These results suggest that while functional co-

activation of these regions supports robust active maintenance of WM contents, this relationship may not apply under conditions of greater competition.

Discussion

The aim of this experiment was to identify the neural regions involved in executive distraction during a concurrent working memory task. It was hypothesized that under conditions where attentional resources were required to be actively allocated to distracters, different subregions of the prefrontal cortex would take on specific roles in carrying out the simultaneous demands of the task. The fMRI results did indeed generally support these hypotheses, and indicated different patterns of delay-period activation in dorsal and ventral prefrontal regions during the control and one-back conditions. While performance during both the control and one-back conditions generally activated similar regions in the working memory network, activation within prefrontal regions was modulated by the degree of distracter difficulty. Additionally, the relationship was assessed between activation in the primary regions of interest with measures of performance on the task, with the results suggesting that less activation in vIPFC regions predicted better performance.

For the behavioral data, it was hypothesized that greater amounts of attention required to be allocated to a secondary distracter task would significantly impair performance on the primary working memory task. However, the results suggested that performance on the secondary distracter task (identification of control shapes and one-back targets) was more susceptible to disruption, rather than the working memory task performance itself. That is, while working memory retrieval performance was similar under both distraction conditions, participants were less accurate at identifying one-back

targets than the perceptual/motor control stimuli. This suggests that perhaps participants were employing a strategy where they focused the bulk of their attentional resources on the primary task (spatial rehearsal), at the expense of secondary selective attention processes. Although the effects of competition were present on the distracter task rather than the working memory task, the results are still consistent with a pattern of greater competition during the executive distraction manipulation. While active maintenance processes were left relatively intact by the one-back task, the distracter task impairment suggests there was a greater need for selection mechanisms under the difficult distraction condition. Also, because the distraction manipulation left the processes of active maintenance intact, the neural activity (on correct trials) can be interpreted in terms of successful working memory rehearsal in the face of greater competition.

During the neuroimaging task, it was expected that greater activation would be elicited in ventrolateral PFC regions during executive distraction. The results indeed suggested that the ventrolateral prefrontal regions were recruited to a greater degree when more attention was required to be actively allocated to the distracters. These findings are consistent with the proposed role of this region in selecting among highly competing alternatives. Indeed, a multitude of studies examining the effects of interference on working memory have identified greater activity in the vlPFC, and it has been interpreted as having a greater role when certainty about an item's task-relevance is low and the need for selection is high (Jha et al., 2004). vlPFC activation during the one-back distraction manipulation in this experiment is consistent with a need to deal with competing demands of both spatial rehearsal and selective attention processes.

There has been some controversy in the literature as to whether the vLPFC also plays a role in working memory maintenance processes. The results of the current study did not indicate that maintenance activity in the vLPFC was still sustained by the end of the delay period in the control condition. Its activity was only increased during one-back distraction, suggesting a specific role in resolving interference but not in WM maintenance. In contrast, some other studies have found that vLPFC activity is modulated during manipulation of working memory load, which has been interpreted as the vLPFC having a role in WM maintenance (D'Esposito, Postle, Ballard, & Lease, 1999; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). However, a study by Bunge et al. (2001) specifically dissociated the effects of working memory load and proactive interference, and found that vLPFC activity was associated with the ability to resolve interference, but not load. It may be possible that in many studies of memory load, selection processes may still come into play that could influence vLPFC activity. As working memory is taxed more by memory load, performance also becomes more susceptible to distraction (de Fockert et al., 2001). As the processes of working memory and inhibition have been conceptualized to reflect different aspects of the same mechanism (Miller & Cohen, 2001), it is possible that the relative functional recruitment of the vLPFC may reflect the degree to which task-relevant information must be selected in the face of competition.

It was hypothesized in the current study that the dorsolateral prefrontal regions would be more involved in the active maintenance of the spatial locations in working memory, and that activity patterns would reflect sustained levels across the delay period regardless of the distracter task. While the fMRI results did indicate that activity was

sustained during the control task, the activity was further enhanced by the executive distracter manipulation. This suggests that dlPFC is able to support both processes of active maintenance and distracter resolution simultaneously. The current study's finding of dlPFC involvement in active maintenance is consistent with a large number of studies using lesion methods (Chao & Knight, 1998), electrophysiological recordings (Chafee & Goldman-Rakic, 1998), and functional neuroimaging (Curtis & D'Esposito, 2003) that support its role in delay-spanning sustained activity in working memory. While the role of the dlPFC in resolving interference has been debated, several studies have similarly found that its activity is indeed modulated by distraction (Bunge et al., 2001; Garavan, Ross, & Stein, 1999; Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000). As maintenance and interference resolution are conceptualized as emergent properties of the same attention-based system, it may be that the dlPFC activates to greater degrees depending on how much the system is engaged and to what type of information (e.g., more cognitive or more social-emotional). In the current study, the greater engagement of the system through the need for selective attention to one-back distracters may have explained the greater recruitment of the dlPFC.

It may also be that the vlPFC and dlPFC have an interacting role with one another in carrying out the processes of active maintenance and interference resolution. Jha et al. (2004) suggest that the ventrolateral prefrontal regions may provide selection input to the dorsolateral PFC, so that when the vlPFC fails to select among competing alternatives, activity in the dlPFC may similarly fail during active maintenance processes. They suggest that these failures in active maintenance may occur when interference from neural noise is not appropriately filtered out by the vlPFC. Therefore, rather than

characterizing the vIPFC and dlPFC as reflecting processes of interference resolution and maintenance per se, it may be more appropriate to characterize these regions as parts of the same system whose functions are tapped differentially the amount of competition present, the degree of task-relevance and irrelevance, and the type of information present.

The present study also found that activity in the anterior cingulate gyrus was sustained during the working memory delay, but that it was not differentially modulated according to distracter degree. The ACG has been proposed to be critical for identifying conflict and for guiding response-related processes, and is proposed to be critical for sending signals to the dlPFC for allocation of attentional control (Botvinick et al., 1999; MacDonald, Cohen, Stenger, & Carter, 2000; Milham et al., 2003). Given this proposed role, it was surprising to find that in the current study, ACG activity was not enhanced during the more conflicting one-back distraction task. It could be that by the end of the delay period when distracter-related activity was assessed, the requirement for detecting conflict had already passed. Additional analyses were performed to examine distraction effects at earlier time points in the ACG, and while a trend towards a significant distraction effect was found, these effects still did not reach significance. It is possible that as the task design blocked the one-back and control conditions together, activity in the ACG may have habituated to the greater conflict condition across runs, therefore diluting the effects of conflict in the one-back condition.

Another possibility to explain the lack of ACG modulation by the one-back distracter is that this region may be specifically involved in mediating inhibition for pre-programmed responses (Smith & Jonides, 1999). For example, the ACG has frequently been found to activate during conflict in the Stroop task, which requires the inhibition of

a prepotent, automatic response. By contrast, Jonides et al. (1998) manipulated conflict through a proactive interference design, and did not find increased ACG activation. It could be that in the current study, because no prepotent responses were involved, the ACG was equally engaged during both distracter manipulations. Finally, the anterior cingulate is found to be activated in a multitude of other tasks that do not require inhibition, suggesting that it may have a range of functions in attention, monitoring, and effortful cognitive control (Bush et al., 2000). It may be that as working memory performance levels were similar across conditions, the ACG played a similar role in these processes for both the control and one-back conditions.

In the posterior parietal cortex, the results of the current study showed that activity followed a similar pattern as in the ACG. The IPS activity was sustained above baseline levels during the delay period, but was not differentially modulated according to distracter degree. These findings are consistent with the posterior parietal cortex having an important role in spatial working memory rehearsal (Awh, Vogel, & Oh, 2006). While it might have been predicted that parietal activity would be disrupted by the distracter manipulation, because the current manipulation was not difficult enough to impede performance the IPS activity patterns could likely reflect the allocation of similar resources for rehearsal under both conditions. Alternatively, the activity in posterior perceptual regions has also been characterized as supporting distracter-resistant working memory storage processes (Postle, Druzgal, & D'Esposito, 2003). It could be that in the current study, parietal areas reflected spatial rehearsal and storage regardless of the other competing distracters that were dealt with through prefrontal mechanisms.

The brain-behavior correlations assessing the relationship between delay-period activity and performance indicated that the vIPFC showed an inverse correlation with both WM and distracter task performance on the one-back task. That is, a lower degree of vIPFC activation predicted better ability for active maintenance during one-back distraction and for the ability to actively allocate attention to the one-back task. The brain-behavior correlations in the dlPFC and ACG indicated relationships in the same direction, although these correlations were not strong enough to be significant. These relationships suggest that in the current study, perhaps more engagement of the prefrontal-cingulate circuitry reflects greater interference and a greater need for selection mechanisms to deal with competition. When enough resources are freely available to allocate to both tasks simultaneously, the system may operate at a lower activity level.

These inverse relationships conflict, however, with previous findings that more vIPFC activation is associated with better performance (Jha et al., 2004). It could be that task differences may account for these discrepancies, because previous studies examining distraction effects have typically required the distracters to be ignored rather than actively attended. Greater vIPFC activity may be beneficial for preventing completely irrelevant information from interfering, but when distracters must be actively attended its activity may index greater interference, given the competition on available processing resources. Finally, in regions where brain-behavior correlations did not reach significance, it could be because the distraction manipulation was not difficult enough to significantly impair active maintenance processes. If activity in the dlPFC or IPS was dependent upon working memory performance, these effects may not have been evident due to the relatively similar WM performance levels across both conditions.

Finally, the delay-period activity in the IPS and the dlPFC were correlated with one another to determine whether a functional coupling of activation was observed for correct trials, similar to Sakai et al. (2002) who used a similar executive-distraction type of manipulation. The results indicated that the correlation was significant for the control condition, but not for the one-back condition. The prefrontal-parietal coupling of activity in the current study likely reflects the interaction between prefrontal biasing signals that enhance the representation of spatial locations in the parietal cortex during working memory rehearsal. Sakai et al. (2002) argue that increased correlation between these areas represents a stronger representation of the information, or the robustness of the working memory representation in the face of distraction. While the study by Sakai et al. (2002) employed distracters that were actively attended during the delay, it differs notably from the current study in that distracter task consisted of a secondary spatial WM task. Greater prefrontal-parietal functional coupling that predicted resistance to interference in the Sakai et al. (2002) experiment may have reflected the spatial nature of the task, as the distracters would have recruited the same parietal regions as the primary WM task. It could be that during the one-back task in the current experiment, this functional coupling may have been more disrupted when attention was diverted to an aspect of the task requiring different processing (i.e., selective attention to objects, which are processed in inferior temporal areas).

A limitation of the current study is that it could be argued that the results are simply due to an increase in task difficulty that might explain the greater recruitment of prefrontal regions. One way that this criticism could be addressed in future studies would be to provide a manipulation of memory load that disrupts performance to the same

degree as the interference manipulation. A similar load manipulation was done with a proactive interference paradigm by Bunge et al. (2001), who found a high degree of overlap in the regions involved in load and interference, with the anterior cingulate (but not prefrontal regions) showing a specific effect of memory load. These results would suggest that the prefrontal patterns in the current study likely reflect the mechanisms of cognitive control required to deal with increased competition, rather than simply task difficulty.

In conclusion, the results from this experiment suggest that although the prefrontal cortex may be characterized by a unitary mechanism that allows for the ability to simultaneously keep information in and out of mind, there are specific prefrontal subregions whose functions may be tapped to a greater degree depending on task requirements. The current study found that while activity in the dorsolateral PFC reflected both processes of active maintenance and active allocation of attention to distracters, the ventrolateral PFC activity was indicative of a more specialized role in dealing with increased response competition. It may be that when distracters have some task-relevant aspect where attention must be divided, more ventral regions of the prefrontal cortex carry out processes of selection among competing alternatives, while the interconnected dorsal regions carry out the attentional processes required more for active maintenance and selective attention. Future studies employing functional connectivity analyses may be able to better characterize how the different prefrontal subregions interact with one another when carrying out these multiple simultaneous processes.

CHAPTER III

EXPERIMENT 2

Experiment 2 assessed the effects of emotional distraction on active maintenance of rule information in healthy controls using fMRI. Degree of distracter demand in this experiment was manipulated according to whether the interfering stimulus was emotional or neutral. This experiment required the active maintenance of rules over a delay period, and furthermore assessed the effects of rule switches and their interactions with emotional and neutral distraction.

Method

Participants

Fifteen healthy volunteers were recruited for the functional neuroimaging task. The methods of recruitment and inclusion/exclusion criteria were the same as those used in Experiment 1. The average age of the sample of participants was 24 years (range 18-30 years).

Imaging Task

During functional MRI scanning, participants performed a task requiring the active maintenance of rules over a delay period. Prior to scanning, participants underwent a practice session during which they learned the stimulus-response associations for each rule. Participants were presented with a blue or yellow square,

which provided a contextual cue as to which rule should be followed when responding to a subsequent probe stimulus. During maintenance of the rule, participants were presented with distracters that consisted of complex scenes taken from the International Affective Picture System (IAPS) database, which is a standardized database of photos that have been normalized for ratings of arousal and valence (CSEA, 1999). Cues were presented for 2 seconds, followed by a delay period of 10 seconds, followed by a circle or triangle probe stimulus presented for 2 seconds and an intertrial interval of 15 seconds. During the delay, two distracter pictures from the same condition were each subsequently presented for 3 seconds, in a design similar to Dolcos and McCarthy (2006) (Figure 6). While the shorter 10 second delay period in this design did not allow for the complete temporal dissociation of cue and rule maintenance activation, it still importantly distinguished interference effects on the peak activation during the delay, while having the advantage of including more trials per condition.

The rules to be maintained over the delay were bivariate, that is, operating on a shared set of probe stimuli so that the correct responses were conditional upon the currently relevant rule. In the current study, blue cues indicated that the left and right buttons should be pressed for circles and triangles, respectively. Following yellow cues, the button mappings were the opposite, with the left and right buttons for triangles and circles, respectively. The cue colors changed unpredictably throughout the experiment, so that approximately half of the trials maintained the same rule as the previous trial, and the other half required a rule switch (in a similar design as Cools, Clark, & Robbins, 2004). This design allowed for the testing of activation related to active maintenance of

rule information, and activation related to switching attentional set away from previously relevant rules.

The distraction condition was manipulated according to the valence and arousal ratings of the pictures, which were irrelevant to the primary rule task. The neutral (low distraction) condition included low-arousing neutral pictures (e.g., scenes of mundane activities), with normative valence ratings between 4.5 and 5.5 and arousal ratings below 5 on a scale of 1-9. The emotional (high distraction) condition included high-arousing negative emotional pictures (e.g., scenes of aggressive behavior) with valence ratings below 4 and arousal ratings above 5. The pictures in the neutral and emotional conditions were equated for human presence. Trials containing the neutral and emotional conditions were randomly distributed throughout the experiment with equal probability of either condition occurring. Therefore, the experiment assessed activity related to 4 primary conditions: 1) Rule maintained with emotional interference (Emo-Maintain); 2) Rule switched with emotional interference (Emo-Switch); 3) Rule maintained with neutral interference (Neutral-Maintain); 3) Rule switched with neutral interference (Neutral-Switch).

Image Acquisition

Participants underwent fMRI scanning on a General Electric 3.0 Tesla MRI scanner using a functional echo-planar imaging sequence allowing for full-brain coverage (TR: 2000 msec; TE: 27 msec; FOV: 24 cm; image matrix: 64 x 64; Flip Angle: 60; voxel size: 3.75 x 3.75 x 3.8 mm; 34 axial slices). Functional runs consisted of 204 time points. All other imaging parameters were the same as in Experiment 1.

Analyses

Imaging Data

Voxel-Based and ROI Analyses

All image preprocessing steps and basic voxel-based and ROI analyses were identical to those in Experiment 1. Epochs synchronized to the onsets of each trial were excised containing 3 images preceding and 14 images following the onset of the cues, to cover the rule retrieval, delay, and probe periods of each trial. Epochs for the neutral (low distraction) and emotional (high distraction) trials were separated and averaged, along with rule switch and maintain trials. This allowed for the examination of which regions activated differentially according to emotional or neutral distraction during rule maintenance and switching. Regions of interest included the ventrolateral PFC (vIPFC), dorsolateral PFC (dlPFC), anterior cingulate gyrus (ACG), amygdala-hippocampal complex (AHC)³, and intraparietal sulcus (IPS).

Behavioral Data

Behavioral measurements of accuracy and RT for the probe responses were analyzed using repeated-measures ANOVAs to assess the effects of distracter type and rule switching. Similar to Experiment 1, additional exploratory analyses were conducted to correlate the behavioral measurements with the percent signal change data in order to assess whether the activation patterns were related to performance on the rule task.

Results

Behavioral Performance

³The activation in the amygdala-hippocampal complex was treated as a single functional ROI because too few voxels were activated within the circumscribed border of the amygdala itself.

To examine the hypothesis that emotional distraction would impair the ability to maintain the currently relevant rule, a repeated-measures ANOVA was conducted on the percent correct and RT at the probe stimulus. Behavioral data from one participant was excluded from these analyses due to below-chance performance on the task. Contrary to the study's hypotheses, behavioral performance on the rule task did not significantly differ according to the degree of emotional interference ($F(1,13)=1.1, p=.314$) (Figure 7). Participants performed at 95.61% accuracy ($SD=.04$) for emotional trials and 94.22% ($SD=.06$) for neutral trials. Similarly, reaction time did not differ according to emotional interference ($F(1,13)=.24, p=.634$). Average RTs were 1008.21 msec ($SD=317.87$) for the emotional condition and 986.9 msec ($SD=303.39$) for the neutral condition.

The effects of rule switching were also assessed with repeated-measures ANOVA. The results again contradicted the hypothesis that switching the currently relevant rule from the previous trial would impair performance. Rule switching did not have a significant impact on percent correct ($F(1,13)=.45, p=.513$) or reaction time ($F(1,13)=.28, p=.603$). Additionally, no significant interactions between emotion and rule switching were found on percent correct ($F(1,13)=.8, p=.388$) or reaction time ($F(1,13)=.01, p=.943$).

