August 2016

Neural Circuitry Underlying the Intrusion of Task-irrelevant Threat into Working Memory in Anxiety

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by

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A Dissertation Submitted in

Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

in Psychology

at

The University of Wisconsin-Milwaukee

August 2016

ABSTRACT

NEURAL CIRCUITRY UNDERLYING THE INTRUSION OF TASK-IRRELEVANT THREAT INTO WORKING MEMORY IN ANXIETY

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The University of Wisconsin-Milwaukee, 2016
Under the Supervision of Professor Christine L. Larson

Dispositional anxiety is an important risk factor for the development of anxiety and other psychological disorders. Symptoms commonly expressed by highly anxious individuals include intrusive memories, uncertainty, and worry — all occurring in the absence of immediate threat. This raises the possibility that anxious individuals have difficulty governing threat's access to working memory, the mental workspace where goal-related information is actively retained for guiding on-going behavior. Using functional magnetic resonance imaging (fMRI) while 81 subjects completed a well-validated working memory task, I show that threat-related and neutral distracters unnecessarily gain access to working memory, as evidenced by increased neural activity in the fusiform face area and the posterior parietal cortex. Critically, this pattern was exaggerated in individuals with high levels of self-reported dispositional anxiety. Moreover, an amygdala-based circuit mediated this anxiety- related unnecessary storage. These results provide evidence for a novel neural circuit that subserves impaired working memory filtering of threat-related distracters, and sets the stage for understanding the maladaptive cognitive profile characteristic of extreme anxiety.

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ACKNOWLEDGEMENTS

I would like to thank those who helped me along the way so that I could make it to this point. I first want to thank my advisor, Dr. Christine Larson for giving me the space to pursue my research goals, and bringing me into the world of affective neuroscience. More importantly, I want to thank her for being undoubtedly, the most amazing advisor and mentor that any young scientist could ask for. I also want to thank Dr. Alexander Shackman. His support and guidance has been highly influential in shaping my approach to science. Thanks to the members of my dissertation committee: Dr. Adam Greenberg, Dr. Deborah Hannula, Dr. Han Joo Lee, and Dr. Ira Driscoll for all the advice and direction they gave to me during this project. Thanks to my lab mates: Emily Belleau, Lauren Taubitz, Walker Pedersen, Tara Miskovich, and Kevin Haworth for all the hours we shared together learning to become psychologists and neuroscientists. Many thanks to all my friends and family for the support they have given me during these past several years. Finally, I want to give a special thanks to my wonderful wife Olivia and to my daughter Emily. They have been the primary source of inspiration, motivation, and strength that got me through the numerous challenges I faced during the last five years. Specifically, I thank Olivia for encouraging me to go back to graduate school to pursue my dreams. Without her, none of this would have been possible.

INTRODUCTION

Anxiety disorders are highly prevalent, debilitating, and associated with substantial morbidity and mortality, making them a growing concern for clinicians, health economists, and public policy makers (Collins et al., 2011; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Whiteford et al., 2013). The total societal burden of anxiety disorders is extremely high, with yearly costs surpassing $42 billion (DiLuca & Olessen, 2014; Greenberg et al., 1999) and up to a third of anxiety patients do not benefit from available treatments (Bystritsky, 2006). Thus, more work is necessary to understand the basic mechanisms behind the etiology and maintenance of pathological anxiety.

Dispositional or temperamental anxiety is a well-established risk factor for the development of anxiety disorders as well as co-morbid depression and substance abuse (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014; Fox & Kalin, 2014; Kotov, Gamez, Schmidt, & Watson, 2010; Ormel, Riese, & Rosmalen, 2012). Dispositional anxiety is a multidimensional collection of traits that emerges early in life, and reflects exaggerated and stable cognitive, behavioral, and biological reactivity to mild threat (Barlow, Ellard, Sauer-Zavala, Bullis, & Carl, 2014; Bieling, Antony, & Swinson, 1998; Fox & Kalin, 2014); with each of these dimensions likely reflecting dissociable neural circuits (Bijsterbosch, Smith, Forster, John, & Bishop, 2014; Shackman et al., 2013). In the cognitive domain, many of the symptoms expressed by anxious individuals occur when there is no direct physical threat present in the immediate environment (Davis, Walker, Miles, & Grillon, 2010; Thiruchselvam, Hajcak, & Gross, 2012) and include anxious apprehension, intrusive memories/thoughts, expectation of negative outcomes, uncertainty, and worry (Barlow, 2004; Browning, Behrens, Jocham, O'Reilly, & Bishop, 2015; Grupe & Nitschke, 2013).

These maladaptive cognitive symptoms are highly debilitating, as they serve only to increase negative affect, promote avoidant behavior, and emotion dysregulation, despite the absence of imminent threat (Barlow, 2004; Duits et al., 2015). Here and in other work, I propose that a potential neurocognitive mechanism underlying the debilitating cognitive symptoms characteristic of dispositional anxiety, and the anxiety disorders, is the difficulty controlling the access of task- irrelevant information in working memory, particularly if that irrelevant information is threat-related (Stout, Shackman, & Larson, 2013; Stout, Shackman, Johnson, & Larson, 2015).

Anxiety-related working memory filtering deficit

Working memory is a limited capacity workspace that evolved to support the internal maintenance and manipulation of task sets and other goals (Baddeley, 2012; Carruthers, 2013; Cowan, 2005). Adaptive behavior and cognition necessitate the internal representation of these sets in working memory when there is potential for distraction and competition from multiple sources of interference (D’Esposito & Postle, 2015; D'Ardenne et al., 2012; Miller and Cohen, 2001). Theories of working memory have placed a significant role of attentional control in governing the information that is granted access to working memory (Cowan, 2005; Engle, 2002; Oberauer, 2002; Postle, 2006; 2015). Consistent with this, tasks that assess the storage capacity of working memory are thought to measure the amount of information in the focus of attention (Cowan, 2001; Lewis-Peacock & Postle, 2012; Majerus et al., 2015; Postle, 2015; Tsubomi, Fukuda, Watanabe, & Vogel, 2013). Likewise, some investigators equate measures of working memory capacity with attentional control (Engle, 2002; Kane, Conway, Hambrick, & Engle, 2007; Shipstead, Lindsey, Marshall, & Engle, 2014). Neurobiologically, the neural systems governing

attentional control and working memory highly overlap within the frontoparietal network, suggesting these processes are intimately linked at the neural level (Ikkai & Curtis, 2011; Gazzaley & Nobre, 2012; Awh, Vogel, & Oh, 2006). Therefore, for successful goal-directed action, intact attentional control is critical for selecting relevant information for continued processing in working memory, and preventing irrelevant information from being unnecessarily stored in this important memory buffer (Chun, 2011; Cowan, 2008; Kane, Conway, Hambrick, & Engle, 2007; Vogel, McCollough, & Machizawa, 2005).

It should be noted that certain forms of distracting information, particularly threat-related, necessitate the reorienting of attention that temporarily disrupts on- going behavior. This is critical for determining the biological relevance of distracting stimuli and whether it warrants further processing in working memory (Corbetta, Patel, & Shulman, 2008). Consistent with this, recent neuroimaging research indicates that threat-related distracters presented during working memory delay intervals are difficult to filter, and subsequently disrupt task-relevant working memory (Banich et al., 2010; Dolcos et al., 2013; Iordan, Dolcos, & Dolcos, 2013; Ziaei, Peira, & Persson, 2014). Although it may be adaptive to halt goal-directed action to attend to potentially threatening stimuli to determine their relevance, it is also necessary to disengage further processing once it is deemed irrelevant (Sheppes, Luria, Fukuda, & Gross, 2012). If task-irrelevant information is unsuccessfully gated from working memory, a consequence is that it can compete for the same mental workspace where goal-relevant information is maintained (McNab & Klingberg, 2008; Vogel et al., 2005).