Imaging Data

Effects of Emotional Distraction

The imaging analyses indicated that the rule maintenance task, under conditions of both emotional and neutral distraction, activated a network of areas including the dlPFC and vlPFC. Differential activations to emotional and neutral distraction were assessed to test the hypothesis that emotional distraction would elicit greater VAPS

activation and decreased DECS activation. Consistent with this hypothesis, random effects contrast maps indicated that emotional distraction elicited relatively greater activation in the vIPFC (inferior frontal gyrus) and other limbic system structures, including the parahippocampal area near the amygdala. Emotional distracters also elicited more activation in ventral perceptual regions, including the fusiform gyrus and inferior occipital cortex (Table 4). Neutral distraction, in contrast, elicited more activation in the dlPFC (middle frontal gyrus), cingulate gyrus, and parietal cortex (Table 5). Within these regions in the DECS, activation patterns showed marked decreases in activation during emotional processing.

Repeated-measures ANOVAs were conducted within each region of interest to determine whether activity significantly differed according to emotional interference. These analyses were carried out at sampled time points within 10-16 seconds after the beginning of each trial, where the greatest differences were found between emotional and neutral conditions. Consistent with the contrast maps, significant effects of emotionality were found in several regions of interest within the VAPS (left vIPFC, $F(1,14)=17.27$, $p=.001$; amygdala-hippocampal complex (AHC), $F(1,14)=4.79$, $p=.046$) and DECS (dlPFC, $F(1,14)=15.94$, $p=.001$; ACG, $F(1,14)=13.46$, $p=.003$; IPS, $F(1,14)=4.83$, $p=.045$) where emotional distraction elicited relatively greater and less activation, respectively.

Within the left vIPFC and the bilateral AHC, the time courses of activation showed a pattern where activity was responsive to the rule task, but the activity was then further enhanced as a result of emotional distraction (Figures 8 and 9). Activity in the DECS regions, however, showed a different pattern where activity was disrupted by the

emotional distraction. The delay-period activity in the dlPFC was reduced to below-baseline levels during emotional interference (Figure 10). Activity in the ACG (Figure 11) and IPS similarly showed patterns where the delay activity was markedly reduced during emotional distraction relative to neutral distraction. These time courses provided further support for emotional distraction leading to differential effects in dorsal and ventral regions, with more dorsal executive regions being taken “off-line” by the affective interference.

In addition, further analyses were conducted to assess whether activation patterns in the dorsal and ventral systems together interacted with one another. Peak activity levels for each condition in the dlPFC, PPC and ACG were averaged together to create a dorsal “system” activation (as in Dolcos & McCarthy, 2006). Similarly, peak activity for the vlPFC and AHC were averaged together to represent the ventral system. A 2 (dorsal versus ventral system) by 2 (emotional versus neutral distraction) ANOVA indicated a significant neural system x distracter interaction ($F(1,14)=26.41, p<.001$), where activation was greater for emotional distraction in ventral regions and for neutral distraction in dorsal regions (Figure 12).

Laterality Effects

In order to assess whether emotional distraction differentially affected lateralized activation, interactions between hemisphere and distracter type were assessed in each ROI. Contrary to previous findings (e.g., Dolcos & McCarthy, 2006), the results did not indicate significantly greater right hemisphere lateralization according to emotionality. While the vlPFC showed a strong effect of laterality on emotional distraction ($F(1,14)=21.9, p=.0004$), the pattern of activation indicated that the left hemisphere

responded more to emotional distraction. No significant hemispheric interactions were found in the dlPFC during emotional distraction ($F(1,14)=.4, p=.537$), or in any other regions of interest.

Brain-Behavior Correlations

In order to assess whether activation patterns in dorsal and ventral regions predicted behavioral performance on the task, the peak percent signal change and number of active voxels in prefrontal regions was correlated with accuracy and RT. Consistent with the postulated role of the vlPFC in interference processing, the results indicated that the peak vlPFC activation was significantly correlated with accuracy on the rule task. This relationship was significant for the emotional condition ($r = .68, p = .007$), but did not reach significance for the neutral condition ($r = .47, p = .09$). In the dlPFC, no significant associations were found between peak activation and accuracy. No additional significant correlations between activity and performance were found in any other ROIs.

Effects of Switching

Random effects difference maps were calculated to determine the areas that were recruited more on rule-switch trials than non-switch trials. Only two primary areas were activated in this condition, the anterior cingulate and the vlPFC (inferior frontal gyrus) (Table 6). No significant differences in lateralization during switching were observed in any ROIs.

Interactions between Emotion and Switching

Finally, the interactions between emotional distraction and rule switching were assessed. Random effects difference maps indicated that the areas activated more during emotional switching than neutral switching included the cingulate gyrus, medial frontal

gyrus, and fusiform gyrus (Table 7). Within functional ROIs, the AHC showed a significant interaction between emotion and switching ($F(1,14) = 10.21, p = .007$), where activation during emotional distraction was increased during switch trials than non-switch trials. Post-hoc analyses indicated a near-significant effect of switching on emotional trials ($F(1,14) = 3.91, p = .068$), but no significant effect on neutral trials ($F(1,14) = 2.49, p = .137$). The vlPFC showed a similar interaction between emotion and rule switching ($F(1,14) = 6.54, p = .03$). Post-hoc analyses again indicated that during emotional trials, rule switching led to a near-significant increase in activation ($F(1,14) = 3.38, p = .087$), while during neutral trials, no significant effect of switching was observed ($F(1,14) = 1.99, p = .18$).

Discussion

The primary goal of this experiment was to assess the effects of emotional versus neutral interference during concurrent performance of an abstract rule active maintenance task. It was expected that differential activity would be present in regions corresponding to two different systems, the dorsal executive control system (DECS) and the ventral affective processing system (VAPS), where greater emotional interference would enhance VAPS activity and disrupt DECS activity. The results overall supported this hypothesis, as delay-period activity was modulated in opposite directions within each system. This suggests that interactions between these systems may underlie emotional distraction not only in working memory tasks, but also during maintenance of abstract rules. Additionally, the results indicated that activity in the vlPFC, a region categorized as part of the VAPS, was significantly associated with performance on the rule

maintenance task, suggesting that it may play a role in helping to resolve competition during presentation of emotionally salient information.

On the behavioral measures, it was hypothesized that the emotional interference condition would lead to a significant impairment in performance of the rule maintenance task. However, the results did not support this hypothesis, and indicated that the emotional distraction did not divert enough attentional resources away to lead to a significant performance disruption. These results suggest that there were relatively similar amounts of resources available for performing the rule maintenance task under both distraction conditions. Because the emotional distracters did not significantly impair performance on the task, it could be argued that the amount of competition is not necessarily greater under the emotional manipulation, and that selection processes are not necessarily being engaged. However, the emotional manipulation did differentially engage regions in the VAPS circuitry, suggesting that these distracters were processed as more emotionally salient despite not diverting enough attention to impair performance. It may be that the specific task design, where emotional information was presented in the middle of the delay period, led to relatively less interference as compared to a potential scenario where distracters would interfere during the earlier process of rule retrieval⁴. Future studies will be needed to delineate the temporal characteristics of when susceptibility to distraction is greatest, whether it occurs during the processes of rule retrieval or during the active maintenance of rules.

Additionally, it was expected that the secondary manipulation of rule switching would lead to a significant impairment in performance due to requirements for updating

⁴This manipulation was tested in an earlier pilot study, which suggested that presenting distracters concurrently with the rule cue did indeed impair performance more.

the currently relevant rule. Again, this manipulation was not strong enough to significantly impair performance on the task. These findings may be due to the long delay periods in the task and the long intertrial intervals, which may have allowed enough time for participants to actively update the rules' representations relatively easily. While the long delays in the current study allowed for the assessment of neural activity related to active maintenance processes in a temporally segregated way, a design where rules would need to be switched more quickly may be more advantageous for specifically assessing switching mechanisms. Additionally, the behavioral performance did not indicate an interaction between emotional interference and rule switching. Again, it could be that the switching manipulation was not difficult enough to elicit the inhibitory mechanisms that would be needed if the rule switches took place more quickly and frequently. Neither switching nor emotional distraction created enough interference to impact performance or lead to any interactions. Given that performance was not impaired by emotional distraction (and as only correct trials were included in the analyses), the imaging data can be interpreted in terms of successful abstract rule maintenance and switching during presentation of task-irrelevant emotional information, while the degree of attentional diversion and inhibitory mechanisms required cannot be necessarily determined by the current design.

For the imaging data, it was hypothesized that interactions between regions in the DECS and VAPS would reflect the processes of emotional distraction, where more VAPS activity would be associated with reductions in DECS activity. The results were indeed supportive of this hypothesis, as evidenced by patterns of activation in the more executive dorsolateral PFC, anterior cingulate, and intraparietal sulcus, and in the more

emotional amygdala-hippocampal complex and ventrolateral PFC. These results were consistent with several neuroimaging studies showing that emotional distraction disrupts activity in dorsal regions (Wang et al., 2005; Yamasaki et al., 2002), and are consistent with animal studies that show prefrontal lesion-like effects of emotional stress on cognition (Arnsten & Goldman-Rakic, 1998). It is notable that in the current study, these DECS-VAPS interactions were present even when distraction was below the threshold where it would influence behavior. The findings indicate that these system interactions do not necessarily depend on the presence of more overt emotional distraction, but may also underlie more subtle processes of emotional distraction when attention is engaged elsewhere.

The activity in the vIPFC was significantly enhanced during emotional distraction, which was expected as part of its role in the VAPS. However, activity in the vIPFC is also consistent with other studies of rule complexity, where it activates more for bivalent rules (where response is contingent upon a currently relevant rule) compared to univalent rules (simple stimulus-response associations) (Bunge, 2004; Crone et al., 2006). Indeed, the time course of activation suggested that the left vIPFC was engaged during the rule retrieval and maintenance phases, but was further enhanced during emotional interference. This suggests the possibility that it may play specific roles in both abstract rule processing and interference resolution, or that its role in resolving interference is simply tapped more under the emotional distraction condition. It is difficult to dissociate whether its modulation by rule complexity in previous studies is due to a specific role in rules per se, or whether it is because more complex rules by nature require greater use of selection processes.

Additionally, the analyses of laterality indicated that only the left vIPFC showed a significant enhancement of activity to the emotional distraction. This finding contrasts with those of Dolcos and McCarthy (2006), who instead found a greater right vIPFC response to emotion. It may be in this case that the performance differences between the two studies could have explained this discrepancy, as the right vIPFC was found to be dependent upon the participants' ratings of how distracting the emotional pictures were in Dolcos and McCarthy's (2006) experiment. Since the current study's distracter pictures were restricted to those with social-emotional content (to be consistent with the hypotheses of Experiment 4), it is possible that these stimuli were less disturbing to participants and did not activate the same corresponding lateralized circuitry. Activation of the left vIPFC is consistent with the findings of Crone et al., who found that it was particularly involved in bivalent rule processing. Perhaps in the current experiment the vIPFC activation was driven more by response contingencies involved in abstract rule maintenance, with the additional emotional enhancement reflecting greater amounts of competition.

The patterns of activity in the dlPFC, where delay-period activation was reduced to below-baseline levels, are also consistent with other findings suggesting emotional distraction takes its activity off-line (Arnsten & Goldman-Rakic, 1998; Wang et al., 2006). This deactivation is thought to reflect patterns of functional connectivity where the dorsal regions receive inhibitory input from the VAPS (Mayberg et al., 1999). It should be noted again that in the current study, this activation pattern was evident even when no performance deficit was present. This again emphasizes that these activation patterns are not necessarily dependent on attention being significantly diverted by

emotion, but may reflect the mechanism's function below the threshold where performance would be affected.

The anterior cingulate region in the current study showed a pattern where activity was sustained across the delay during the rule maintenance task, but was disrupted by emotional distraction. Because it has been implicated in the requirements for detecting conflict and monitoring the need for cognitive control, it has been identified as an “executive” region, which is supported by the data from the current study support showing that its response to emotional distraction followed a similar response as the dlPFC. However, there are other subregions of the ACG that are thought to also respond to emotional information, in the rostral ventral-affective division (Bush et al., 2000). While these subregions are thought to important for monitoring more affective information, the more dorsal regions support more cognitive and executive processing. Bush et al. (1999), for example, have found differential effects of emotion in dorsal and ventral ACG subregions, where performing a task like the emotional Stroop activates the emotional subdivision and deactivates the cognitive subdivision. As the current study only examined activity within the dorsal ACG and not the ventral subregions, the patterns likely reflect the disruptive effects of emotion as similarly demonstrated by Bush et al. (1999). Future studies parceling out the contribution of individual cingulate subregions may further elucidate the mechanisms of how the VAPS and DECS interact with one another under emotional distraction conditions.

During the rule switching manipulation, activation was also modulated in the ACG and the vlPFC. The increased activity of the ACG in switching is consistent with a greater need for allocation of control when the currently relevant rule needed to be

updated. A recent study by Johnston, Levin, Koval and Everling (2007) found results similar to the current study where task-selective activity in ACG was temporarily enhanced immediately following a rule switch, consistent with its role in identifying conflict between competing stimulus-response associations. Similarly, the vLPFC has also been identified in many studies as an important region in both task switching and dealing with interference (Konishi et al., 2005), suggesting that its posited role in selection processes during increased competition may also be tapped by the need to inhibit previously relevant rules. Again, as these changes occurred at a level below a threshold that affected performance, they suggest these regions carry out these mechanisms regardless of how difficult the switching manipulation is.

The imaging data also identified regions that responded differently for emotional versus neutral switching, including the medial PFC and cingulate gyrus. It could be that these regions represent areas that are similarly involved in inhibitory mechanisms during the updating of new task rules and coping with emotional distraction. Medial prefrontal regions have been specifically identified in the ability to reconfigure task set, while lateral PFC may have a more important role in rule retrieval and maintenance (Crone et al., 2006). According to Crone et al. (2006), activation of lateral PFC in switching may represent retrieval of a more recent rule rather than the switching process per se, while the medial regions are more important for the inhibition of previously relevant rules. As the medial PFC is also considered to be a part of the VAPS, it could be an important region for coordinating inhibitory mechanisms involved during both emotional and switching processes. Activity in the cingulate gyrus that showed an interaction between emotion and switching was found in a more posterior region, which may be characterized

by processing both emotional and affective information. It may be that the cingulate carries out similar roles in integrating affective and executive processes as medial prefrontal regions, which is consistent with findings that the two areas are neuroanatomically connected (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006).

Finally, the brain-behavior correlations indicated that activity in the vIPFC was associated with the ability to resist distraction, where more activity predicted better performance. As discussed above, this may reflect its role in resolving competition from the emotional distracters. This relationship is consistent with the findings of Dolcos and McCarthy (2006), who found that more vIPFC activation was associated with lower ratings of distractibility. The brain-behavior correlations in the dIPFC, however, did not indicate a significant relationship between activation and performance. This lack of correlation in the dIPFC was contrary to the hypothesis that the mechanism of taking the executive regions off-line would reflect concomitant impairment in active maintenance abilities. In this experiment, this was most likely due to the distraction manipulation not being strong enough to influence performance. As the active maintenance processes of the dIPFC were left relatively intact in the current manipulation, there was likely not enough variation in performance-related activity to identify this relationship.

In conclusion, the results of the current experiment showed that presentation of task-irrelevant emotional information elicited differential patterns of activation in VAPS and DECS regions. Emotional distraction enhanced activity in ventral affective regions and disrupted activity in more cognitive executive regions. The results indicated that these interacting brain systems underlie emotional interference not only in working memory tasks, but also extend to the active maintenance of abstract rules. Additionally,

the results demonstrated that these differential effects can be elicited by emotional distraction even at a level below the threshold where performance is disrupted. Finally, this experiment identified brain regions where emotional interference interacts with task switching processes, which may inform future hypotheses about the common inhibitory mechanisms that may be involved in emotional-executive tasks.

CHAPTER IV

EXPERIMENT 3

Experiment 3 employed behavioral testing methods to test a group of individuals with schizophrenia and a group of control participants. The behavioral task assessed the same processes of active allocation of attention to distracters during working memory as in Experiment 1. While the goal of Experiment 1 was to identify the neural circuits normally recruited during these processes, the current experiment assessed whether behavioral performance on these processes is impaired in schizophrenia.

Method

Participants

Fifteen individuals with schizophrenia and fifteen controls matched for age, gender, ethnicity, and handedness were recruited for this study. Individuals with schizophrenia were recruited from the Schizophrenia Treatment and Evaluation Program (STEP) at UNC, and had a diagnosis of schizophrenia or schizoaffective disorder according to the Structured Clinical Interview for DSM-IV (SCID). Participants were additionally evaluated using the Positive and Negative Syndrome Scale (PANSS), which provided scores of symptom severity on a scale of 1-7. In the group with schizophrenia, the average total scores for positive, negative, and general psychopathology symptoms were 15 ($SD=4.94$), 16.08 ($SD=6.04$), and 31.75 ($SD=7.09$), respectively. Exclusion criteria for the group with schizophrenia included the presence of a clinically significant

neurological or medical disorder or a current diagnosis of substance dependence. All participants with schizophrenia were taking antipsychotic medication. The control group and the group with schizophrenia did not significantly differ on variables of age ($F(1,29)=3.05, p=.092$), although there was a trend for the group with schizophrenia to be older than the controls. Age was therefore included as a covariate in the group difference analyses. The groups also did not significantly differ on ethnicity ($\chi^2=.166, p=.983$), handedness ($\chi^2=0, p=1$) or gender ($\chi^2=.003, p=.96$).

Behavioral Task

As in the imaging task in Experiment 1, this experiment used the same delayed-response working memory design where information was encoded (S1 phase), maintained over a delay period, and retrieved (S2 phase). Participants again encoded the spatial locations of squares, but the memory load was reduced to 2 locations to ensure that the primary task would not be too difficult for the group with schizophrenia to perform. A delay period of 14 seconds ensued, during which 7 distracter shapes were presented in randomly chosen locations, followed by the probe stimulus and a 5 second intertrial interval. All task instructions for the low distraction and high distraction conditions remained the same as in Experiment 1, with the conditions grouped together in runs and the order counterbalanced across subjects. There were 24 trials presented per condition (including S1, delay period, and S2), with 8 trials presented per run and a total of 6 runs.

Additionally, a second task was administered to a subset of the control participants only ($n=13$) to compare performance on a higher load of 4 locations, in the same paradigm as Experiment 1. This allowed for the assessment of more general

difficulty effects on the task, to aid interpretation of the effects in the patient group. If the patients at a lower load showed similar patterns as the controls at a higher load, this would suggest that a more general effect of task difficulty (particularly with active maintenance processes) may explain the observed deficits. Additionally, this load manipulation provided a closer approximation of the cognitive processes involved for both groups, so that the patient data could be interpreted in the context of the neural regions recruited during Experiment 1.

Analyses

The behavioral analyses examined whether the two groups differed on working memory performance during the two distraction conditions. Repeated measures ANOVAs were conducted to assess whether measurements of accuracy and RT for the working memory retrieval responses differed between groups and distracter conditions, and whether the groups showed an interaction with distracter difficulty, indicating a greater sensitivity to executive distraction in the group with schizophrenia. Responses on the distracter task (i.e., control versus one-back performance) were also assessed with ANOVAs to determine whether the groups differed on the amount of attention allocated to distracters. To examine differences in attention allocation between the two groups, difference scores between difficulty conditions were calculated for working memory and distracter performance for each group. If the group with schizophrenia allocated too much attention to distracters, it would be expected that their patterns of performance decrement for each task (WM and distracter) would be significantly different than controls. In contrast, if the group with schizophrenia allocated attention similarly to controls, the difference scores would be expected to be similar on each task for both

groups. Finally, D-prime analyses were carried out to determine whether changes in the ability to discriminate the stimuli could account for group differences.

Results

Within-Group Performance: Controls

Repeated-measures ANOVAs were performed to assess the effects of executive distraction on working memory performance, RT, and performance on the secondary distracter task. During the low-load condition (2 locations), the healthy control group showed no significant effect of distracter degree on working memory performance ($F(1,14)=.41, p=.533$) or reaction time ($F(1,14)= 0.0, p=.982$). Participants performed at 88.99% correct ($SD=.08$) for the control condition, and 87.14% ($SD=.13$) for the one-back condition (Figure 13 A). Average reaction times were 1125.13 msec ($SD=246.51$) for the control condition and 1124.27 msec ($SD=260.11$) for the one-back condition. These results indicated that, at a lower working memory load, active maintenance processes were not differentially disrupted by the distracter manipulation in controls.

Performance on the secondary distracter task also did not significantly differ according to condition ($F(1,14)=.16, p=.694$) (Figure 13 B). Participants performed at 96.19% correct ($SD=.1$) for the control condition, and 95.0% ($SD=.05$) for the one-back condition, indicating that enough attentional resources were available to actively allocate similar amounts of attention to both tasks. Finally, no significant interactions were found between performance on the primary working memory and secondary distracter tasks in the control group ($F(1,14)=.06, p=.815$).

In the control group, distraction effects on the high-load condition (4 locations) were more enhanced compared to the low-load condition. There was a significant effect

of distraction on working memory performance ($F(1,12)=20.7, p=.001$), where the one-back condition led to a significantly greater disruption of the working memory task (Figure 14 A). Average working memory performances were 86.22% ($SD=.08$) for the control condition and 71.51% ($SD=.14$) for the one-back condition. There was also a significant effect of distraction on reaction time ($F(1,12)=11.91, p=.005$), where RTs were slower during the one-back condition. Average reaction times were 1137.06 msec ($SD=287.68$) for the control condition and 1310.11 ($SD=339.38$) for the one-back condition. Notably, these effects differed from the fMRI version of the task performed with a different group of participants in Experiment 1, where the distraction task did not significantly impact working memory performance.

Performance on the secondary distracter task on the high-load condition was not significantly impaired by the distracter task, although it showed a trend towards a decrease in accuracy on the one-back task ($F(1,12)=3.92, p=.071$) (Figure 14 B). Participants performed at 98.72% ($SD=.02$) for the control task and 95.98% ($SD=.06$) for the one-back task. The data suggests that in this experiment, the attentional resources were taxed more in control participants, leading to impairments in the working memory task. Again, these data contrast with the fMRI findings of Experiment 1, where the performance on the distracter task (and not working memory) was impaired during one-back distraction.

Finally, a comparison of performance on the low-load and high-load conditions in controls showed that working memory performance was significantly impaired by the higher load (4 location) condition ($F(1,12)=62.56, p=.0001$). There was also a significant interaction between load and distracter level ($F(1,12)=6.0, p=.031$), where distraction had

a greater impact on WM performance at the higher memory load. Memory load also had a significant impact on reaction times ($F(1,12)=9.88, p=.009$), where RTs were slowed more by distraction under high load conditions. Finally, load did not significantly impair performance on the secondary distracter task ($F(1,12)=.4, p=.541$). There was also no load by distraction interaction on the secondary distracter task performance ($F(1,12)=1.83, p=.201$). This data therefore indicated that under greater memory load in controls, working memory performance was particularly susceptible to distraction, while performance on the secondary distracter task was less affected.

Within-Group Performance: Patients

Performance effects were assessed in the group with schizophrenia to test the hypothesis that active maintenance processes would be impaired by greater executive distraction, due to changes in attentional resource allocation. Two individuals with schizophrenia did not respond at all to parts of the working memory task, and their data was excluded from the analysis. Consistent with the study's hypothesis, the results indeed indicated that the group with schizophrenia was significantly impaired during working memory performance on the one-back relative to the control condition ($F(1,12)=4.89, p=.047$) (Figure 15 A). The group with schizophrenia performed at 69.55% ($SD=.14$) on the control condition and 64.42% ($SD=.12$) on the one-back condition. Reaction time analyses showed no differences between conditions ($F(1,12)=.03, p=.855$). RTs in the schizophrenia group were 1297.9 msec ($SD=420.22$) for the control condition and 1252.67 ($SD=460.05$) for the one-back condition.

On the secondary distracter task, the group with schizophrenia also showed greater impairment in performance on the one-back relative to the control task

($F(1,12)=8.40, p=.013$) (Figure 15 B). The patient group performed at 95.71% ($SD=.04$) during control distraction, but at 72.92% ($SD=.29$) during one-back distraction.

Therefore, performance on both the working memory task and the distracter task was impaired by executive distraction in the group with schizophrenia.

Between-Group Comparisons

Finally, the performance in both groups was compared to test the hypothesis that active maintenance would be disproportionately impaired by the distracter condition in the group with schizophrenia. The group effects were first assessed on each outcome measure separately (WM performance, RT, and distracter task performance). Overall, performance on the working memory task was significantly impaired in the group with schizophrenia relative to the controls ($F(1,26)=26.74, p<.001$), a finding which was replicated in the d-prime analyses ($F(1,26)=22.52, p<.001$). This group effect remained significant after controlling for age ($F(1,25)=23.04, p<.001$). However, on the working memory task, the group with schizophrenia was not differentially more susceptible to distracter degree than the control group. That is, even though the distraction effect was apparent on the patients' WM performance and not the controls', the interaction between group and distraction did not reach significance for the accuracy ($F(1,26)=.86, p=.362$) or d-prime measures ($F(1,26)=.1, p=.752$) (Figure 16). Reaction time data showed no significant differences between the groups ($F(1,26)=2.3, p=.141$) and no significant interaction between group and distraction ($F(1,26)=.03, p=.856$).

When comparing the groups' performance on the secondary distracter task alone, there was again a significant overall group difference ($F(1,26)=5.96, p=.023$), with the patient group performing worse than controls. There was also a significant interaction

between group and distracter degree ($F(1,26)=7.49, p=.011$) (Figure 17). While the controls' performance was very similar on the control and one-back distracter tasks, the patients' performance showed a significant impairment on the one-back relative to the control task. These effects also remained significant after controlling for age, with a significant group effect ($F(1,24)=4.45, p=.046$) and group by distraction interaction ($F(1,24)=6.51, p=.018$).

To test whether the two groups were differentially affected by distraction, the interactions between the control and one-back tasks were assessed with performance measures (WM and distracter task performance) as a repeated factor. These analyses indicated a significant group by distraction interaction, indicating that the group with schizophrenia was indeed differentially affected by the manipulation ($F(1,26)=7.54, p=.011$). The effect remained significant after controlling for age ($F(1,25)=7.20, p=.013$). This pattern of results is consistent with the hypothesis that individuals with schizophrenia have difficulty in attentional resource allocation. While the patient group was not differentially affected by distracter difficulty on the active maintenance task, their performance on the secondary distracter task was more impaired by the one-back manipulation. These findings were replicated with the d-prime analyses, which further indicated that the group with schizophrenia was impaired at discriminating one-back targets relative to controls ($F(1,27)=9.26, p=.005$).

Additional analyses were performed on difference scores, that is, the difference in performance between the control and one-back conditions, on the performance measures (WM and distracter performance). The results were generally consistent with the findings from the repeated measures ANOVAs. The results indicated that the group with

schizophrenia was impaired overall ($F(1,26)=7.54, p=.011$), but the groups had differential effects of distraction on the two performance measures (primary and secondary tasks) ($F(1,26)=4.6, p=.042$). Therefore, the data suggests that trade-offs in performance between the primary and secondary tasks were different for the group with schizophrenia (Figure 18).

Finally, to address whether a general difficulty effect could explain the group differences in performance, measures from each group were compared from the high-load condition for controls (where available attentional resources would be taxed more), with the low-load condition for the patients. However, the group effects were very similar to those found when both groups were compared at low load. The group with schizophrenia was still significantly more impaired on the working memory task relative to controls at high load ($F(1,24)=13.81, p=.001$). Also, the interaction between group and distraction still was not significant ($F(1,24)=0, p=.989$). On the secondary distracter task, however, the interaction was significant ($F(1,24)=6.28, p=.019$), with the patient group's performance more impaired on the one-back relative to the control task. As this pattern of results is largely similar to the comparisons at low load for the controls, it suggests that in the current study, working memory for four locations in controls still left enough resources for allocation to distracters, while the patient group lacked resources for attention allocation even at a lower memory load of two locations.

Correlational Analyses

Additional correlational analyses were conducted to determine whether positive or negative symptoms (as assessed by the PANSS) were associated with performance on the working memory or distracter tasks. No significant relationships were found between

the positive symptom, negative symptom, or general pathology scores and the behavioral measurements.

Discussion

The goal of the current experiment was to assess whether the group with schizophrenia would be characterized by changes in how attentional resources were allocated to executive distracters during a concurrent working memory task. If the processes of resource allocation were intact, it was expected that a pattern would be seen where the group with schizophrenia would show an overall impairment in performance on the working memory and distracter tasks, but would show no differential effect of distracter difficulty compared to controls. This would suggest that despite an overall reduction in the pool of attentional resources available, attentional resources in schizophrenia can still be distributed normally. In contrast, the alternative hypothesis was that changes would be seen in the group with schizophrenia where performance during the one-back distraction condition would be disproportionately affected, suggesting changes in how attention was distributed. The results of the current experiment supported the latter hypothesis, and indicated that while resources were allocated similarly between groups on the working memory task itself, the group with schizophrenia was disproportionately affected by distraction during performance of the secondary distracter task.

During the low-load manipulation, the control group was able to perform at similar levels during both the control and one-back distracter manipulation. Because only two locations needed to be held in working memory, the control group likely had sufficient available attentional resources that could be simultaneously allocated to both

spatial rehearsal and to the selective attention processes needed during one-back distraction. During the high-load manipulation, however, only the active maintenance processes (and not the secondary task performance) were significantly disrupted by distracter difficulty.

This pattern of performance was notably different from the same task that a different group of participants performed in Experiment 1 during fMRI scanning, where it was the performance only on the distracter task itself, and not the working memory task, that reflected the interference effect. There are several factors that could have influenced these different patterns of performance. First, as two different groups of participants participated in Experiment 1 and 3, it could be that the groups happened to differ in the strategies that they used. One group may have focused more on the spatial rehearsal processes, while the other may have allocated more attention to the distracters. It is possible that gender differences could also have contributed to these differences, as the group recruited for the current experiment included more males so that they would match the group with schizophrenia. Another difference between the experiments was that most of the participants in the current study performed the high-load manipulation after already performing both the low-load task and the behavioral task from Experiment 4. Therefore, factors of being more fatigued, or simply having recently done an easier version of the task, could have influenced the strategies used during the high-load task and biased attention differently.

In the group with schizophrenia, the executive distracter manipulation led to significant impairments in both working memory and distracter performance. These findings are consistent with a multitude of other studies indicating impairments in both

active maintenance and the ability to resist distraction (Braver et al., 1999; C. Carter et al., 1996). As individuals with schizophrenia tend to have difficulty with tasks with high processing demands, it has been suggested that they reach their limit at lower processing loads than controls (Granholm et al., 1996; Silver & Feldman, 2005). The current experiment's results are consistent with this idea, as the group with schizophrenia was significantly impaired by distraction on both the working memory and distraction task at a load of 2 locations, while the control group had enough resources to allocate to both tasks at this memory load.

Analyses specifically comparing the two groups on the working memory task indicated that the group with schizophrenia showed a significant overall impairment relative to the controls. However, contrary to expectations, the group with schizophrenia did not show a differential effect of distraction on the working memory task relative to controls. Even though the patient group's WM performance was significantly impaired by distraction while the effect did not reach significance in the controls, there was no significant interaction in distraction effects between the two groups. The working memory performance therefore seems to suggest that the group with schizophrenia, despite having an overall reduction in processing resources, was able to allocate attention to working memory rehearsal relatively normally. These results contrast with Fleming et al. (1995), who found that verbal working memory performance in a group with schizophrenia was differentially susceptible to executive distraction. The discrepant results in the current study may reflect the use of different strategies, where perhaps more attention was paid to the primary working memory task itself at the expense of the distracter task. As the Fleming et al. (1995) study did not assess performance on the

distracter task itself, it was not able directly address trade-offs in performance between the primary and secondary tasks.

In contrast to the working memory findings, the group analyses did indicate that there was a significant interaction between group and distraction on the performance of the secondary distracter task itself, that is, the ability to identify control and one-back targets. While the control group had sufficient attentional resources to allocate to both the control and one-back distracters, the group with schizophrenia was markedly impaired at identifying the one-back targets compared to the control task. These results suggest that the group with schizophrenia was characterized by changes in how attention was allocated to the secondary task, rather than only a reduction in the overall amount of resources. These data contrast with the findings of Granholm et al. (1996), who found that, during simultaneous performance of a visual search and reaction time task, attentional resources were allocated similarly for both easier and more difficult manipulations. However, because the current study involves greater involvement of prefrontal mechanisms, including greater working memory requirements, it is likely that overloading the PFC led to changes in attentional allocation processes in the group with schizophrenia. It may be that when the more limited available attentional resources were taxed by difficult distraction in the patient group, there was not enough left to apply the selective attention needed to identify the one-back targets. Therefore, the group with schizophrenia appeared to be characterized not by allocating too much attention to distracters, but by lacking in sufficient resources to actively apply to both tasks simultaneously.

Finally, in order to compare performance at the same level as the imaging task in Experiment 1 (and to assess the contribution of general task difficulty), the performance of the group with schizophrenia at low load (2 locations) was compared to the control group at a higher load (4 locations). Notably, the larger memory load for the controls did not disrupt working memory enough to equate performance levels across groups. This comparison indicated that the effects of the distraction task were very similar to the comparisons of both groups at low load, where group differences in susceptibility to interference were only evident during performance of the secondary distracter task. These results indicated that even when prefrontal mechanisms were taxed to a greater degree in controls with higher load, the group with schizophrenia still showed relative changes in how attention was allocated to the primary and secondary tasks. In order to directly assess these changes independent from general task difficulty, future studies will need to equate working memory performance between the two groups to assess whether attention is allocated differently in schizophrenia independent from the degree that PFC mechanisms are taxed.

A notable limitation of the current study is that the design has the potential to be vulnerable to individual differences in the strategies chosen for how attention should be allocated during the task. As discussed above, there could be several factors that influence whether participants choose to focus primarily on the working memory task at the expense of distracters, or whether they place more emphasis on identifying the one-back targets. In the current study, the task instructions given to participants did not explicitly emphasize greater importance of any aspect of the task, and the instructions were given in the same way across experiments. Future studies could perhaps emphasize

attention to be allocated primarily towards the working memory task, and obtain feedback afterwards about the individual strategies used.

In conclusion, the study's results suggested that schizophrenia is characterized by not only a general reduction in the amount of attentional resources available, but also by changes in how attention is allocated during concurrent working memory and distraction. Unlike the previous study of executive distraction by Fleming et al., the current study was able to assess the trade-offs between different aspects of the task, and identified greater vulnerability during distracter processing in the group with schizophrenia. While similar resources were available for spatial working memory rehearsal across conditions, the distracter task performance suggests that too little attention remained in the patient group to be actively allocated under more attention-demanding conditions. Future studies may be able to more directly address the effects of resource limitations on these changes by equating the difficulty of the primary task between groups, and perhaps assessing distraction effects in schizophrenia under different levels of working memory difficulty.

CHAPTER V

EXPERIMENT 4

Experiment 4 assessed the same effects of emotional distraction on task switching as in Experiment 2, but employed behavioral testing methods to examine performance in a group with schizophrenia and healthy controls. The experiment tested whether individuals with schizophrenia were differentially impaired on rule maintenance and task switching when task-irrelevant distracters had emotional versus neutral content.

Method

Participants

Participants included the same individuals as those who participated in Experiment 3. Both experiments were conducted in a single session, with experiment order counterbalanced across subjects. The two groups did not significantly differ on measures of age, parental education, ethnicity, handedness or gender.

Behavioral Task

As in the functional neuroimaging study in Experiment 2, participants performed a task requiring the active maintenance of rules over a delay period. Before the behavioral testing began, participants similarly underwent a practice session during which they learned the stimulus-response associations for each rule. The task again required the retrieval of a bivariate rule depending on whether the cue was blue or yellow, followed by the active maintenance of the relevant rule information over a delay

period and response to a probe stimulus. Cues were presented for 2 seconds, and a delay period of 10 seconds ensued, followed by a circle or triangle probe stimulus presented for 2.5 seconds and an intertrial interval of 5 seconds. Like Experiment 2, two distracter pictures from the same condition were presented during the delay period for 3 seconds each. All other parameters of the task design remained the same as in Experiment 2. The task assessed whether effects of the Emotional-Maintain, Emotional-Switch, Neutral-Maintain, and Neutral-Switch conditions differed between the group with schizophrenia and the controls.