From a translational perspective, this model may provide a neurocognitive explanation for the cognitive symptoms characteristic of dispositional anxiety and the

anxiety disorders. Anxious individuals over-attend to and have difficulty disengaging from mild threat, even when not necessary to the task at hand (Bishop, Duncan, Brett, & Lawrence, 2004; Sheppes et al., 2013). I propose that a consequence of this deficit is that anxious individuals also more readily allow task- irrelevant threat to gain access to working memory. Once irrelevant and threat- related information is allowed undue access to working memory, it may compromise online goal-directed processing and hijack neural resources to favor task-irrelevant processing. Here it can be maintained and further elaborated on, long after the threat-stimulus is removed from the environment — prolonging negative affect, promoting mood-congruent memory recall, and worry (Bomyea, Amir, & Lang, 2012).

This proposed anxiety-related working memory gating deficit is also consistent with a key tenant of one of the most prominent neurocognitive models of anxiety, the attentional control theory (ACT; Eysenck & Derakshan, 2011; Eysenck, Derakshan, Santos, & Calvo, 2007). According to ACT, anxious individuals have problems with cognitive and behavioral efficiency because task-irrelevant and worrisome cognitions are active in working memory. This unnecessary storage of irrelevant information in working memory requires compensatory attentional control to overcome this load (often reflected by increased neural activity in frontoparietal regions), and to perform at the same level as their non-anxious peers (Basten, Stelzel, & Fiebach, 2012; Berggren & Derakshan, 2013; Fales et al., 2008). Until recently, there has been little empirical evidence that anxious individuals are unnecessarily storing irrelevant information in working memory (Stout et al., 2013; 2015; Qi, Ding, & Li, 2014).

For example, I conducted one of the first studies to directly test this hypothesis

(Stout et al., 2013). In that study, I recorded an event related potential component (ERP) called the contralateral delay activity (CDA) while subjects completed an emotional variant of the change detection task. The CDA is a well- validated ERP measure of the number of items stored in working memory (Vogel & Machizawa, 2004; Vogel et al. 2005). I harnessed the CDA to assess the ability of anxious individuals to prevent neutral and threat-related face distracters from gaining access to working memory. When distracters are added to this task, the CDA can assess whether the distracters are stored in working memory (Vogel et al. 2005). I found that on average, threat-related distracters but not neutral distracters were difficult to filter, as indexed by an increase in the CDA amplitude for threat distracters compared to a no distracter condition. Importantly, this pattern was exaggerated in individuals with elevated levels of dispositional anxiety. In a subsequent study, I found behavioral evidence that individual differences in worry are associated with difficulty controlling the access of threat to working memory (Stout et al., 2015). These studies provide some of the first evidence supporting the hypothesis individuals with elevated dispositional anxiety mis-allocate working memory storage to task-irrelevant threat, and that this could be a key mechanism underlying the cognitive symptoms of anxiety. However, no study to date has delineated the neural architecture subserving this.

Neural correlates of unnecessary storage

In the present study, I used a well-established task (see Figure 1) that measures the attentional capacity of working memory (Majerus et al., 2015; McNab & Klingberg, 2008; Stout et al., 2013; 2015; Vogel et al. 2005) to directly test whether dispositionally anxious individuals have difficulty preventing threat- related face distracters from gaining access to working memory, and to characterize the neural systems subserving this. I focused on two

key regions important for face working memory processing, the fusiform face area (FFA) and the posterior parietal cortex (PPC).

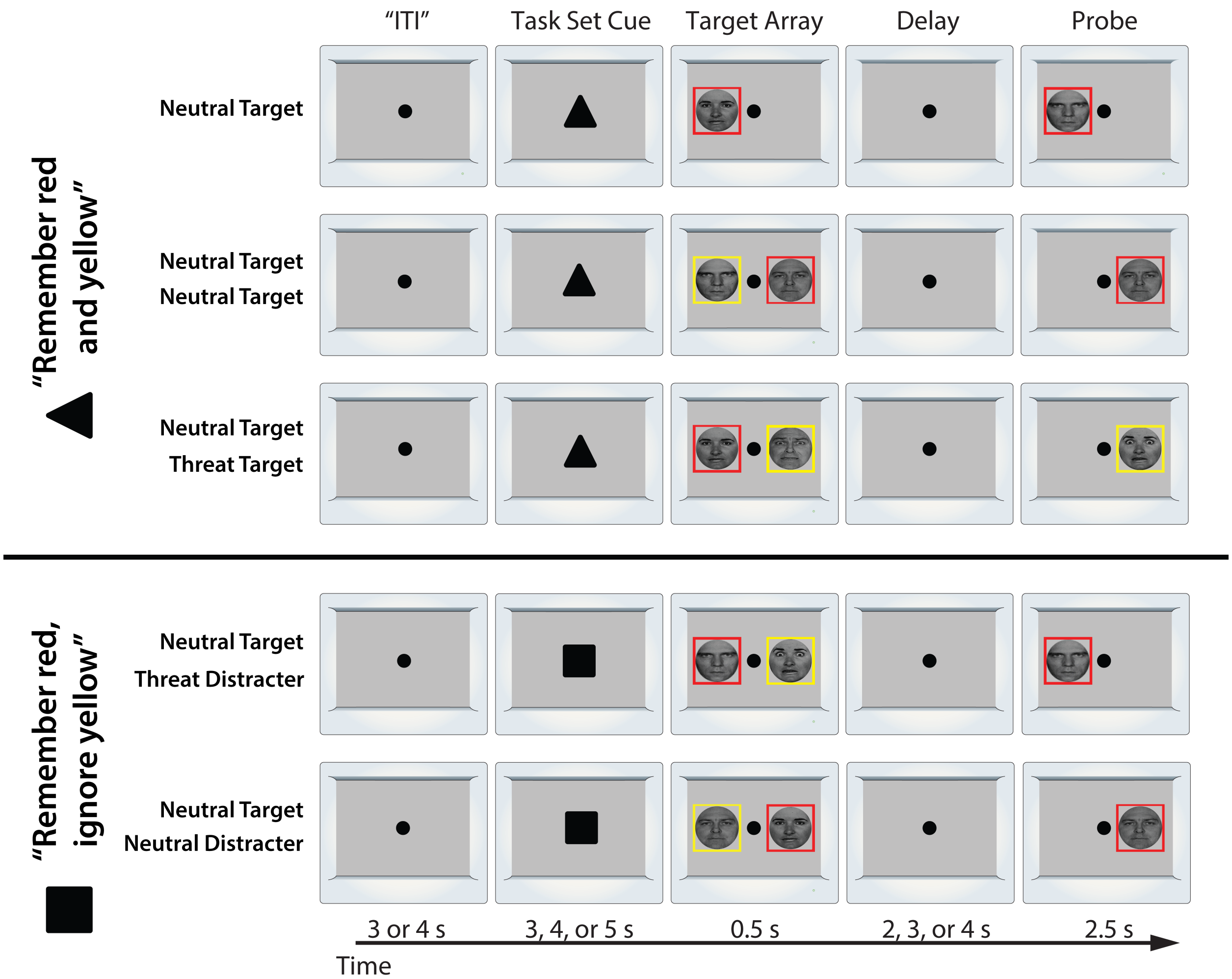

Figure 1. Rows depict conditions from the working memory change detection task. The trial sequence began with a variable fixation cross (3 or 4 s), followed by a task-set cue (3, 4, or 5s). Participants were instructed to remember all upcoming faces stimuli (top three rows) or to remember the face in red and ignore the face outlined in yellow (last two rows; colors counterbalanced). Next, the memory array was briefly presented (500 ms) followed by a variable delay interval (2, 3, or 4 s) representing the delay period of working memory. Finally, a single-probe face was presented (2.5 s) where participants were asked to identify whether the target face changed while the expression (i.e., fearful or neutral) did not. Portions of this figure were adapted from a figure originally published in Stout et al. (2013).