In addition, participants performed behavioral tasks assessing the ability to identify emotional facial expressions to determine whether these abilities predicted the ability to ignore task-irrelevant complex emotional scenes. The pictures were chosen from Ekman's Pictures of Facial Affect (1976), and included the Face Emotion Identification Task (Kerr & Neale, 1993), which requires participants to view faces from six categories of emotion (happy, angry, afraid, sad, surprised, or ashamed) and to identify which category best fits the facial expression. Participants were also given the Face Emotion Discrimination Task (Kerr & Neale, 1993), where they viewed two faces side by side and judged as to whether the faces showed the same or different emotional expressions.

Analyses

Behavioral measurements of accuracy, RT, and d-prime for the probe responses were analyzed using repeated-measures ANOVAs to assess the effects of distracter type and rule switching. Furthermore, correlational analyses were conducted to assess the relationship between positive and negative symptoms and degree of emotional

interference from social-emotional distracters. Finally, the measures of emotional facial expression processing were correlated with the distraction task to determine whether differences in processing of emotional faces accounted for any group differences in the rule task performance.

Results

Within-Group Performance: Controls

The controls' performance on the emotional distraction task was similar to the findings in the fMRI version performed in Experiment 2. No significant differences in accuracy ($F(1,14)=.31, p=.587$) on the rule retrieval task were found as a result of emotional distraction. Participants responded according to the relevant rule at 98.63% correct ($SD=.02$) for emotional trials and at 98.89% ($SD=.02$) for neutral trials. Similarly, there was no significant effect of emotional interference on reaction time ($F(1,14)=.02, p=.899$). Average RTs were 987.52 msec ($SD=387.02$) for emotional trials and 990.73 msec ($SD=342.66$) for neutral trials.

While rule switching did not have a significant effect on accuracy in Experiment 2, in the current experiment there was a significant impairment in accuracy on trials where the rule switched ($F(1,14)=6.79, p=.021$), a finding more consistent with the hypothesis that requirements for updating the currently relevant rule would lead to impairments in performance (Figure 19). Rule switching did not have a significant effect, however, on reaction time ($F(1,14)=.04, p=.85$). There was no significant interaction between emotionality and rule switching for accuracy ($F(1,14)=.13, p=.724$) or reaction time ($F(1,14)=1.78, p=.204$).

Within-Group Performance: Patients

In order to test the hypothesis that the group with schizophrenia would show equal impairment on emotional and neutral distraction, accuracy and RTs were compared with repeated-measures ANOVAs. Data from one participant with schizophrenia, who performed at below-chance levels, was excluded from the analyses. Consistent with the hypothesis, the group with schizophrenia did not show a significant effect of emotional interference on accuracy at the rule retrieval task ($F(1,13)=.3, p=.591$) (Figure 20). Participants with schizophrenia performed at 79.67% correct ($SD=.22$) for the emotional task and 80.26% correct ($SD=.22$) for the neutral task. Also, there was no significant effect of emotional distraction on reaction time ($F(1,13)=.25, p=.626$). Average RTs were 1399.87 msec ($SD=451.03$) for emotional trials and 1382.34 ($SD=372.62$) for neutral trials.

The effects of rule switching were assessed to test the hypothesis that the patient group would show impairments in the flexible updating of information. While rule switching had a significant effect in controls on accuracy measures, there was no significant effect of switching on accuracy in the group with schizophrenia ($F(1,13)=1.24, p=.286$). However, in the patient group, switching rules did lead to a significant decrease in reaction times at rule retrieval ($F(1,13)=10.55, p=.006$), a finding which was consistent with the hypothesis of impaired switching in schizophrenia. There was no significant interaction between emotionality and switching for either accuracy ($F(1,13)=.25, p=.623$) or RT ($F(1,13)=1.34, p=.267$) in the patient group.

Between-Group Comparisons

To test the hypothesis that the group with schizophrenia would show an overall impairment on the rule maintenance task, accuracy and RT measures for the rule task

were compared across the two groups. Consistent with this hypothesis, the results indicated that the group with schizophrenia performed at a significantly lower level of accuracy ($F(1,27)=12.61, p=.001$) and with significantly longer reaction times ($F(1,27)=7.89, p=.009$). D-prime analyses were also consistent with group differences in sensitivity ($F(1,27)=21.99, p<.001$). However, the two groups did not significantly differ in the effect of emotionality on accuracy ($F(1,27)=.18, p=.671$), RT ($F(1,27)=.24, p=.63$), or d-prime measures ($F(1,27)=.34, p=.563$). Therefore, while the patient group showed an overall impairment in performance of the rule task, both groups performed similarly on emotional and neutral trials (Figure 21).

On accuracy measures, even though only the control group showed a significant effect of switching, there was no significant interaction between group and rule switching ($F(1,27)=.55, p=.463$). However, on reaction time, the interaction between group and switching was significant ($F(1,27)=7.96, p=.009$). While the group with schizophrenia showed slower RTs on switch trials, the control group's RTs did not differ between switch and non-switch trials. Finally, no significant three-way interactions (group by emotion by switching) were found for accuracy ($F(1,27)=.36, p=.552$) or RT ($F(1,27)=.44, p=.515$).

Performance on the Ekman Facial Expression Identification Test (FEIT) and the Facial Expression Discrimination Test (FEDT) was also assessed to determine whether differences in processing of facial expressions could account for performance on the rule task. The facial expression tests indicated that on the FEIT, the group with schizophrenia was significantly impaired on the ability to identify emotional facial expressions

($F(1,29)=4.43, p=.044$). No significant group differences were found on performance of the FEDT task ($F(1,29)=.98, p=.331$).

Correlational Analyses

Finally, correlational analyses were performed to determine whether positive and negative symptoms could predict performance on the task. No significant relationships were found between positive symptoms, negative symptoms, or general psychopathology on emotional or neutral task performance. Additionally, performance on the facial expression tasks was correlated with performance on the rule task. In the control group, no significant relationships were found between performance on the facial expression tasks and the ability to perform the rule task under emotional and neutral distraction. In the patient group, better performance on the FEIT was associated with better performance on both emotional ($r=.75, p=.003$) and neutral trials ($r=.7, p=.007$) in the rule task. The FEDT task, however, was found to have a negative relationship with performance on the neutral distraction task ($r=-.61, p=.028$). Therefore, in the group with schizophrenia, the two facial expression tasks seemed to predict different aspects of rule task performance during emotional distraction.

Discussion

The aim of the current experiment was to determine whether emotional distraction in the form of depictions of social-emotional interactions would lead to decreased distraction effects in individuals with schizophrenia. While schizophrenia is typically associated with greater distractibility, the current study sought to assess whether the social-emotional content of the distracters would be associated with decreased attentional bias, as a result of changes in facial affective processing. At first glance, the results

appear to be generally consistent with the hypothesis, indicating similar levels of impairment for emotional and neutral distraction. However, the results must be interpreted with caution in light of the control group's performance, which also did not show differential effects of emotional distraction. Additionally, the current experiment assessed the effects of rule switching and the interactions of switching with emotional distraction. The results indicated that the group with schizophrenia was characterized by slower reaction times following rule switches, but these impairments were not significantly different during emotional versus neutral conditions.

It was hypothesized that because schizophrenia has been associated with changes in social-emotional processing, the patient group would show decreased attentional bias to the emotional distracter pictures. For example, a recent study by Schneider et al. (2006) found that a group with schizophrenia was impaired at discriminating the emotional aspects of facial expressions compared to non-emotional aspects (age and facial recognition). These emotional deficits have been characterized as being greater for specificity (the ability to correctly identify emotions) rather than sensitivity (the ability to correctly reject non-target emotions). Consistent with these findings, the data from the current experiment indicated that the group with schizophrenia was more impaired at identifying emotional facial expressions (FEIT). However, the group with schizophrenia was not significantly impaired on the ability to discriminate facial expressions (FEDT). It may be that the process of generating a categorical decision for a specific emotional label was a generally more difficult task for the patient group. Alternatively, perhaps limited statistical power in the current study contributed to the lack of significant difference between groups on the FEDT, as these results contrast with multiple other

studies suggesting that schizophrenia is indeed characterized by difficulties in emotional discrimination (Edwards et al., 2002; Schneider et al., 2006).

While the FEIT data indicated that the group with schizophrenia was impaired at identifying facial expressions, the data from the emotional distraction task was consistent with the hypothesis that emotional and neutral pictures would be equally distracting as a result of these changes in facial expression processing. However, in the current study, the control group also did not show a significant difference in performance during emotional and neutral distraction. The similar effects of emotional and neutral distraction in the patient group therefore cannot be necessarily attributed to attentional biasing, because it is possible that the emotional pictures were not salient enough to divert significant attentional resources. Because the pictures were chosen to include specifically social interactions with human faces, the pictures may not have been as salient as those used in other studies of emotional distraction, which often include more disturbing images. Despite the emotional pictures in the current study being specifically chosen to have high arousal and low valence ratings, it is possible that pictures at the more extreme ends of the rating scales would have resulted in performance impairment on the rule task.

Also, as discussed for Experiment 2, another factor that may have reduced the distraction effects of the emotional pictures was the timing of the pictures within the delay. While presenting emotional distraction in the middle of the delay did not significantly impair performance on the rule task, future studies could address whether presenting emotional interference during rule retrieval leads to similar effects of emotional and neutral distraction in schizophrenia. Finally, because performance levels on the rule task itself were at ceiling levels in the control group, it may have been that the

primary active maintenance task itself did not engage enough attentional resources to be particularly vulnerable to distraction. Future studies that modulate the degree of primary task difficulty may provide insights on how emotional distraction is affected by the degree of competition from the primary working memory task.

A secondary hypothesis of the current study was that the group with schizophrenia would be significantly impaired relative to the control group during the active maintenance of abstract rule information (regardless of distraction). The bivalent rule task, where the correct response depends on the currently relevant rule, requires the active maintenance of contextual information in order to guide behavior. As a multitude of studies have found that schizophrenia is associated with difficulty in these prefrontally mediated processes (Posada & Franck, 2002; Posada et al., 2005), it was not surprising that the current study's results were consistent with the hypothesis that performance would be worse overall in the patient group.

Additionally, it was hypothesized that the group with schizophrenia would also show differential impairment on trials requiring rule switching, as individuals with schizophrenia have been characterized as having difficulty in flexibly updating task-relevant information. The results from the current study were consistent with this hypothesis, and indicated that the group with schizophrenia was significantly slower to respond on trials where the rule had changed from the previous trial. While there has been some controversy over whether schizophrenia is characterized by task-switching impairments per se (Kieffaber et al., 2006), it seems to be that performance in individuals with schizophrenia is particularly vulnerable during switching tasks that specifically require the active maintenance and updating of goal-related contextual information.

Additionally, because the current task design employed bivalent rules, as opposed to simple stimulus-response associations, there would have been a greater need to inhibit the previously relevant rule from interfering with the current rule on switch trials (Bunge, 2004). These inhibitory requirements of the study design could also have contributed to the group with schizophrenia showing slowed performance when the currently relevant rules changed.

Finally, correlational analyses were performed to assess the relationships between facial expression processing and performance on the emotional distraction task. The data indicated that in the control group, there was no relationship between ability to identify or discriminate facial emotional expressions and performance of the distraction task. In the group with schizophrenia, however, better ability to identify emotions was associated with better ability to perform the rule maintenance task during both emotional and neutral distraction. Therefore the predicted relationship, where reduced ability to process emotional faces would be associated with less emotional distraction, was not observed.

It could be that the significant relationship between the FEIT and rule task in the current study reflects the integrity of general attention mechanisms in the patient group, where individuals with a better capacity for sustained attention were better at performing the tasks overall. The control group, in contrast, may not have been variable enough in their performance to show this relationship, as performance was at ceiling levels for the rule task. While the performance on the facial expression discrimination task showed an opposite relationship where better emotional discrimination predicted worse performance, this relationship was only significant during neutral distraction. It may be that this particular relationship between FEDT and rule task performance was significant

by chance alone, as it did not reach significance when applying a more stringent statistical threshold through Bonferroni correction for multiple correlations ($p=.0125$). In general, the current study did not find evidence to support the idea that differences in emotional face processing in schizophrenia influence attentional biasing to complex scene distracters. Future studies may be able to further characterize the role of social-emotional distraction in schizophrenia by modulating whether distracters are social or non-social, perhaps by comparing emotional and neutral faces with other non-social, equally complex task-irrelevant stimuli.

In conclusion, the results of the current study indicated that the group with schizophrenia was significantly impaired during processes of active rule maintenance and switching processes, and showed similar impairments for both emotional and neutral distraction. While the group with schizophrenia was also significantly impaired at the ability to identify emotional facial expressions, this deficit did not predict reduced attentional bias to social-emotional distracters. It is possible that because the emotional distracters in the current study may not have been salient enough to significantly divert attentional resources away from the primary active maintenance task, there were similar amounts of attentional resources allocated to the rule task under both emotional and neutral distraction conditions for both groups. However, it is notable that the social-emotional distracters in the current study were found in Experiment 2 to not only activate ventral affective regions of the brain, but also to disrupt processing in dorsal executive regions. Therefore, it is possible that the social-emotional distracters did indeed divert attentional resources, but to a lesser degree than necessary to disrupt performance. Future studies characterizing the neural correlates of emotional distraction in

schizophrenia may be able to better elucidate how the mechanisms for processing task-irrelevant emotional information interact with those involved in executive function.

CHAPTER VI

GENERAL DISCUSSION

Overall, the four experiments taken together assessed the effects of distraction on active maintenance processes in both healthy controls and individuals with schizophrenia. The primary goals were to identify the neural circuits recruited during normal processing of executive and emotional distraction during concurrent active maintenance, and to determine how attentional biasing to these distracters affected performance of these tasks in a group with schizophrenia. The results from the neuroimaging experiments elucidated the roles of specific prefrontal subregions in the processes of active maintenance and coping with distraction, as well as the interacting neural systems involved in resolving emotional interference. The behavioral studies, in turn, helped to further characterize the effects of distraction on active maintenance in schizophrenia, suggesting that attentional resources are allocated differently during executive distraction and are perhaps recruited normally during emotional distraction.

The ventrolateral PFC was identified across studies as playing an important role in selection processes needed to resolve competition. While previous studies supporting this role of the vLPFC had typically examined effects of task-irrelevant sensory distracters that were ignored by the study participants, the role of the vLPFC in resolving other types of distraction had remained unexplored. It was not known whether distracters that interfered through voluntary or involuntary diversion of attention would recruit the vLPFC

in the same way as previous paradigms. The results of the current experiments extended this knowledge to better characterize the role of the vIPFC, and indicated that the vIPFC played a specific role in the active allocation of attention to a competing distracter task. Therefore, the vIPFC appears to be important for not only resisting interference from irrelevant information, but also for more active processes of dividing attention and allocating limited amounts to secondary tasks. Furthermore, it seems to play an important role in emotional distraction as part of the VAPS circuitry, with its activation patterns showing opposite effects of emotion as the dorsolateral PFC. This evidence taken together supports the view that the vIPFC has a specific role in selection processes that allow for the resolution of interference, while these processes are recruited by a variety of tasks where there are competing alternatives for potential behaviors.

The fMRI studies also supported the view that the dlPFC is primarily involved in active maintenance processes, but furthermore suggested that it may also play a role in executive distraction processes. As the only region that was able to support both processes simultaneously, the current results suggest that the processes of dividing and selectively applying attention further recruit the dlPFC beyond its role in actively maintaining information in working memory. As previously suggested (Jha et al., 2004), the vIPFC and dlPFC may interact with one another during performance of working memory and distraction tasks, where the ability of the vIPFC to select among competing alternatives influences the ability of the dlPFC to actively maintain task-relevant information. Furthermore, the results also demonstrated that the sustained maintenance-related activity of the dlPFC could be disrupted by emotional interference in the absence of a behavioral consequence. It could be that emotional distraction affects the dlPFC

differently through inputs from multiple VAPS regions (Mayberg et al., 1999), leading to inhibition of maintenance-related activity.

The behavioral experiments in the group with schizophrenia addressed the effects of executive and emotional distraction on performance of a concurrent active maintenance task. While previous behavioral studies of schizophrenia have indicated impairments in both working memory and resisting distraction, few studies have directly assessed how schizophrenia affects the ability to perform these tasks simultaneously. The findings in the current studies indicated that the group with schizophrenia allocated attentional resources to a secondary distracter task differently than controls, where they were specifically impaired at being able to identify one-back distracters. However, they showed similar effects of emotional and neutral distraction, without showing differential impairment relative to the control group.

As the executive and emotional distraction tasks in the behavioral experiments were the same as those performed with control subjects during fMRI scanning, the behavioral data can be interpreted in terms of the neural regions that are normally recruited under those specific conditions. The advantage of this design is that it can allow for the generation of specific hypotheses for future studies assessing the neural changes in schizophrenia during these cognitive processes. As the group with schizophrenia showed overall impairment in the ability to perform active maintenance tasks, whether during spatial working memory or abstract rule maintenance, it is possible that these changes would be associated with dysfunction in dlPFC activation. This would be consistent with previous findings of dlPFC hypoactivation in schizophrenia during other working memory tasks (Glahn et al., 2005; Perlstein et al., 2001; Perlstein et al.,

2003). It should be noted, however, that as the current studies did not specifically identify a relationship between dlPFC activation and performance in the control group, it cannot necessarily be extrapolated that dysfunction in this region would appear in a group with schizophrenia. Rather, these findings may provide informative hypotheses for specific regions of interest where changes in activity may be expected to occur.

Given the fMRI findings of the vlPFC being normally involved in both executive and emotional distraction, it is possible that specific dysfunction in this region may partially explain the changes in attention allocation observed in the group with schizophrenia. As the patterns of behavioral performance in the control group during Experiment 1 indicated relative impairment on the secondary distracter task (that was correlated with vlPFC activity), the similar patterns observed in the patient group behaviorally suggests the possibility that changes in vlPFC function could contribute to these attentional allocation changes in schizophrenia. However, the control groups' performance differed in the fMRI and behavioral (high-load) versions of the same task, in terms of whether the primary or secondary tasks were more affected by executive distraction. Therefore, it may be that individual variability in other factors like strategies could influence these prefrontal patterns of activity, which should be taken into account when comparing control and patient groups' performance and activation patterns.