According to neurobiological models of working memory, short-term representation of information in working memory is stored in sensory specific regions (e.g., fusiform face area; [FFA] for faces) (Druzgal & D'Esposito, 2003; LaRocque, Lewis-Peacock, Drysdale, Oberauer, & Postle, 2013; Lewis-Peacock & Postle, 2012; Ranganath, DeGutis, & D'Esposito,

2004; Postle, 2015). Lesion and imaging data show that the FFA mechanistically contributes to face perception (Kanishwer, McDermott, & Chun, 1997), maintains face-specific representations in working memory (Han, Berg, Oh, Samaras, & Leung, 2013), and is sensitive to the number of faces held in working memory (Druzgal & D'Esposito, 2003; Jackson, Wolf, Johnston, Raymond, & Linden, 2008).

The posterior parietal cortex (PPC) is a critical hub in the working memory network and has been shown to track working memory load (Todd & Marois, 2004; 2005; Xu & Chun, 2004) including the unnecessary storage of distracters (Edin et al., 2009; McNab & Klingberg, 2008), and predicts individual differences in working memory capacity (Vogel & Machizawa, 2004; Todd and Marois, 2005). Moreover, the PPC is the putative neural generator of the contralateral delay activity (Becke, Müller, Vellage, Schoenfeld, & Hopf, 2015; Robitaille et al., 2010), an ERP component sensitive to working memory load (Vogel et al. 2004; 2005) that I have recently found to be enhanced to threat-related face distracters (Stout et al., 2013). The function of PPC activity in working memory tasks is currently debated — some research shows it reflects objects remaining in the focus of attention and not item- level maintenance (Killebrew, Mruczek, & Berryhill, 2015; Lewis-Peacock & Postle, 2012; Postle, 2015; Tsubomi et al., 2013), while other research shows that it does track the short-term retention of item-specific information (Christophel, Hebart, & Haynes, 2012; Li, Christ, & Cowan, 2014). Regardless of the interpretation, PPC activity in change detection tasks, like the one used in the current study, is a critical region of interest for assessing working memory load for both relevant and irrelevant information (Ikkai & Curtis, 2011; McNab & Klingberg, 2008). I therefore examined whether the PPC would also track undue storage of task-irrelevant face distracters.

To this end, FFA and PPC activity were measured using an emotional variant of the well-validated change-detection working memory task (Vogel et al., 2005). Subjects were instructed to selectively retain one or more faces (target only conditions), or to remember one and ignore another (distracter present conditions) across a delay (Stout et al., 2013; 2015) before determining whether a probe face was identical to the previously presented target face. Faces were either threat- related (i.e., fearful; Whalen, 1998) or emotionally neutral. Because this task has been shown to be sensitive to the number of items retained in working memory (Luck & Vogel, 1997; Vogel & Machiazawa, 2004; Todd & Marios, 2004), FFA and PPC activity served as a direct neural measure of whether or not the threat-related distracters were unsuccessfully filtered, and therefore unnecessarily stored in memory. For example, on trials in which one target face is presented simultaneously with a threat-related distracter (Neutral Target + Threat Distracter), if an individual was perfectly adept at filtering the task-irrelevant threat distracter and storing only the neutral target, then PPC and FFA activity should be equivalent to that for remembering one neutral target face presented alone (1 Neutral Target). In contrast, if an individual completely failed to filter the irrelevant threat-related distracter, both the task-relevant target and the threat-related distracter (Neutral Target + Threat Distracter) would be retained in working memory, resulting in FFA and PPC activity equivalent to the two target condition (Neutral Target + Threat Target). Based upon my previous work (Stout et al., 2013; 2015), I predicted that individuals high in dispositional anxiety, as measured by the well-validated State- Trait Anxiety Inventory (STAI; Spielberger et al., 1983), would display increased FFA and PPC activity for threat distracters (Neutral Target + Threat Distracter) relative to a single neutral target (1 Neutral Target), indicating a failure to

filter threat from entering working memory.

Although characterizing the neural circuitry associated with the intrusion of task-irrelevant faces in working memory is the primary aim of the current project, there is also a need to identify the mechanisms promoting this. To this end, I investigated whether the unnecessary storage in working memory by threat-related distracters is driven by heightened amygdala engagement.

An amygdala-based threat gating mechanism

In Stout et al. (2013), I hypothesized that difficulties filtering task-irrelevant threat are a consequence of an amygdala-driven attentional bias to threat. The amygdala may enhance processing of threat-cues via robust projections to the visual cortex (Freese & Amaral, 2009; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). Indeed, functional connectivity between these two regions is increased when attending to threat cues (Mohanty, Egner, Monti, & Mesulam, 2009; Noesselt, Driver, Heinze, & Dolan, 2005) and threat-induced recruitment of the amygdala precedes enhanced activation of visual cortex (Pourtois, Schettino, & Vuilleumier, 2013; Sabatinelli et al., 2014; Sabatinelli, Lang, Bradley, Costa, & Keil, 2009). Moreover, variation in amygdala activation also predicts the reorienting of attention to threat- related cues (Gamer and Büchel, 2009) and the trial-by-trial detection of threat—an effect mediated by activation in the visual cortex (Lim, Padmala, & Pessoa, 2009).

Research suggests that a central mechanism in dispositional anxiety and the anxiety disorders is the amygdala-driven over-allocation of attention to threat- related cues when they are present in the immediate environment (Calder, Ewbank, & Passamonti, 2011; Cisler & Koster, 2010); even when this comes at the expense of task-goals and on-going

behavior (Bishop et al., 2004; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010). This attentional bias to threat has been proposed to be a specific causal risk factor for the development and maintenance of anxious psychopathology (Hoffmann, Ellard, & Siegle, 2012; MacLeod & Mathews, 2012; Swartz, Knodt, Radtke, & Hariri, 2015; Shechner et al., 2012). Supporting this hypothesis, dispositional anxiety is associated with increased amygdalar volume (Blackford et al., 2014; Clauss et al., 2014), exaggerated reactivity to threat-cues (Bishop, 2008), and novelty, compared to their non-anxious peers (Blackford et al., 2013).

Collectively, these data suggest that the amygdala plays a prominent role in the processing of threat-cues, particularly in those with elevated anxiety. Based on this evidence, I predicted that the unnecessary storage of threat-related distracters in working memory regions of the FFA and PPC would be associated with enhanced amygdala activation. Likewise, I further predicted that this amygdala activity would mediate the relationship between dispositional anxiety and threat-distracter unnecessary storage. Specifically, I predicted that after controlling for amygdala activity for threat-distracters, the relationship between dispositional anxiety and activity in both the FFA and PPC would be significantly reduced.

Secondary analyses

Beyond the primary goal of identifying the neural circuitry underlying the unnecessary storage of threat-related distracters in working memory, I conducted two secondary analyses to better characterize the neural circuitry promoting the effects of unnecessary storage.

Corticostriatal gating. Activity in corticostriatal circuitry is thought to serve as a

gatekeeper to working memory (Awh & Vogel, 2008; Baier, Karnath, Dieterich, Birklein, Heinze, & Müller, 2010). Indeed, input and output gating signals from corticostriatal networks have been associated with reduced distracter processing in visual cortex and reduced storage of distracters in the PPC (Chatham , Frank, & Badre, 2014; Suzuki & Gottlieb, 2013). Consistent with this, patients with lesions of the basal ganglia show increased difficulty gating affectively-neutral distracters and maintaining task-relevant information in working memory (Baier et al., 2010; Voytek & Knight, 2010). Moreover, in a study to specifically identify preparatory gating signals important for working memory filtering, McNab and Klingberg (2008) found that decreased preparatory activity in the basal ganglia was associated with increased distracter storage in the PPC.

The current study included a preparatory task-set cue that preceded the memory array, signaling whether the oncoming faces were task-relevant or task- irrelevant. This design allows for the examination of neural activity associated with the preparation to filter on-coming face-distracters from entering working memory (McNab & Klingberg, 2008). Since a growing body of research has found that dispositional anxiety is characterized by difficulties filtering task-irrelevant information from working memory (Stout et al., 2013; 2015; Qi et al., 2014), identification of the mechanisms underlying this deficit is important. Therefore, I performed a whole-brain mediation analysis to examine whether anxious individuals unduly allow distracters to enter working memory as a result of aberrations in the corticostriatal preparatory working memory filtering network. If dispositional anxiety was indeed associated with a preparatory deficit, I predicted that activity within the cue-period would mediate the relationship between dispositional anxiety and unnecessary storage of distracters in working memory.

Compensatory frontoparietal recruitment. According to the attentional control theory, dispositional anxiety is associated with cognitive and behavioral inefficiency (Eysenck & Derakshan, 2011; Eysenck et al., 2007). This inefficiency is hypothesized to occur because of the increased working memory load by worrisome cognitions. This pattern of behavior is accompanied by an increase in attentional control to compensate for the inefficiency. Indeed, research has shown that dispositionally anxious individuals over-recruit frontoparietal regions when performing challenging cognitive tasks, despite the absence of any overt behavioral differences (Basten et al., 2012; Owens, Derakshan, & Richards, 2015). As a test to this theory, I directly compared neural activity within the frontoparietal network between the threat-distracter and neutral distracter conditions. If anxious individuals require increased recruitment of attentional control to overcome distraction, I predicted that dispositional anxiety will have a positive association with frontoparietal regions in response to threat versus neutral-related distracters.

Summary of aims

To summarize, the primary aim of this project was to examine the neural circuitry associated with the anxiety-related failure to filter task-irrelevant threat from gaining access to working memory. To this end, I examined the relationship between dispositional anxiety and working memory filtering of threat distracters in the FFA and the PPC, key regions for the storage of information in working memory (Druzgal & D'Esposito, 2003; LaRocque et al., 2013; Lewis-Peacock & Postle, 2012; Ranganath et al., 2004; Postle, 2015). If dispositional anxiety is associated with a failure to filter threat distracters, activity in working memory storage regions of the FFA and PPC will be increased. Based upon my previous findings (Stout et al., 2013), I also examined whether an amygdala-based circuit

promotes the unnecessary storage of threat-distracters.

Finally, I performed two secondary analyses to better characterize the neural correlates underlying the unnecessary storage of distracters in dispositional anxiety: (i) I performed a whole-brain mediation analysis to determine whether a preparatory corticostriatal filtering deficit underlies an anxiety-related failure to filter irrelevant threat from working memory. (ii) I tested whether threat- distracters, relative to neutral distracters, require additional recruitment of the frontoparietal network (Clarke & Johnstone, 2013; Dolcos & McCarthy, 2006), consistent with a primary prediction of the ACT of anxiety (Berggren & Derakshan, 2012; Eysenck & Derakshan, 2011; Eysenck, Derakshan, Santos, & Calvo, 2007).

METHOD

Participants

A total of 105 subjects underwent functional magnetic resonance imaging (fMRI) at the Medical College of Wisconsin. Exclusion criteria were bipolar or psychotic disorders. Other exclusion criteria were history of neurological disorder, head injury, or and any fMRI environment contraindications (i.e., metal in body, electronic implants, metallic tattoos, pregnancy). From this sample, 81 subjects (mean age = 22.54, SD = 4.08; 53 women) were included in the final analyses after removing participants due to scanning technical problems (n = 2), excessive motion artifact (n = 16), or poor performance (below chance) on the working memory task (n = 6). All study procedures were approved by the University of Wisconsin- Milwaukee's and the Medical College of Wisconsin's Institutional Review Boards. Subjects were monetarily compensated for completion of the study.

Table 1. Subject Demographics (n = 81)

	Mean (*SD*)	Range
Age	22.54 (4.08)	18 - 35
STAI	39.61 (10.91)	21 - 66
CES-D	12.85 (11.32)	0 - 46

STAI = State Trait Anxiety Inventory;
CES-D = Center of Epidemiological Studies of Depression Scale

Quantifying anxiety

All subjects completed the trait version of the STAI (Spielberger et al., 1983). The STAI is 20-item measure of trait/dispositional anxiety (e.g., *Some unimportant thought runs through my mind and bothers me*; *I take disappointments so keenly that I can't put them out of my mind*; *I worry too much over something that really doesn't matter*). The STAI has been shown to exhibit high internal-consistency reliability (α= .89) and test-retest stability (r = .88; Barnes et al., 2002). Participants also completed the Center of Epidemiological Studies of Depression Scale (CES-D; Radloff, 1977) for the purpose of assessing depressive symptoms. Mean scores (*SD*) were: STAI = 39.10 (11.27; range 21 – 66), and CES-D = 12.85 (11.32; range - 46). For the STAI, scores above 47 have been found in patients meeting criteria for anxiety disorders (Bieling et al., 1998). For the CES-D, cutoff scores above 16 have been shown to characterize clinical versus sub-clinical levels of depression (Radloff, 1977). Thus, the large range found in the current sample for both of these measures indicates a full-spectrum of dispositional anxiety and depressive symptoms severity is represented. These measures were also highly correlated, $r = .84$, $p < .0001$. See Table 1 for subject demographics.

Working memory task and design

The change detection working memory task was adapted from prior ERP and fMRI

research (McNab & Klingberg, 2008; Sessa et al., 2011; Stout et al., 2013; 2015) to examine the neurocircuitry associated with measuring the attentional capacity of the contents in working memory. Black-and-white (luminance equated) face stimuli from Ekman and Friesen's (1976) set (n = 8) and the MacBrain Face Stimulus Set (n = 18) (NimStim; http://www.macbrain.org/faces) were used.

Each trial (see Figure 1) began with a 3-4 s fixation cross, followed by a shape cue (square or triangle) (3, 4, or 5 seconds) instructing participants to either remember all the faces (target only condition) that will appear, or remember an oncoming target face and ignore the other face (distracter condition). Next, participants viewed the memory array where one or two faces were briefly presented (500 ms) in a red or yellow outlined box. Faces were either neutral or threat-related (i.e., fearful; Davis and Whalen, 2001; Whalen, 1998). On target only trials, the red and yellow outlined faces both served as targets. On distracter trials, the yellow outlined face served as a distracter, and allowed for the assessment of unnecessary storage of task-irrelevant information in working memory. The relationship between task-relevance and the color of the box was counterbalanced across subjects. Location (left vs. right) of the colored boxes was counterbalanced across trials. The memory array was followed by a 2, 3, or 4 second delay interval, and finally a single-probe display was presented in which the participant indicated whether the probe-face was the same or different (equiprobable) from the target face that appeared in the memory array.

To examine the extent to which individual differences in anxiety predict the ability to gate task-irrelevant distracters from working memory, the task included conditions with threat-related distracters (1 Neutral Target + 1 Threat (Fear) Distracter) or neutral

distracters (1 Neutral Target + 1 Neutral Distracter). Comparing these conditions to a condition with a single neutral target allowed for examination of unnecessary storage of face distracters (detailed below). Two additional target-only conditions were included (i.e., 2 Neutral Targets, and 1 Neutral Target + 1 Threat (Fear) Target). It should be noted that the memory array for the distracter and target-only conditions (e.g., 1 Neutral Target + Threat Distracter, and 1 Neutral Target + 1 Threat Target respectively) were perceptually matched — the only difference between these conditions were the instruction cue establishing the task-set of remembering only a single target and gating a distracter, or remembering both faces in the array.

Subjects performed 20 practice trials outside of the scanner before completing 140 total experimental trials presented (pseudo-randomized) in an event-related design (40 trials each/distracter conditions and 20 trials each/target- only conditions), separated across four imaging runs.