Finally, the emotional distraction task indicated that while neither controls nor patients showed a differential performance deficit during emotional versus neutral distraction, these manipulations did elicit differential activity in VAPS and DECS regions consistent with other studies of emotional interference. The fMRI experiment indicated that emotional distraction elicited greater activation in VAPS regions and led to

disruption in the sustained activity of the dlPFC below pre-stimulus baseline levels, even while the ability to actively maintain rule information in the face of emotional distraction was intact. Furthermore, the fMRI experiment indicated that significantly greater activation was elicited in the fusiform face area during emotional distraction, which is consistent with the idea that the emotional facial expressions in the distracter scenes are receiving greater top-down attentional bias than the neutral scenes. Therefore, these results indicate that these mechanisms underlying emotional distraction may be operating even when performance is not impaired. This suggests that during the behavioral experiment, the emotional distracter pictures may have indeed elicited some greater diversion of attention than the neutral pictures, despite these effects not impairing rule task performance. While the group with schizophrenia showed no differential behavioral effect of emotional distraction, future studies may be able to determine whether individuals with schizophrenia show similar VAPS and DECS interactions. The fusiform gyrus may be a particularly interesting region to examine in schizophrenia, as its activity patterns may reflect whether attention is biased to emotional faces to a similar degree as control participants.

In conclusion, the current set of studies demonstrated the effects of two novel manipulations of distracter degree on concurrent active maintenance processes. The neuroimaging experiments in healthy controls identified the neural correlates of executive and emotional distraction processes, thus further extending the current knowledge about the roles of specific subregions of the prefrontal cortex. The behavioral experiments allowed for further characterization of the working memory and distracter processing

deficits in schizophrenia, and identified specific impairments in the ability to actively allocate attentional resources.

Furthermore, the findings in the current studies may be informative for future research directions exploring cognitive control deficits in schizophrenia. The neuroimaging results can provide specific target regions of interest for generating new hypotheses about how schizophrenia affects the abilities to cope with both executive and emotional distraction. Future studies will also benefit from functional connectivity analyses to further characterize the interacting neural circuits underlying these processes, and to determine how these neural interactions are affected in individuals with schizophrenia. Finally, as further knowledge is gained about the specific genes that lead to susceptibility to schizophrenia, it will be interesting to assess the neural correlates of cognitive control in at-risk individuals to better characterize how these genes interact with brain function and behavior. The research directions extending from the current work will not only allow for a better characterization of the normal neural correlates of cognitive control, but will also help to generate better understanding of the underlying neural changes in schizophrenia and potential targets for treatment.

Table 1

Foci of Maximum Activation for the Control and One-Back Tasks

Control						
Region	Hemisphere	Talairach Coordinates			Max T-value	Cluster Size
		x	y	z		
Globus Pallidus	Left	-12	6	-6	4.65	5
Globus Pallidus	Right	19	9	-9	5.26	5
Inferior Parietal Lobule	Left	-64	-40	28	4.98	4
Inferior Temporal Gyrus	Left	-50	-49	-12	4.55	5
Insula	Left	-57	-37	18	7.52	26
Middle Frontal Gyrus	Right	43	53	-6	5.25	5
Middle Temporal Gyrus	Left	-61	-25	-8	4.86	21
Postcentral Gyrus	Left	-64	-17	20	4.01	7
Posterior Cingulate	Left	-2	-37	24	4.71	4
Superior Frontal Gyrus	Right	33	57	-6	4.76	5
One-Back						
Region	Hemisphere	Talairach Coordinates			Max T-value	Cluster Size
		x	y	z		
Postcentral Gyrus	Left	-61	-7	20	5.56	12
Middle Temporal Gyrus	Right	64	-19	-14	8.71	6
Medial Frontal Gyrus	Left	-5	29	-16	3.80	6
Inferior Temporal Gyrus	Right	64	-29	-16	7.25	6
Inferior Parietal Lobule	Left	-61	-40	41	3.27	4
Globus Pallidus	Left	-23	-5	-6	4.80	4
Fusiform Gyrus	Right	50	-43	-18	4.64	8
Caudate	Right	5	16	2	4.33	7
Anterior Cingulate	Left	-5	37	11	4.63	4

All values $p < .05$

Table 2

Foci of Maximum Activation (One-Back Greater than Control)

Region	Hemisphere	Talairach Coordinates			Max T-value	Cluster Size
		x	y	z		
Cingulate Gyrus	Left	-2	-6	26	3.86	4
Cingulate Gyrus	Right	5	14	28	3.37	6
Globus Pallidus	Right	26	-18	1	4.37	7
Inferior Frontal Gyrus	Right	54	23	-1	4.68	13
Inferior Parietal Lobule	Right	40	-52	57	3.56	6
Middle Frontal Gyrus	Right	29	15	38	3.31	4
Postcentral Gyrus	Left	-40	-22	53	3.60	6

All values $p < .05$

Table 3

Foci of Maximum Activation (Control Greater than One-Back)

Region	Hemisphere	Talairach Coordinates			Max T-value	Cluster Size
		x	y	z		
Anterior Cingulate	Right	2	47	-2	5.49	35
Inferior Parietal Lobule	Left	-43	-64	39	6.22	25
Posterior Cingulate	Right	2	-51	25	5.12	73
Superior Parietal Lobule	Left	-19	-66	55	4.26	8

All values $p < .05$

Table 4

Foci of Maximum Activation (Emotional Greater than Neutral)

Region	Hemisphere	Talairach Coordinates			Max T-value	Cluster Size
		x	y	z		
Fusiform Gyrus	Right	43	-56	-15	4.12	10
Fusiform Gyrus	Left	-29	-83	-11	4.37	9
Inferior Frontal Gyrus	Left	-54	23	9	3.39	3
Inferior Occipital Gyrus	Right	43	-76	-5	4.88	8
Medial Frontal Gyrus	Left	-2	48	20	5.17	4
Middle Occipital Gyrus	Right	43	-82	7	4.07	7
Middle Occipital Gyrus	Left	-29	-85	20	4.33	5
Middle Temporal Gyrus	Right	54	-72	13	6.51	34
Parahippocampal Gyrus	Left	-26	-46	-9	5.05	4
Posterior Cingulate	Right	5	-51	25	4.32	10
Thalamus	Left	-12	-31	5	4.44	4
Thalamus	Right	12	-31	5	3.92	4

All values $p < .05$

Table 5

Foci of Maximum Activation (Neutral Greater than Emotional)

Region	Hemisphere	Talairach Coordinates			Max T-value	Cluster Size
		x	y	z		
Cingulate Gyrus	Right	2	4	38	3.05	4
Inferior Frontal Gyrus	Right	47	13	-1	3.92	3
Inferior Parietal Lobule	Left	-43	-39	57	3.99	5
Inferior Parietal Lobule	Right	40	-36	41	3.88	3
Medial Frontal Gyrus	Right	9	28	37	3.42	3
Middle Frontal Gyrus	Right	54	31	27	4.42	7
Middle Frontal Gyrus	Left	-36	61	3	4.58	6
Postcentral Gyrus	Left	-40	-19	49	4.98	3
Postcentral Gyrus	Right	64	-24	17	4.15	3
Precentral Gyrus	Left	-40	-15	62	4.13	3
Superior Frontal Gyrus	Right	5	16	60	4.23	6

All values $p < .05$

Table 6

Foci of Maximum Activation (Rule Switching Greater than Rule Maintaining)

Region	Hemisphere	Talairach Coordinates			Max T-value	Cluster Size
		x	y	z		
Anterior Cingulate	Right	2	37	1	4.07	3
Inferior Frontal Gyrus	Left	-47	0	23	3.02	2

All values $p < .05$

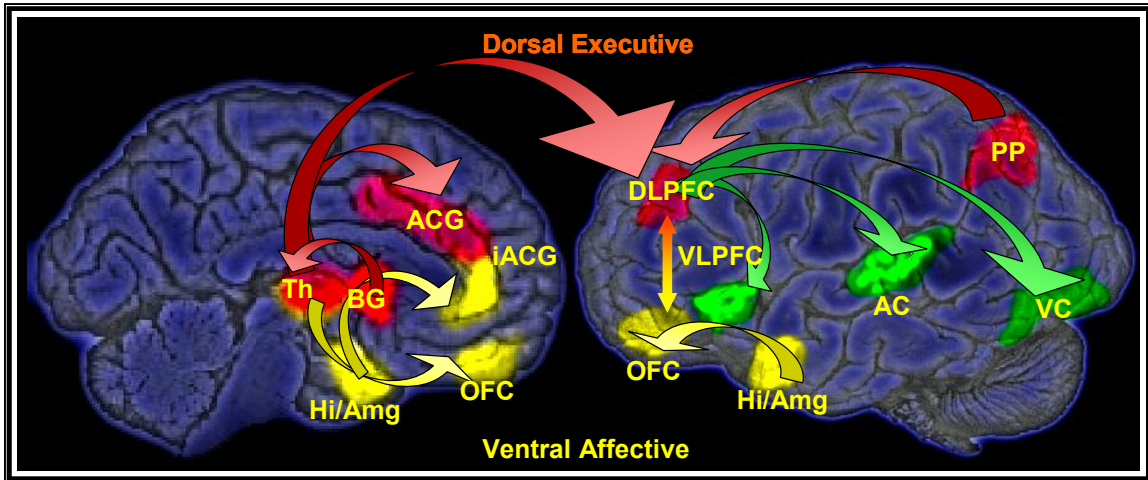
Table 7

Foci of Maximum Activation (Emotional Rule Switching Greater than Neutral Rule Switching)

Region	Hemisphere	Talairach Coordinates			Max T-value	Cluster Size
		x	y	z		
Cingulate Gyrus	Right	2	-43	31	5.20	9
Fusiform Gyrus	Right	40	-46	-15	5.97	4
Medial Frontal Gyrus	Right	5	51	14	3.85	5

All values $p < .05$

Figure 1. Schematic of Dorsal Executive and Ventral Affective Circuitry



ACG = anterior cingulate; AC = auditory cortex; BG = basal ganglia; dIPFC = dorsolateral prefrontal cortex; Hi/Amg = hippocampus/amygdala complex; iACG = inferior anterior cingulate; OFC = orbitofrontal cortex; PP = posterior parietal cortex; Th = thalamus; VC = visual cortex; vIPFC = ventrolateral prefrontal cortex