MRI Data Acquisition

fMRI data were acquired on a 3.0 Tesla GE scanner equipped with a high- speed eight channel birdcage headcoil. Whole-brain functional T_2*-weighted echo- planar images (EPI) were collected during the working memory task (41 interleaved sagittal slices; repetition time [TR] = 2000 ms, echo time [TE] = 25 ms, flip angle [α] = 77°, field of view [FOV] = 240 mm, matrix = 64 x 64, slice thickness = 3.5 mm, slice gap = 0 mm). For each of the functional runs (n = 4), 242 EPI images were acquired. High-resolution T_1-weighted whole-brain anatomical images were acquired for coregistration of functional data across subjects using a spoiled gradient-recalled echo scan (150 slices, TR = 8.2 ms; TE = 3.2 ms; α

= 12°; FOV=240 mm; matrix = 256 x 224; slice thickness = 1 mm). An additional face localizer run was collected in order to identify face-sensitive regions of the fusiform gyrus (Kanishwer et al., 1997. For the face localizer run, 133 whole-brain EPI images were acquired using the same scanner parameters described above.

fMRI preprocessing

Data were preprocessed using AFNI (Cox, 1996). The first 3 volumes of each functional run were removed to account for scanner equilibration. The remaining volumes were slice-time and motion corrected. The functional data was normalized to the MNI template by first using an affine-linear registration of the functional images to the high-resolution T_1*-weighted anatomical scan using FSL's FLIRT (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/flirt). Next, the T_1*-weighted anatomical scan was non-linearly registered to the Montreal Neurological Institute (MNI) template using FSLs FNIRT ((http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fnirt)). Finally the non- linear transformation matrix was applied to the functional data for each run. All volumes were spatially smoothed with a 4 mm full-width half-maximum (FWHM) Gaussian kernel and converted to percent signal change.

fMRI analysis

The fMRI data was analyzed using a general linear model (GLM). Two regressors were used for the cue period conditions (distracter condition and target- only condition*)* and modeled with the canonical hemodynamic response. Five separate regressors were used to model working memory storage for each of the five conditions. To capture more than just encoding, working memory storage activity here is defined as the array + delay period (McNab & Klingberg, 2008), and was modeled using the canonical hemodynamic

response, considering the variable duration of the array + delay (2.5, 3.5, 4.5 seconds) period using a boxcar function. A single regressor for the probe stimulus was modeled with the canonical hemodynamic response. Constant, linear, quadratic, and cubic terms were included to model baseline scanner drifts. In addition, regressors of no interest were included to account for head motion and their derivatives. Only trials with correct responses were included (average of 86% trials retained). Percentage of trials removed did not vary with individual differences in anxiety, $r = .12$, $p = .30$.

Functional localizer task

Subjects also completed a whole-brain functional face localizer task. During this scan, participants passively viewed a series of faces or houses in a block design. Each block consisted of 20 faces or houses presented (600 ms each) at fixation, with each block lasting 12 seconds for a total of 12 blocks (6 blocks per stimulus type; 10 s ITI). Preprocessing (e.g., slice-time, motion, registration, etc.) of face localizer task data was identical to the working memory task. A 12 second boxcar function was used to model the face and house regressors separately. Four subjects did not complete this task, leading to a sample size of 77 for the FFA-localizer analysis. A group-level whole-brain repeated measures Face > House *t*-test was computed to locate face sensitive voxels.

Regions of interest definition

FFA. I performed a conjunction analysis to identify face sensitive activity within the FFA that are involved in (i) perceiving faces, as indexed by the independent face localizer task (Faces > Houses), (ii) storing faces, as indexed by the working memory load contrast for affectively neutral target faces (2 Neutral Targets > 1 Neutral Target), and (iii) restricted

to the anatomically-defined temporal occipital fusiform cortex using the Harvard-Oxford probabilistic atlas in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/atlases). For both contrasts, correction of multiple comparisons was completed using a small-volume correction within the anatomical temporal occipital fusiform cortex mask (600 voxels) at a p-threshold < .005. A cluster threshold of 9 voxels was needed to achieve a corrected p-value < .05. Voxels identified from the conjunction analysis (i.e., voxels that overlapped) were used to create a mask for subsequent hypothesis testing. Mean percent signal change from the array + delay period for each condition was extracted from the left (38 voxels) and right (26 voxels) FFA clusters identified by the conjunction analysis.

PPC. For interrogating the posterior parietal cortex, I identified working memory load sensitive voxels for affectively neutral face targets (2 Neutral Targets > 1 Neutral Target) within the anatomically defined bilateral inferior parietal lobule using the Harvard-Oxford Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/atlases). This mask included the important working memory load-sensitive intra-parietal sulcus (Todd & Marios, 2004; Xu & Chun, 2004). Correction of multiple comparisons was completed using a small-volume correction within the mask (1146 voxels) at a p- threshold < .005. A cluster threshold of 13 voxels was needed to achieve a corrected p-value < .05. Mean percent signal change from the array + delay period activity for each condition was extracted from the left and right PPC cluster identified within the inferior parietal lobule mask.

Amygdala. I performed a conjunction analysis to identify face sensitive activity within the bilateral amygdala that are involved in (i) perceiving faces, as indexed by the independent face localizer task, and (ii) from an anatomically- defined amygdala ROI created using the Harvard-Oxford probabilistic atlas in FSL (25% probability threshold). A

large amygdala extent was used to incorporate important threat-processing regions of the amygdala, including the dorsal and extended amygdala (Fox, Oler, Tromp, Fudge, & Kalin, 2015). Correction of multiple comparisons for the localizer task was completed using a small-volume correction within the amygdala atlas mask (166 voxels) at a *p*-threshold < .005. Voxels that overlapped (86 voxels) were used to create a mask for subsequent hypothesis testing. Mean percent signal change was separately extracted from the threat and neutral unnecessary storage contrast (1 Neutral Target + Threat Distracter > 1 Neutral Target; & 1 Neutral Target + Neutral Distracter > 1 Neutral Target).

Hypothesis testing (unnecessary storage)

To test whether dispositional anxiety is associated with a failure to regulate access to working memory, neural indices of FFA and PPC "unnecessary storage" activity (McNab & Klingberg, 2008) were separately computed for the threat and neutral distracter conditions. The logic of this is that if individuals fail to filter task- irrelevant threat, the consequence will be that it will be stored in working memory, and be reflected in these load sensitive regions (McNab & Klingberg, 2008; Vogel et al., 2005). Here, unnecessary storage for threat-related distracters was calculated as the difference in mean percent signal change between trials in which 1 Neutral Target was paired with a Threat Distracter (1 Neutral Target + Threat Distracter) and trials in which 1 Neutral Target was presented. Higher unnecessary storage activity reflects a failure to filter as indexed by excess neural activity in working memory load sensitive regions (i.e., FFA & PPC) associated with storing the distracter in working memory. Likewise, unnecessary storage for neutral distracters was calculated as the difference in FFA and PPC activity between trials in which a neutral target was paired with a neutral distracter (1 Neutral Target + 1 Neutral Distracter) and

trials in which 1 Neutral Target was presented. Unnecessary storage activity near zero reflects successful filtering of distracters from being stored working memory.

Hypothesis testing on relations between dispositional anxiety (i.e., STAI) and unnecessary storage was performed using a series of correlations (two-tailed). To assess the specificity of relations between dispositional anxiety and FFA/PPC unnecessary storage, I computed additional correlations controlling for variation in mean-centered age, sex, maximum working memory capacity (i.e., the maximal Cowan's *K* across any of the three target-only conditions), and depressive symptoms (CES-D). Analyses were performed using SPSS (version 22.0; IBM Inc., Armonk, NY).

Amygdala mediation analysis

To examine whether an amygdala-based circuit influences the unnecessary storage of distracters in working memory, I performed a standard mediation analysis (Baron and Kenny; Preacher & Hayes, 2004; 2008). Specifically, I tested the hypothesis that dispositional anxiety is associated with amygdala reactivity to threat-distracters, which then leads to increased FFA and PPC working memory storage activity. To test this, I statistically examined the following: (i) total effect *c* (dispositional anxiety → FFA/PPC Threat-distracter storage), (ii) path *a* (dispositional anxiety → amygdala activity for Threat Distracters), (iii) path *b* (amygdala activity for Threat Distracters → FFA/PPC Threat-distracter storage, after controlling for dispositional anxiety), and (iv) indirect effect *c'* (dispositional anxiety → FFA/PPC threat distracter storage, after controlling for amygdala activity for Threat Distracters). Significant relationships between the variables followed the logic of Barron and Kenny (1986) but incorporated a non-parametric bootstrapping method (Preacher & Hayes, 2004; 2008; Wager, Davidson, Hughes, Lindquist, & Ochsner,

2008). The mediation effect was examined by computing the 95% bootstrapped (10,000 samples) confidence interval for the product of paths *a* and *b*. Mediation would be satisfied if steps 1, 2, and 3 are statistically significant with a meaningful decrease between paths *c* and *c*' as indicated by step 4 (i.e., the *a**b* 95% confidence interval does not cross zero). I also calculated confirmatory tests of significance using the parametric *Sobel's Z.*

Secondary analyses

Preparatory corticostriatal gating mediation. I performed a whole-brain mediation analysis (Denny, Ochsner, Weber, & Wagner, 2014; Wager et al., 2008) to identify corticostriatal neural activity during the preparatory cue period that statistically mediates the relationship between dispositional anxiety and unnecessary storage of threat in the FFA or the PPC. This mediation analysis was completed to test the hypothesis that a preparatory gating mechanism during the cue period influences anxious individuals' ability to gate irrelevant information from working memory (Stout et al., 2013). This analysis utilized the *Mediation Toolbox* (Wager et al., 2008; http://wagerlab.colorado.edu/tools). This toolbox requires that two of the three variables (i.e., *X*, *Y*, or *M*) be known, and it will conduct a whole- brain search for the unknown variable that satisfies the statistical mediation. Similar to the proposed amygdala-based analysis outlined above, I entered self-reported dispositional anxiety as the predictor variable (*X*), and unnecessary storage FFA/PPC activity, identified from the unnecessary storage contrast ([1 Neutral Target + Threat Distracter] - [1 Neutral Target]), as the outcome variables (*Y*). The preparatory task-set contrast (Distracter Present Cue - Remember-All Cue) served as the proposed mediating variable (*M*) for the purpose of identifying significant voxels across the brain that mediate the effect of dispositional anxiety on unnecessary storage. To test each path

(*a, b, c, c′, and a*b*), bootstrapped 95% confidence intervals were used for significance testing. Thresholding was set at $p < .005$, and whole-brain corrected to achieve a cluster-corrected threshold of $p < .05$.

Compensatory frontoparietal recruitment. To investigate whether dispositional anxiety is related to compensatory activity in frontoparietal regions when confronted with threat-related distracters, I examined the extent to which neural activity differed between threat and neutral distracter conditions. I computed a whole-brain repeated-measures *t*-test comparing 1 Neutral Target + Threat Distracter with 1 Neutral Target + Neutral Distracter. Thresholding was set at $p < .005$. A cluster threshold of 38 voxels was needed to achieve a whole-brain corrected *p*-value < .05. Furthermore, I extracted mean percent signal change from significant clusters identified from the condition contrast, and correlated them with individual differences in dispositional anxiety.

Behavioral Data Analysis

Behavioral indices of working memory capacity was estimated using Cowan's (2001) formula: $K = S \times (H - \text{FA})$, where K is the estimated number of items maintained in WM, S is the set-size of the memory array, H is the hit-rate, and FA is the false alarm rate. This formula for estimating the number of items retained in working memory is suited for change detection tasks that use a single-probe display (Rouder, Morey, Morey, & Cowan, 2011).

An index of "filtering cost" was separately computed for the threat and neutral distracter conditions. Filtering cost for threat-related distracters was calculated as the difference in working memory capacity (K) between 1 Neutral Target + Threat Distracter

trials and 1 Neutral Target trials. A larger filtering cost indicates greater degradation of working memory capacity for the task-relevant neutral face in the face of competition from a task-irrelevant threat-related distracter (Stout et al., 2015). Filtering cost for emotionally-neutral distracters was similarly computed as the difference between *K* scores in 1 Neutral Target + Neutral Distracter trials and 1 Neutral Target trials.

RESULTS

Behavioral results

As **Figure 2a** shows, working memory capacity, as indexed by *K*-scores, increased from one neutral target face to two neutral target faces ($p < .001$). Moreover, working memory capacity was impaired in the face of distraction for both threat (1 Neutral Target *K* > Neutral Target + Threat Distracter *K*: $p < .001$) and neutral distracters (1 Neutral Target *K* > Neutral Target + Neutral Distracter *K*: $p < .001$). Working memory capacity was more impaired for threat than neutral distracters (Neutral Target + Neutral Distracter *K* > Neutral Target + Threat Distracter *K*: $p = .001$).

Analysis of reaction time (**Figure 2b**) revealed that as working memory load increased, so did reaction time (2 Neutral Targets RT > 1 Neutral Target RT: $p < .001$). Reaction time also increased in the face of threat (Neutral Target + Threat Distracter RT > 1 Neutral Target RT: $p < .001$) and neutral distracters (Neutral Target + Neutral Distracter RT > 1 Neutral Target RT: p < 001. However, reaction time was not different between the two distracter conditions (Neutral Target + Threat Distracter RT ≈ Neutral Target + Neutral Distracter RT: $p = .21$). Individual differences in dispositional anxiety were unrelated to K-score or RT measures of filtering cost (*p*s > .05), defined as the increase in RT in the presence of distracters, or the drop in K estimates in the presence of a distracter

respectively.

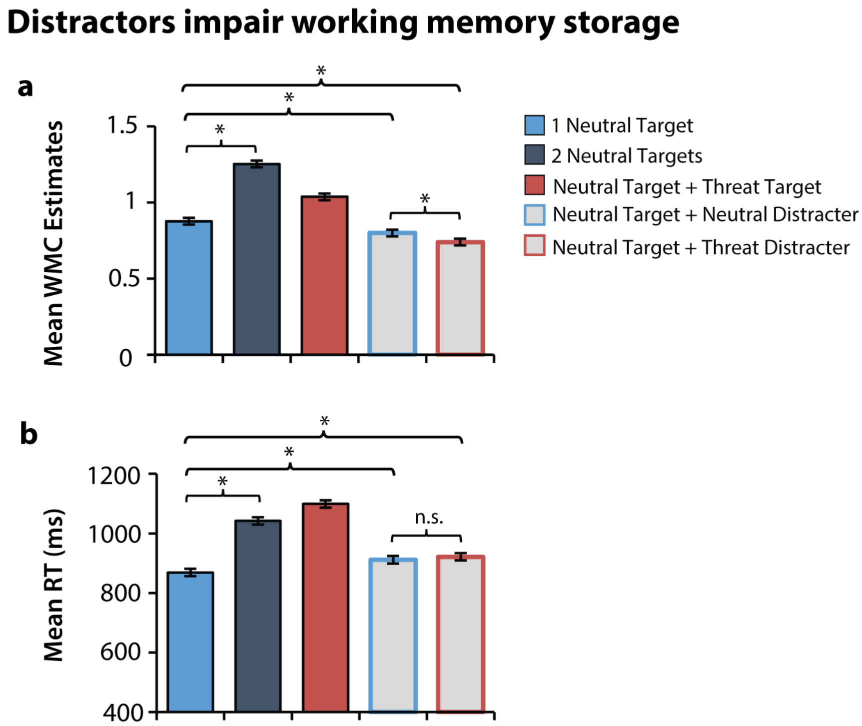

Figure 2. Face distracters impair working memory performance. Bar graphs display behavioral performance in the working memory task. **a**) Working memory capacity estimates (*K*-scores) increased with working memory load, and decreased in the face of distraction. **b**) Reaction time (RT) results show that RT was higher with working memory load, and RT increased when distracters were present. Asterisks denote significant pairwise comparisions ($p < .05$). Error bars reflect the probability of the null hypothesis being rejected by chance: $p < .05$ (non-overlapping error bars).