Figure 2. Schematic of Executive Distraction Task Design

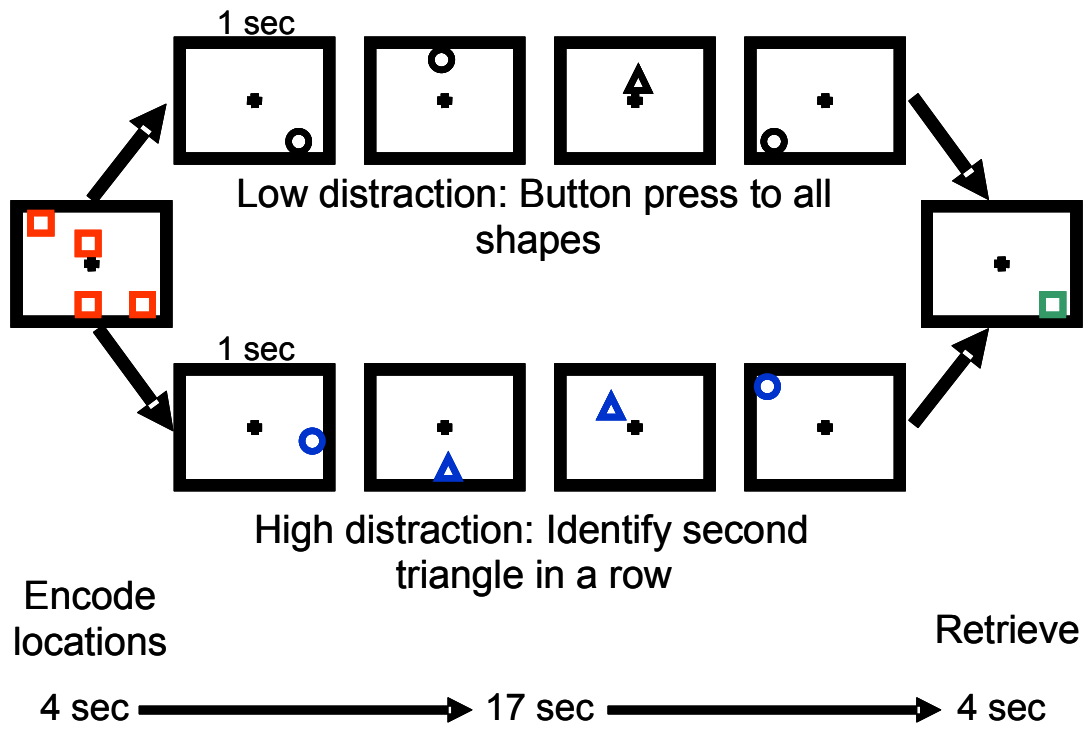


Figure 3. Accuracy on Working Memory and Distraction Tasks

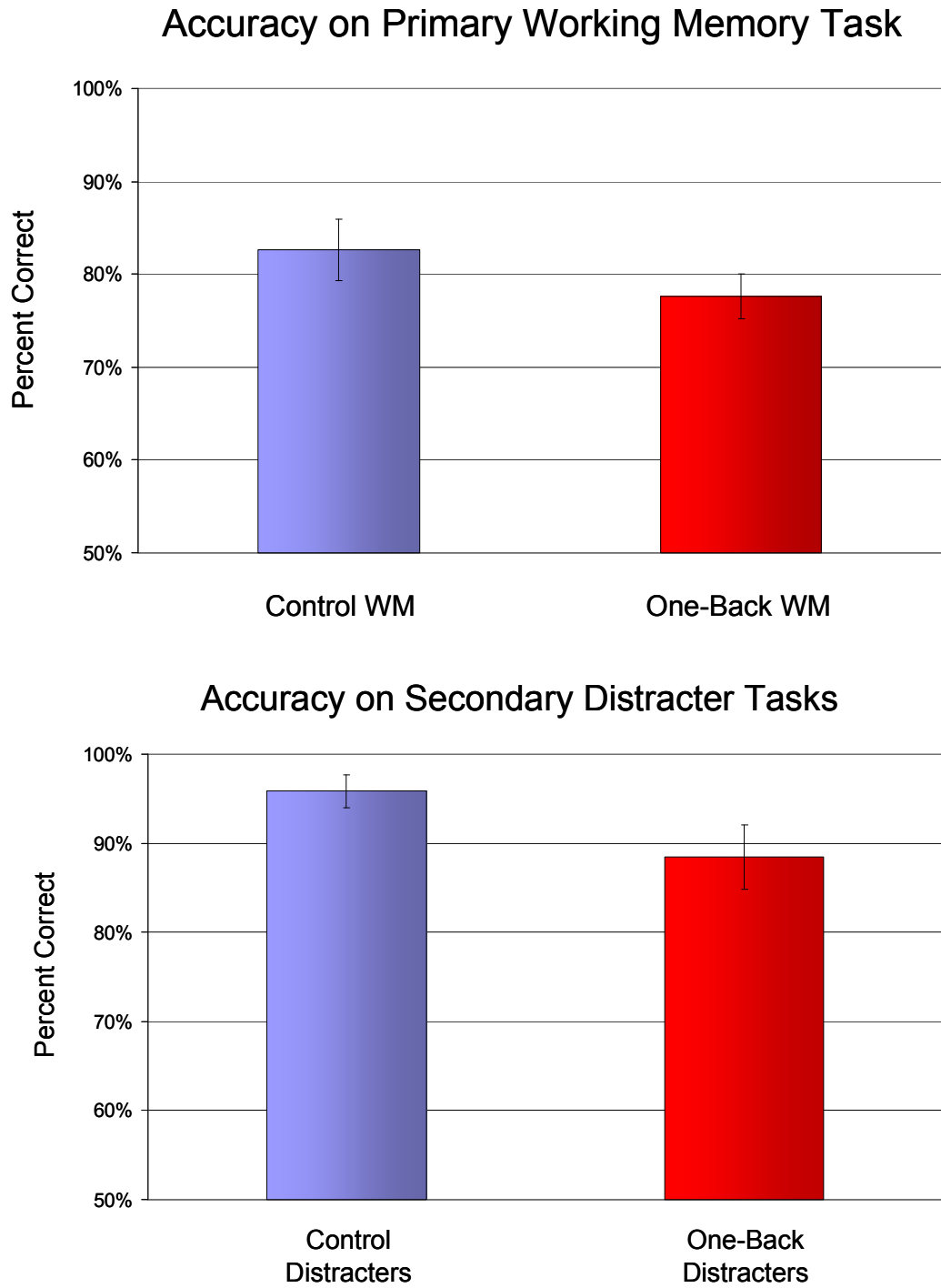


Figure 4. Ventrolateral PFC Activation in Executive Distraction

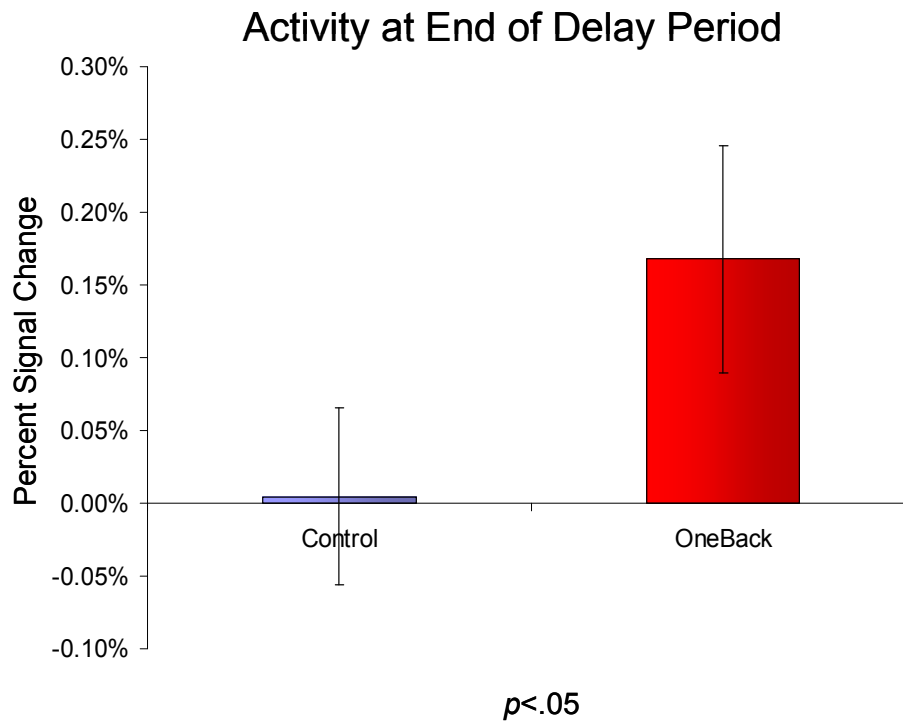
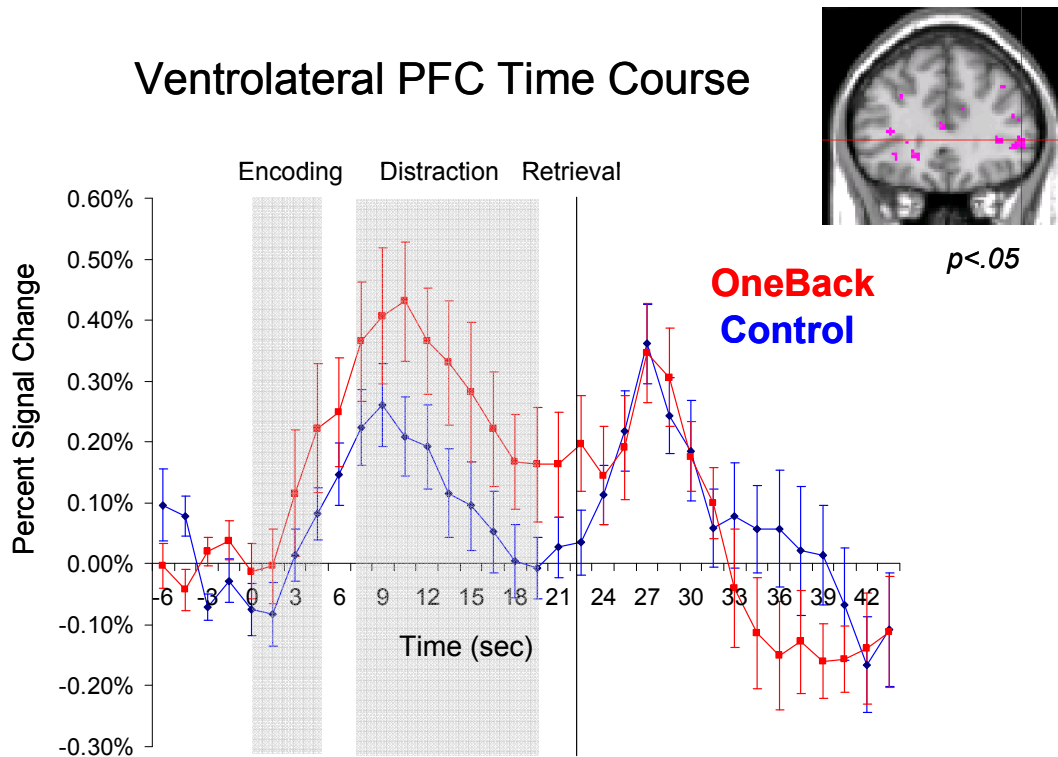


Figure 5. Dorsolateral PFC Activation in Executive Distraction

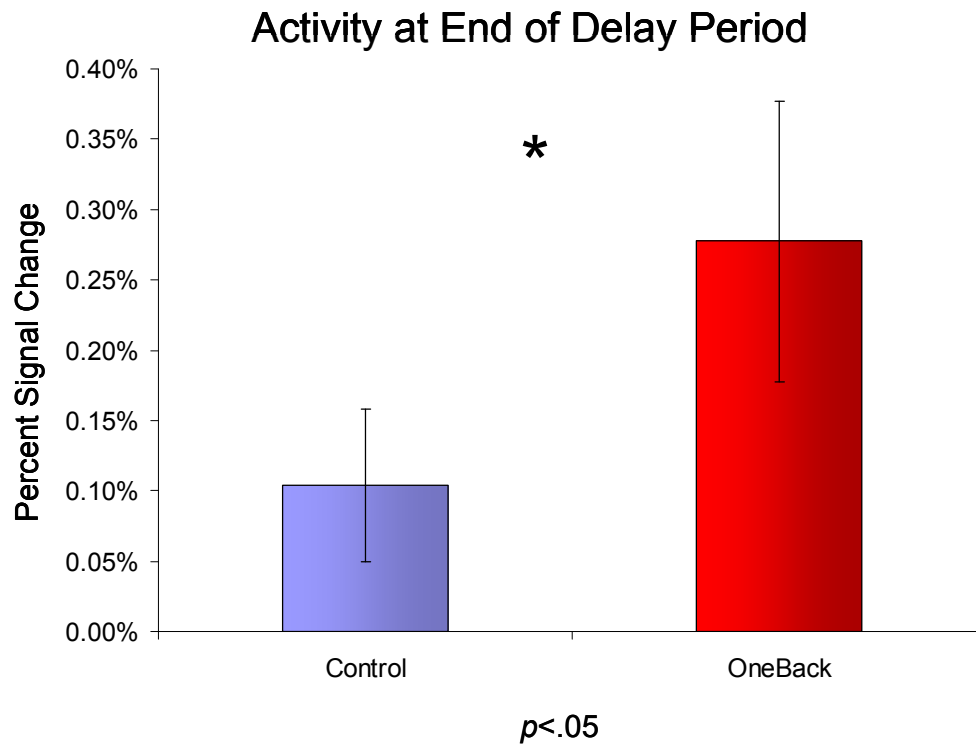
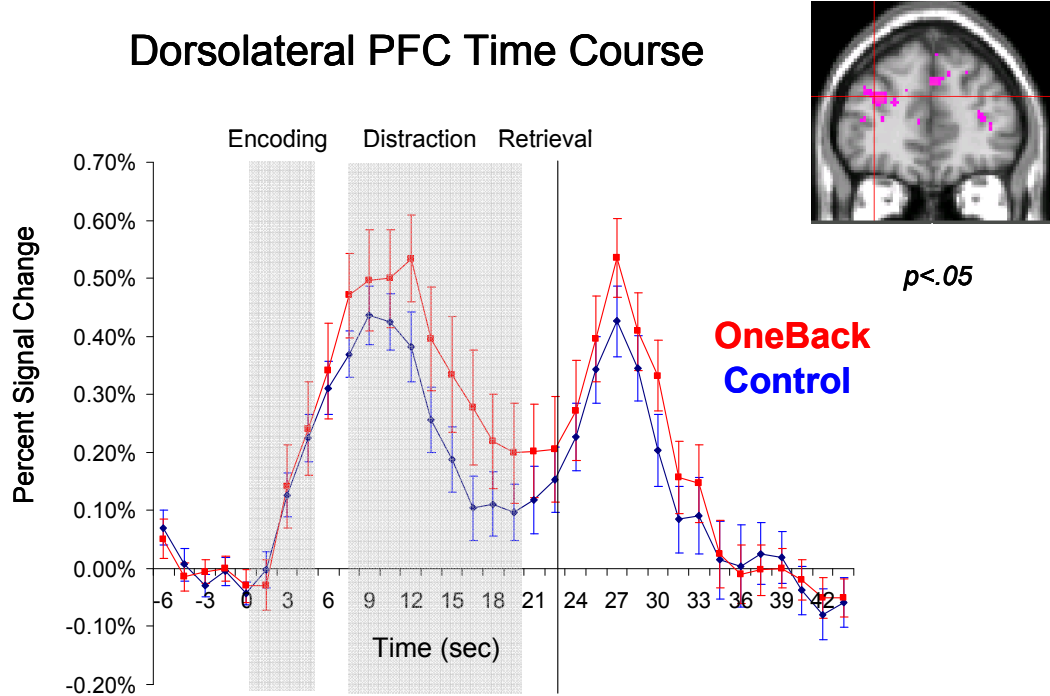


Figure 6. Schematic of Emotional Rule Task Design

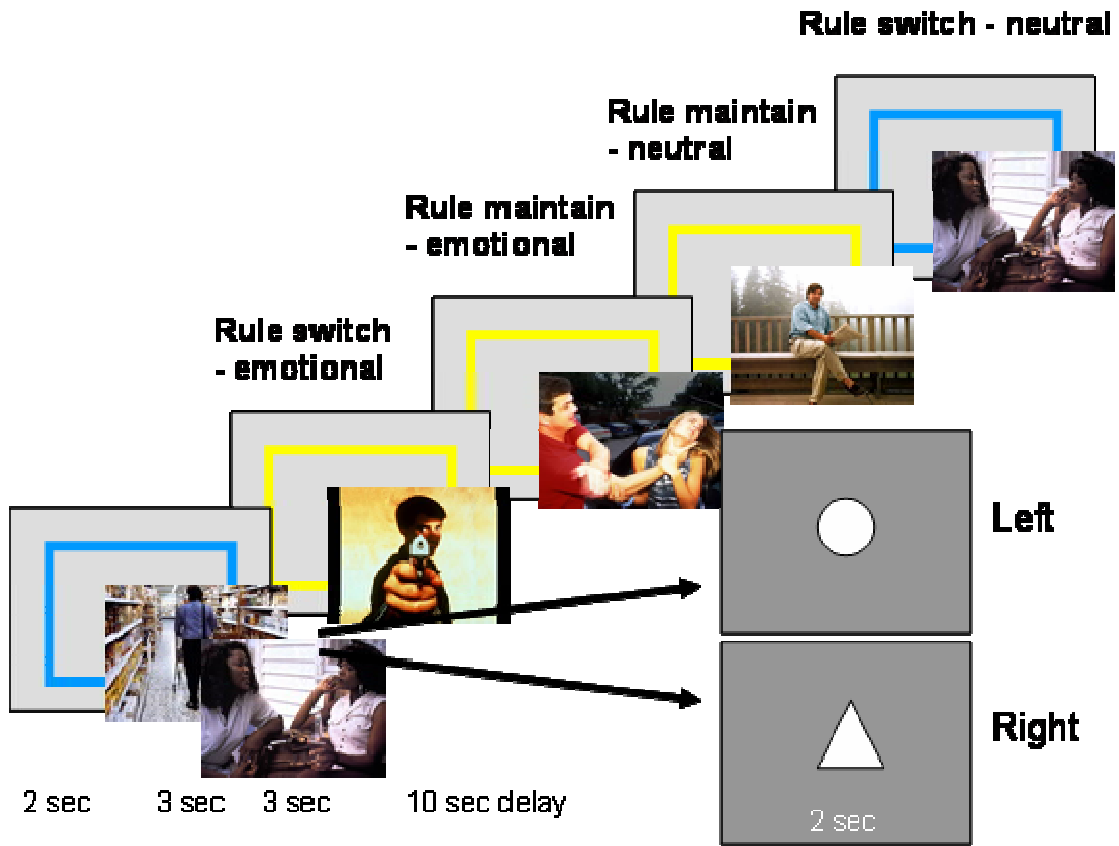


Figure 7. Accuracy during Rule Maintenance Task

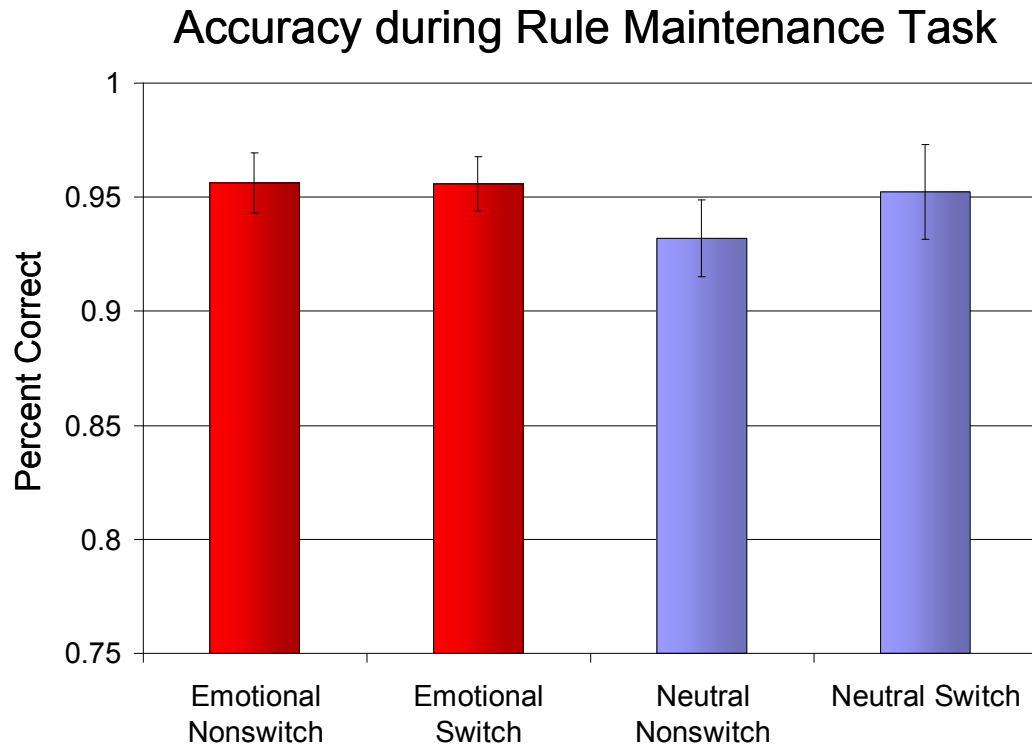
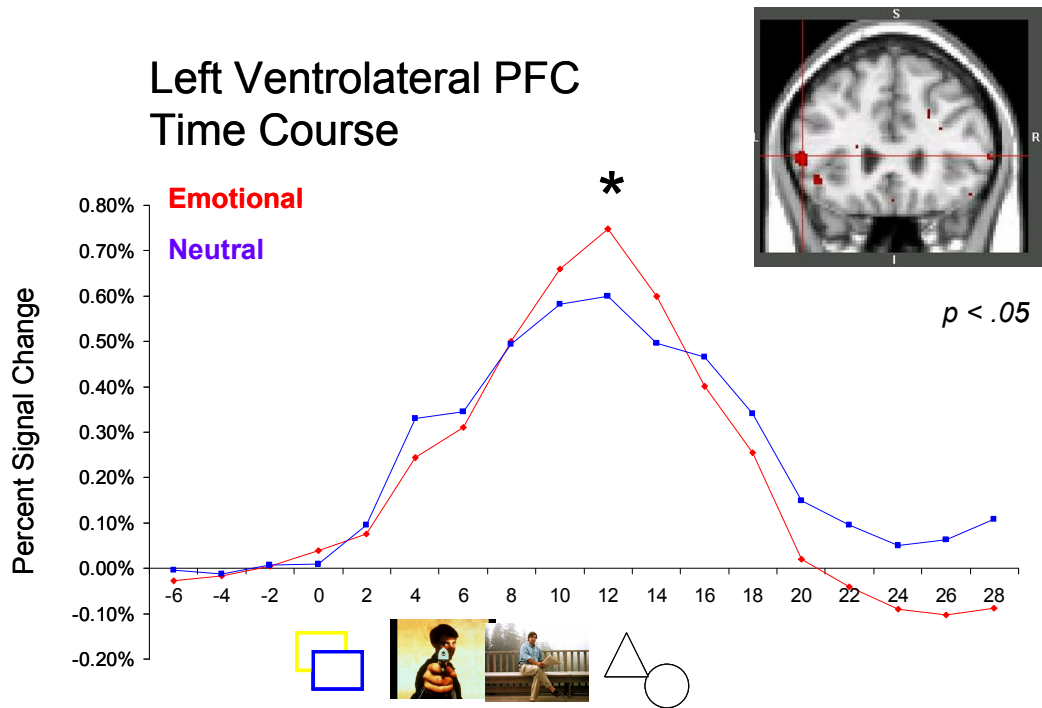


Figure 8. Ventrolateral PFC Activation in Emotional Distraction



Left Ventrolateral PFC Activation (Time Point 12)