Unnecessary storage of threat distracters in the FFA

If task-irrelevant face distracters do indeed enter working memory, I expect the FFA to track this unnecessary storage. As described in the Method section, I first identified bilateral fusiform gyrus clusters that were sensitive to working memory load in the absence of threat (2 Neutral Targets > 1 Neutral Target), and restricted this activity to the anatomically defined region of the temporal occipital fusiform cortex. To confirm whether this activity reflects the storage of faces in working memory, I additionally identified bilateral face-sensitive voxels in the fusiform cortex in an independent face-localizer task

(see Methods).

I then performed a conjunction analysis between the working memory load contrast (2 Neutral Targets > 1 Neutral Target; $p < .05$, small volume corrected) and face localizer activity ($p < .05$, small volume corrected) to define a bilateral FFA region of interest (See **Figure 3a**). I extracted mean percent signal change from the conjunction cluster and computed a Hemisphere (Left vs. Right) × Load (1 Neutral Target vs. 2 Neutral Targets) ANOVA. FFA activity increased with Load, F (1, 80) = 24.48, $p < .0001$. There was no significant difference between the Left and Right FFA for working memory load; the main effect of Hemisphere, and the Hemisphere × Load interaction were not significant, Fs < 2.5, ps > .12. For parsimony, I collapsed across hemisphere for the remainder of the analyses. Virtually identical results were obtained when I considered the left and right FFA separately.

Figure 3b shows that threat-related distracters gained unnecessary access to working memory as indicated by increased FFA activity for threat-distracters compared to a single neutral target, $t(80) = 3.61$, $p = .001$. However, on average, FFA activity in the 1 Neutral Target + Threat Distracter condition was significantly lower than the perceptually-matched display that included 1 Neutral Target + 1 Threat Target, $t(80) = -2.20$, $p = .03$. Together these data indicate that although subjects were able to partially filter irrelevant threat from working memory, they were inefficient at doing so. In contrast, participants were able to successfully filter emotionally neutral distracters from entering working memory. FFA storage activity for neutral distracters was similar to 1 Neutral Target, $t(80) = 0.998$, $p = .32$, and significantly lower than 2 Neutral Targets, $t(80) = -4.60$, $p < .001$ (**Figure 3c**). Storage of threat-related distracters was significantly greater than storage of neutral-

related distracters ([1 Neutral Target + Threat Distracter] > [1 Neutral Target + Neutral Distracter], t (80) = 2.64, p = .01).

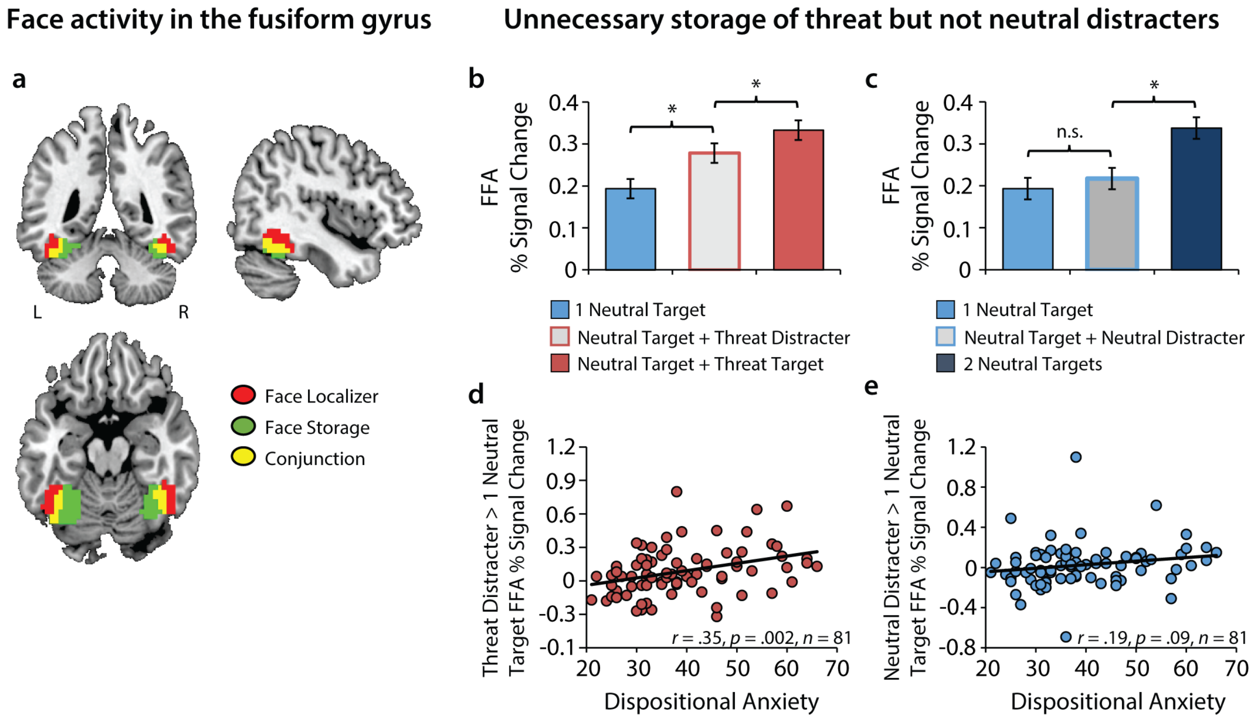

Figure 3. FFA activity reveals that threat related distracters are unnecessarily stored in working memory. **a**) A conjunction analysis in the fusiform gyrus shows working memory load and face sensitive voxels (yellow). **b**) Mean percent signal change in the FFA was significantly increased for threat distracters (Neutral Target + Threat Distracter) compared to 1 Neutral Target. **c**) Mean percent signal change in the FFA was not significantly increased on trials with a neutral distracter (Neutral Target + Neutral Distracter) compared to 1 Neutral Target alone. **d**) Dispositional anxiety was associated with increased distracter storage for threat distracters. **e**) Dispositional anxiety was weakly associated with neutral distracter storage. Asterisks denote significant pairwise comparisons (p < .05). Error bars reflect the probability of the null hypothesis being rejected by chance: p < .05 (non-overlapping error bars).

Unnecessary storage of threat distracters in the PPC

I extracted mean percent signal change from the left and right PPC clusters and then entered them into a Hemisphere × Load ANOVA. There was a significant main effect of Load, F (1, 80) = 54.71, p < .001; a marginal effect of Hemisphere, F (1, 80) = 3.72, p = .06, and a significant Hemisphere × Load interaction, F (1, 80) = 8.84, p = .004. The left PPC (**Figure 4a**) was associated with enhanced activity when storing two affectively neutral faces compared to the right PPC, t (80) = 2.27, p = .01. There were no hemispheric

differences for 1 Neutral Target face, $p = 0.46$.

Consistent with the results in the FFA, the left PPC was associated with greater activity for threat-related distracters relative to 1 Neutral Target, $t(80) = 2.41$, $p = .02$, but significantly lower activity compared to the condition where a threat-target was also present (1 Neutral Target + 1 Threat Target), $t(80) = -3.87$, $p < .001$ (**Figure 4b**). Likewise, participants were able to successfully filter emotionally neutral distracters from entering working memory. PPC storage activity for neutral distracters was similar to 1 Neutral Target, $t(80) = 0.736$, $p = .46$, and significantly lower than 2 Neutral Targets, $t(80) = -6.93$, $p < .001$ (**Figure 4c**). Storage of threat-related distracters was significantly greater than the storage of neutral-related distracters ([1 Neutral Target + Threat Distracter] > [1 Neutral Target + Neutral Distracter], $t\ (80) = 2.09$, $p = .04$). I did not find evidence of unnecessary storage in the right PPC.

Anxious individuals fail to filter distracters

To test whether individuals with dispositional anxiety have greater difficulty preventing threat-related distracters from gaining access to working memory, I computed difference scores between the FFA and PPC activity in each distracter condition minus 1 Neutral Target condition (see Method). These difference scores are indicators of unnecessary storage of distracters (McNab & Klingberg, 2008), and high unnecessary storage activity indicates working memory filtering deficits. In other words, if distracters are not successfully filtered and infiltrate working memory, FFA/PPC storage activity in the distracter conditions would be increased compared to FFA/PPC activity for the 1 Neutral Target condition alone (see McNab & Klingberg, 2008 for a similar method).