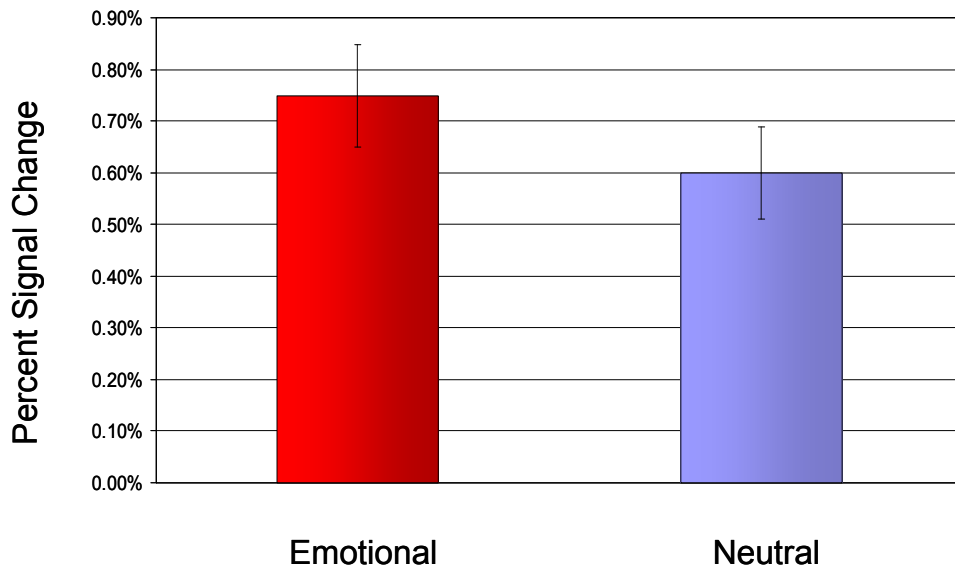
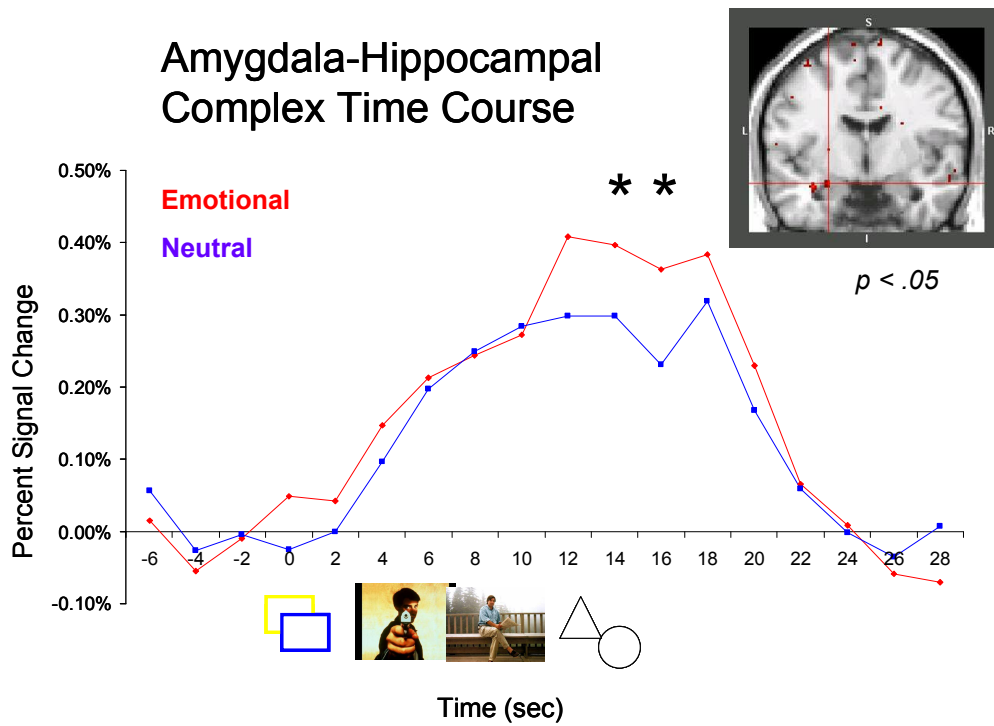


Figure 9. Amygdala-Hippocampal Complex Activation in Emotional Distraction



Amygdala-Hippocampal Complex Activation (Time Point 14)

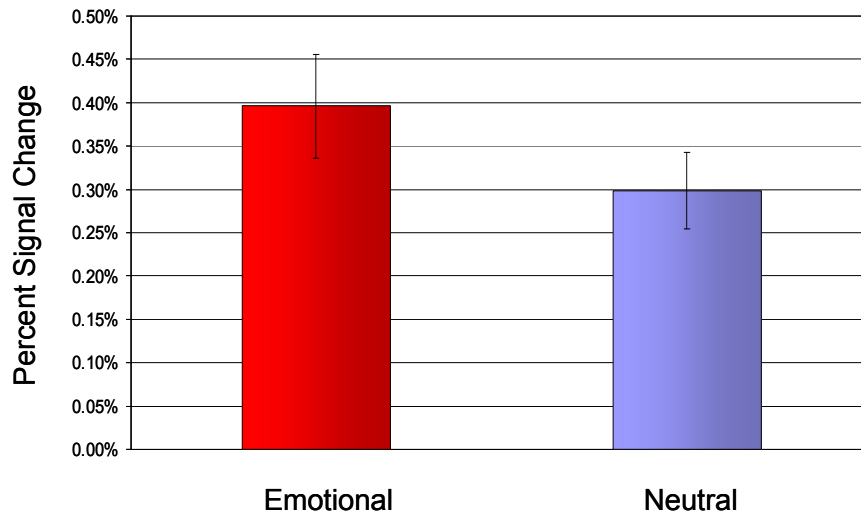
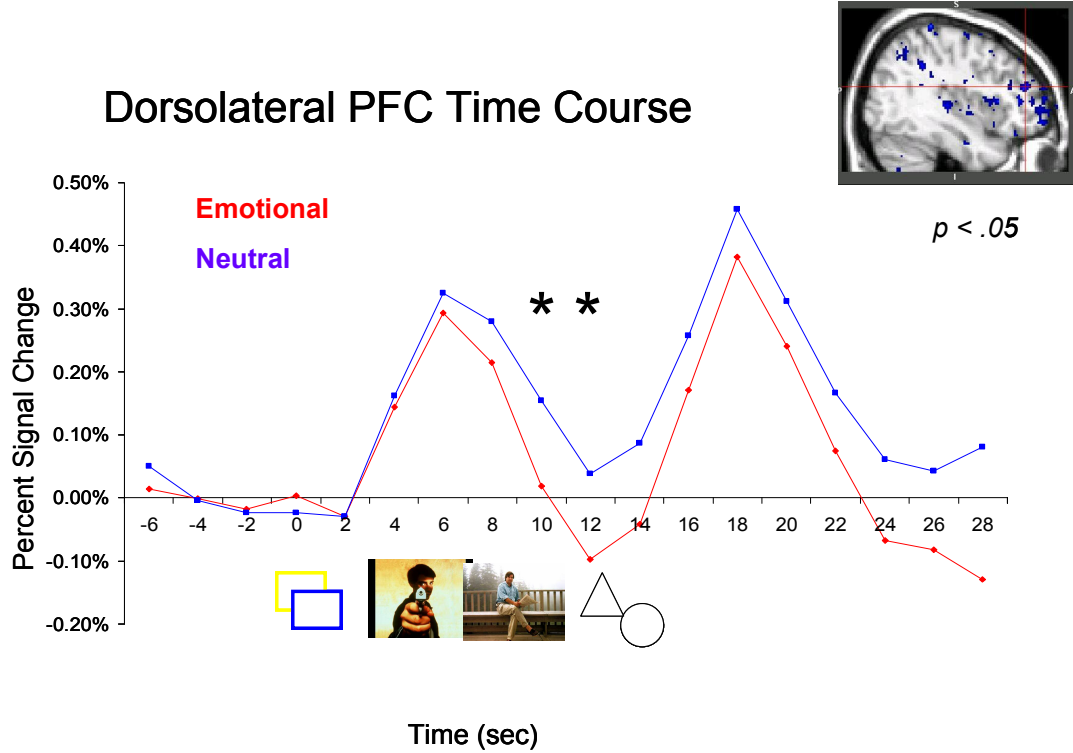


Figure 10. Dorsolateral PFC Activation in Emotional Distraction



Dorsolateral PFC Activation (Time Point 12)

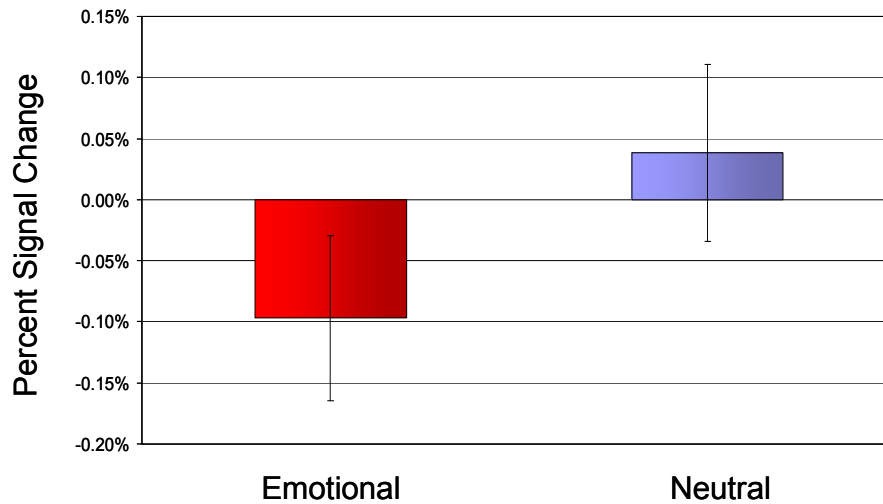


Figure 11. Anterior Cingulate Activation in Emotional Distraction

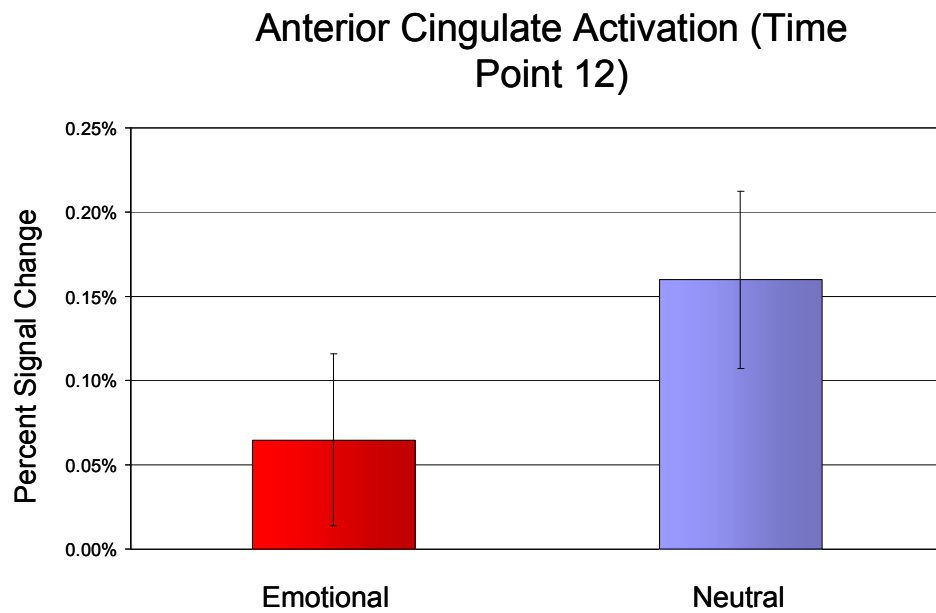
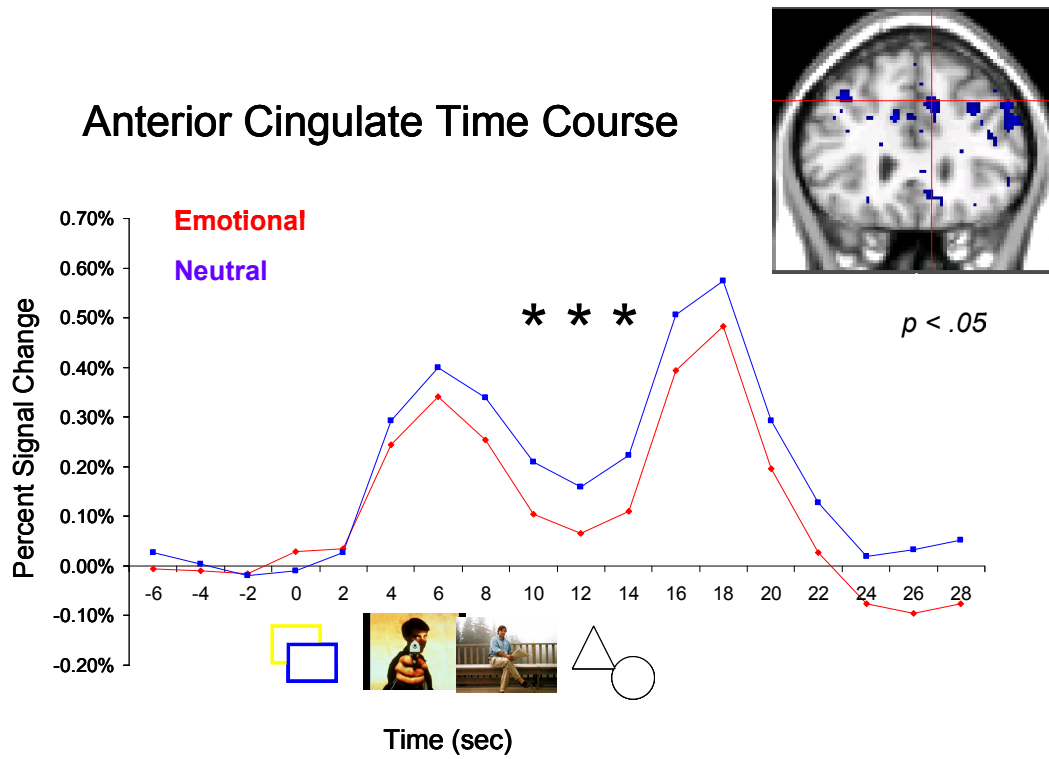


Figure 12. System Interactions during Emotional Distraction

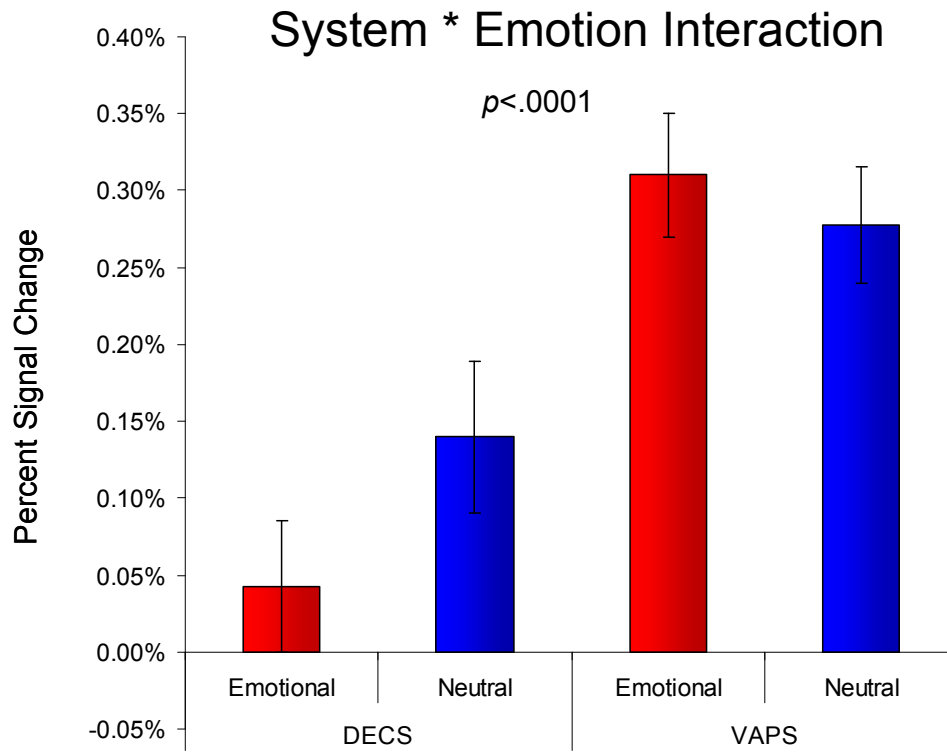


Figure 13. Control Group Accuracy during Low Memory Load

Control Group Accuracy during Low Memory Load

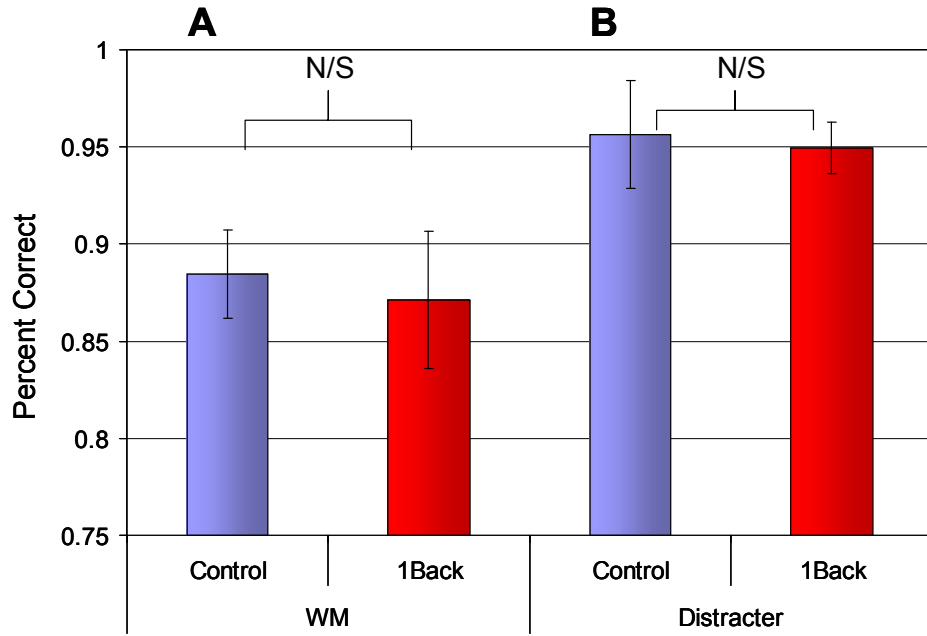


Figure 14. Control Group Accuracy during High Memory Load

Control Group Accuracy during High Memory Load

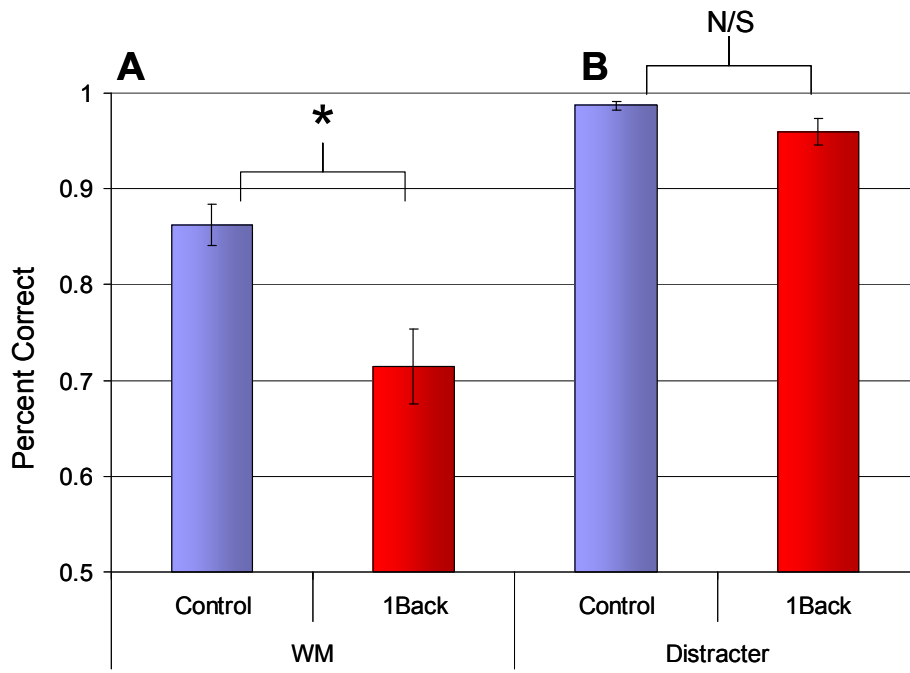


Figure 15. Accuracy in Group with Schizophrenia

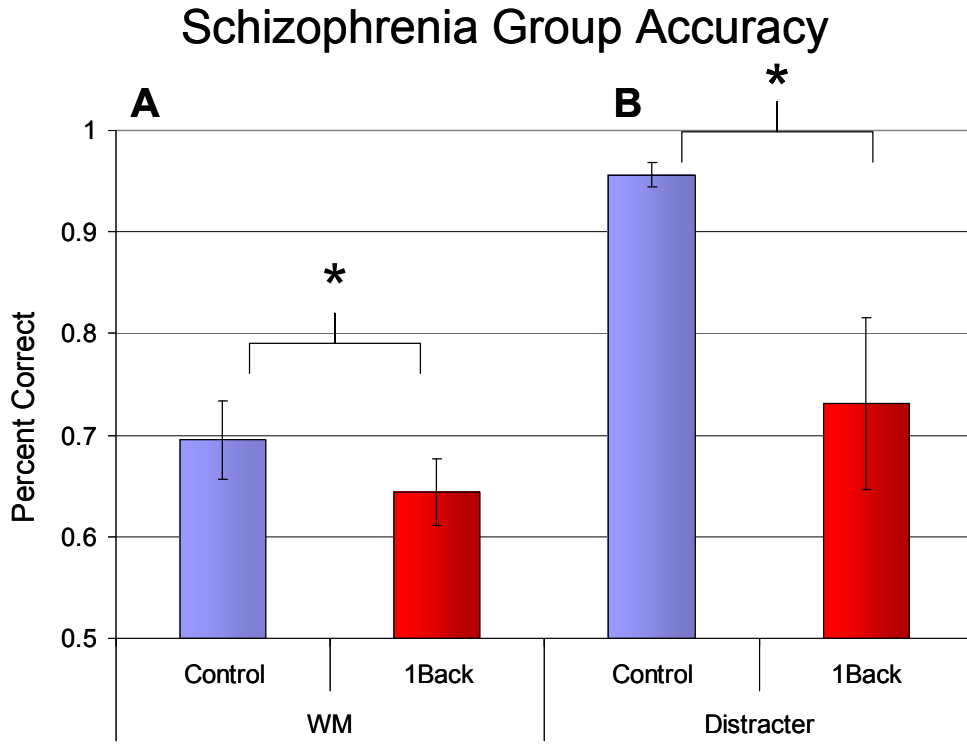


Figure 16. Group Differences on Working Memory

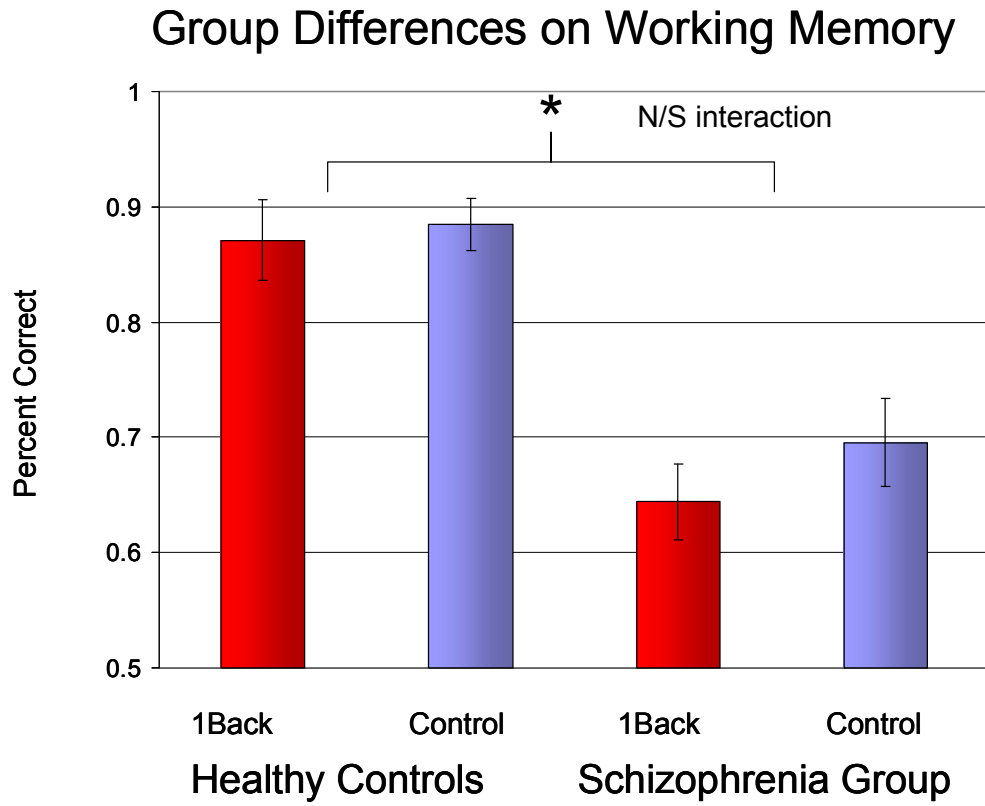


Figure 17. Group Differences on Distracter Task

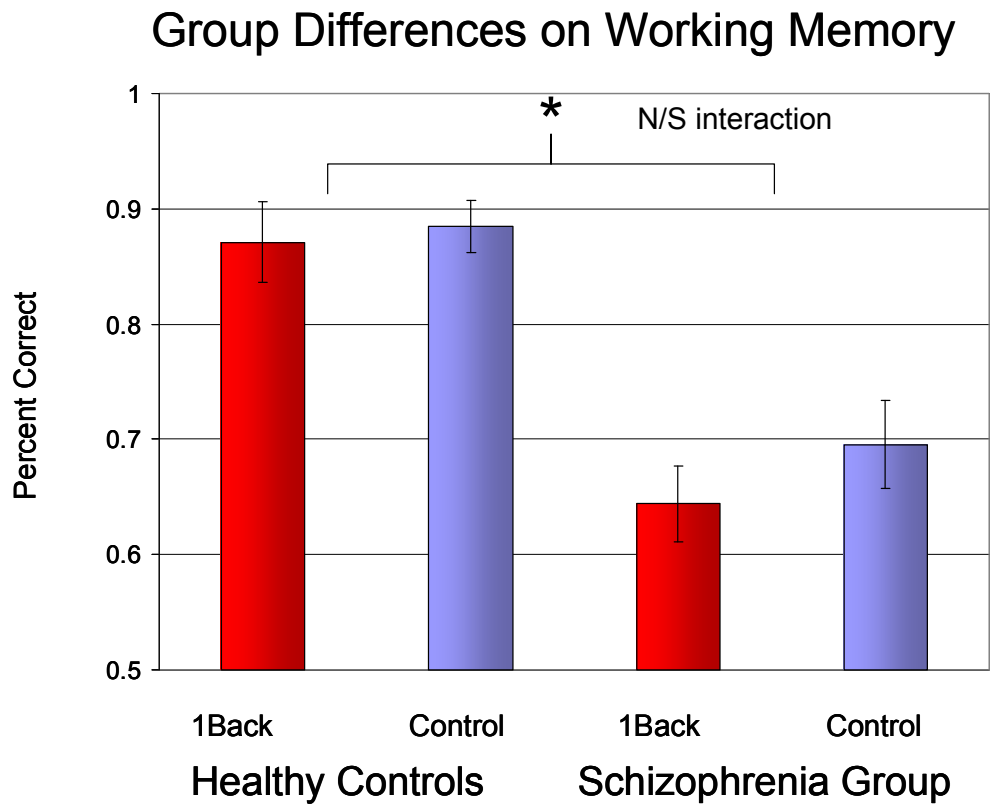


Figure 18. Trade-Offs in Performance (Control – One-Back)

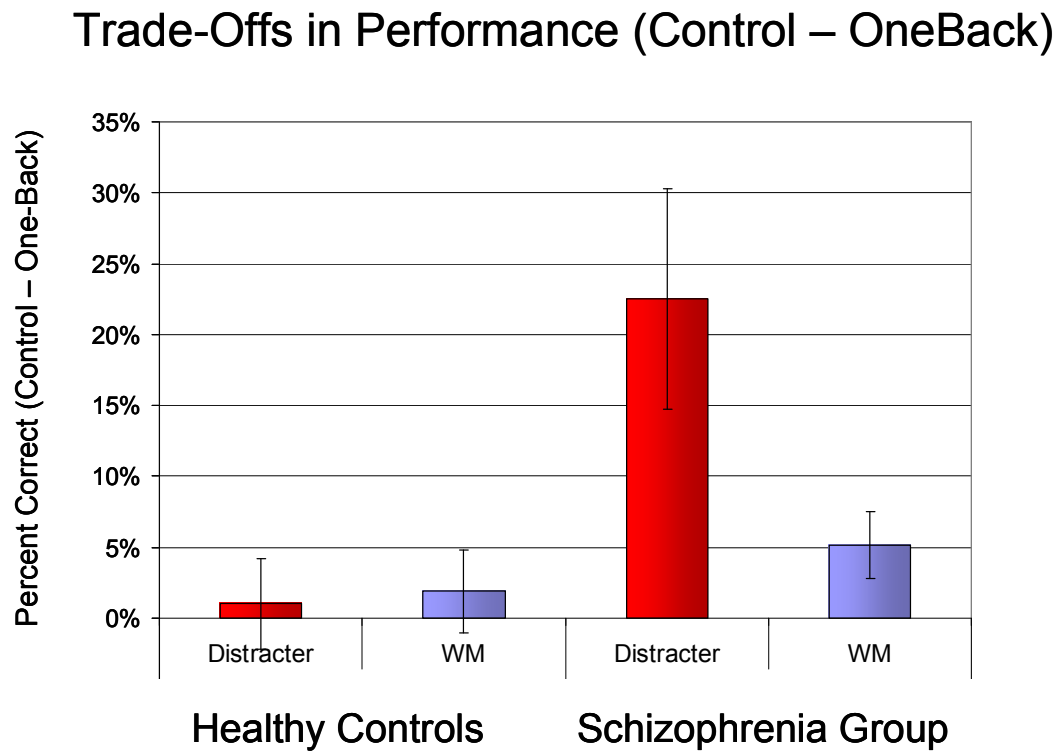


Figure 19. Accuracy in Control Group during Emotional Distraction

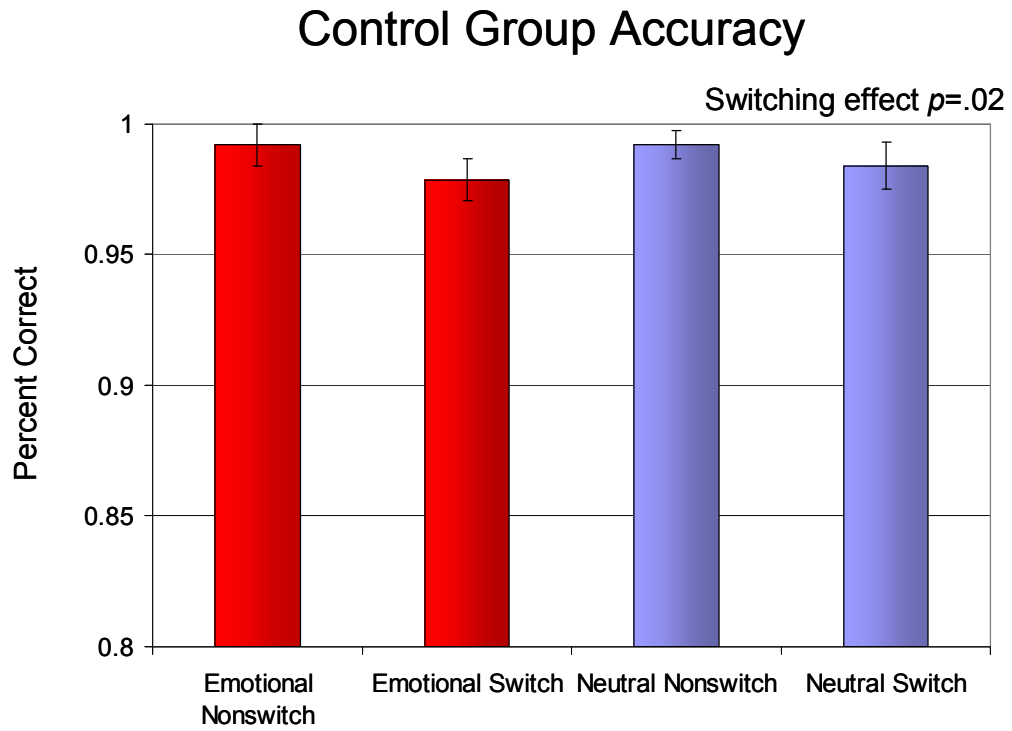


Figure 20. Accuracy in Group with Schizophrenia during Emotional Distraction

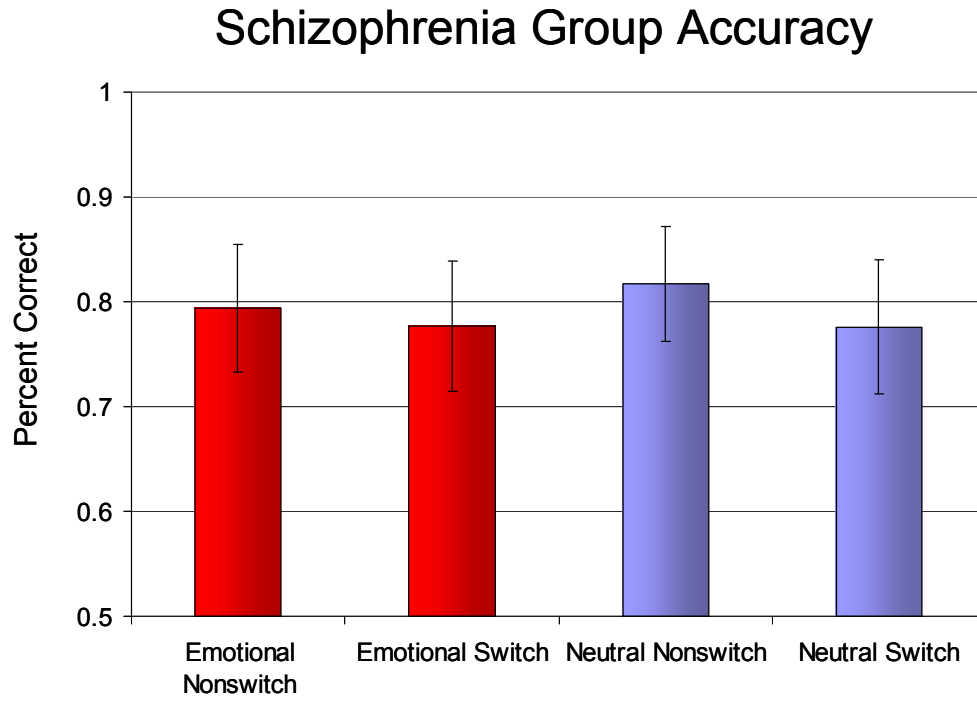
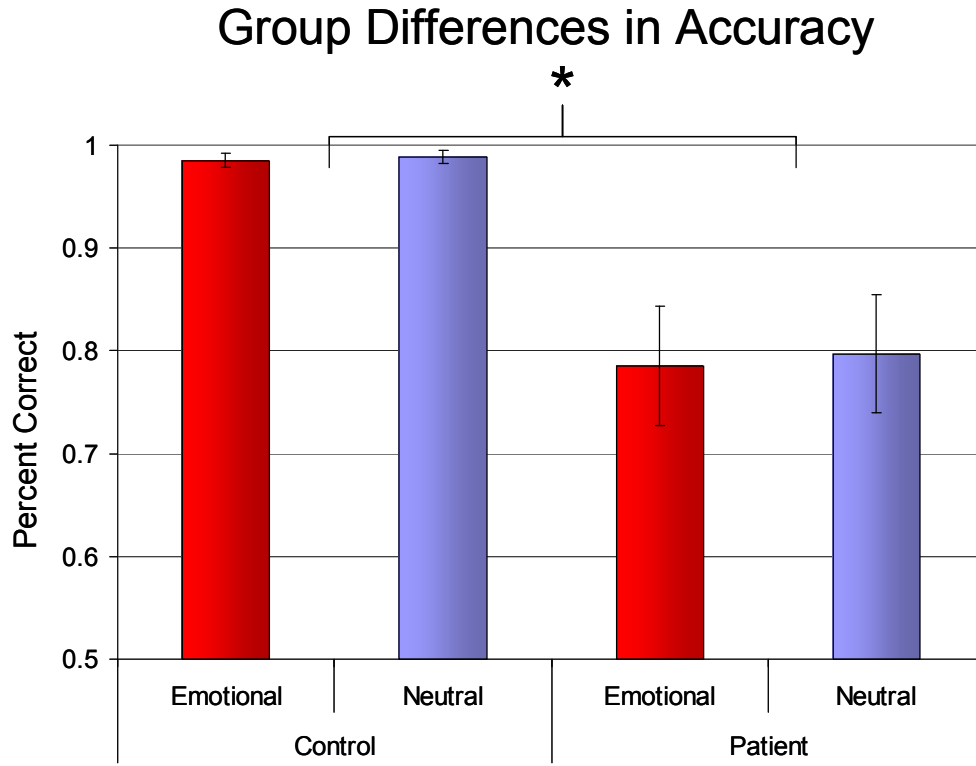


Figure 21. Group Differences in Accuracy during Emotional Distraction



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