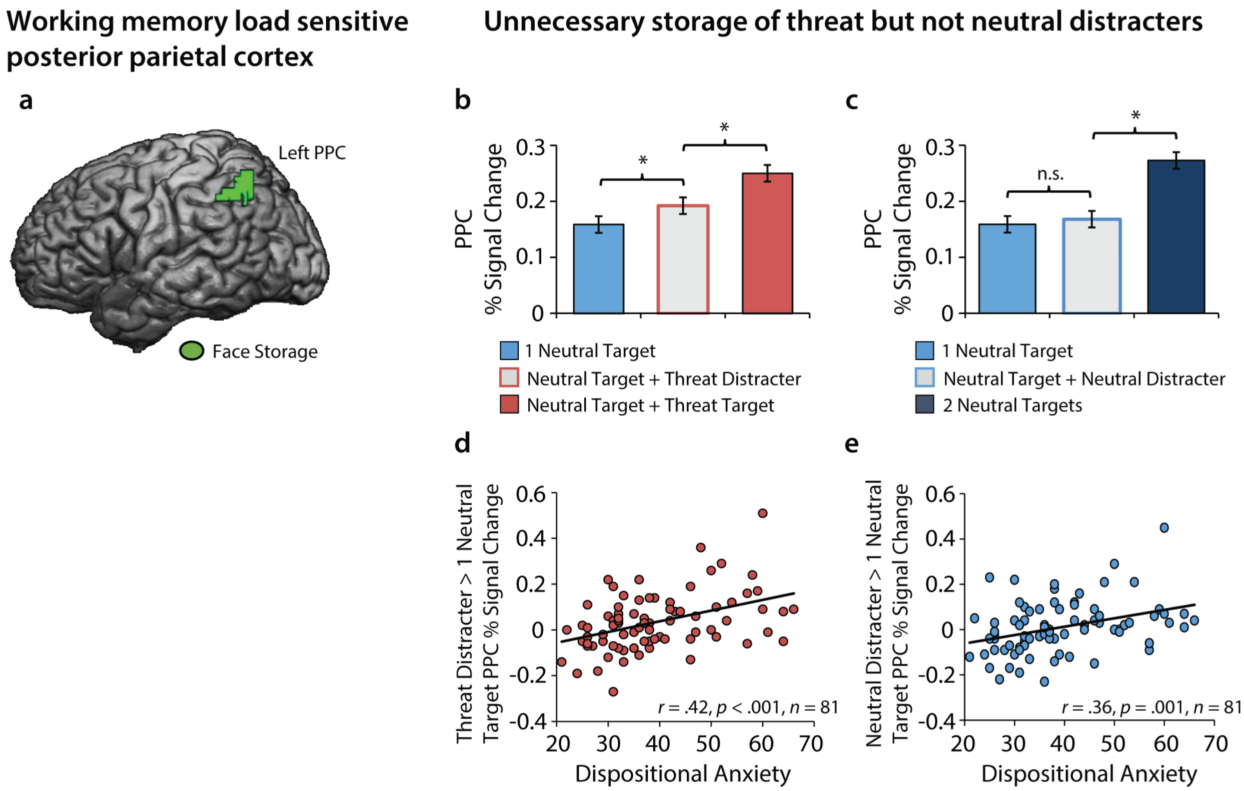

Figure 4. Left posterior parietal cortex tracks unnecessary processing of threat distracters. **a**) Significant working memory load cluster in the left posterior parietal cortex (from 2 Neutral Targets > 1 Neutral Target contrast; *p* - threshold < .005, and cluster corrected *p* < .05). **b**) Similar to the FFA, mean percent signal change in the left PPC was significantly increased for the threat distracters (Neutral Target + Threat Distracter) compared to 1 Neutral Target. **c**) Mean percent signal change in the left PPC was not significantly increased on trials with a neutral distracter (Neutral Target + Neutral Distracter) compared to 1 Neutral Target alone. **d**) Dispositional anxiety was significantly related to increased processing of threat distracters and **e**) neutral distracters. Asterisks denote significant pairwise comparisons ($p < .05$). Error bars reflect the probability of the null hypothesis being rejected by chance: $p < .05$ (non-overlapping bars).

Analyses of FFA unnecessary storage demonstrated that anxious individuals were more likely to store threat-related distracters in working memory, $r = 0.35$, $p = 0.002$ (**Figure 3d**). Similar effects were obtained after controlling for variation in age, sex, and maximum working memory capacity (partial $r = .36$, $p = 0.001$) and depressive symptoms (partial $r = .26$, $p = 0.019$). Dispositional anxiety was weakly related to filtering emotionally neutral distracters, $r = 0.19$, $p = 0.09$ (**Figure 3e**). This effect was specific to distracter storage: anxiety was unrelated to the storage of threat-relevant targets (1 Neutral Target + 1 Threat Target > 1 Neutral Target); $r = .13$, $p = .25$; or neutral targets (2 Neutral Targets > 1 Neutral Target); $r = .01$, $p = .96$.

Consistent with findings from the FFA, anxiety significantly predicted increased unnecessary distracter storage in the left PPC, $r = .42$, $p < .0001$ (**Figure 4d**). However, this was not threat-specific; individual differences in anxiety also predicted excess mis-allocation of working memory storage devoted to neutral- distracters, $r = .36$, $p = .001$ (**Figure 4e**). These relationships remained significant for both threat and neutral distracter storage after controlling for variation in age, sex, and working memory capacity (partial $r = .36$, $p = .001$), and depressive symptoms (partial $r = .26$, $p = .02$). This observed pattern is consistent with neurocognitive models positing a general attentional filtering deficit that may not be threat-specific (Bishop, 2008; Berggren & Derakshan, 2013; Owens, Koster, & Derakshan, 2012).

Collectivity, these data show that dispositional anxiety is associated with a working memory filtering deficit; conceptually replicating previous work using event-related potentials (Stout et al., 2013).

Amygdala-mediated filtering

Next, I examined whether amygdala activation statistically mediates the relationship between anxiety and unnecessary storage of threat distracters in the FFA and the PPC. Using a conjunction analysis, I identified face sensitive voxels in the bilateral amygdala that are involved in perceiving faces, as indexed by an independent localizer task, and restricted to the anatomically-defined amygdala ROI ($p < .05$ corrected for the volume of the anatomically defined bilateral amygdala; see Method). I extracted mean percent signal change from the contrasts representing unnecessary storage activity (i.e. 1 Neutral Target + Threat Distracter > Neutral Target; and the 1 Neutral Target + Neutral Distracter > Neutral Target contrasts) within the face sensitive bilateral amygdala. Dispositional anxiety

was significantly correlated with amygdala response to threat distracters (r = .32, p = .004) but weakly to neutral distracters (r = .13, p = .25).

After establishing the significant relationship between dispositional anxiety and amygdala activity to threat-distracters, I next examined how amygdala reactivity to threat-distracters relates to unnecessary storage. Threat-related amygdala activity was positively associated with activity in both the FFA (r = .64, p < .0001) and the PPC (r = .51, p < .0001) in the contrast representing unnecessary storage of threat distracters. Next, I performed a mediation test using the logic of Barron and Kenny (1986) but incorporating a non-parametric bootstrapping method (See Methods; Preacher & Hayes, 2004, 2008; Wager et al., 2008). **Figure 5ab** shows that amygdala activity for threat-distracters mediated the relationship between dispositional anxiety and unnecessary storage of threat-related distracters in the FFA and the PPC. The mediation effect was additionally confirmed by computing *Sobel's* parametric significance test of the product of paths a and b, (FFA: Z = 2.70, p = .007; PPC: Z = 2.42, p .02). Collectively, these results provide compelling evidence of an amygdala-mediated neural circuit underlying the anxiety-related unnecessary storage of task-irrelevant information in working memory.

Amgdala-based circuit promtes the anxiety-related storage of threat-related distracters in working memory

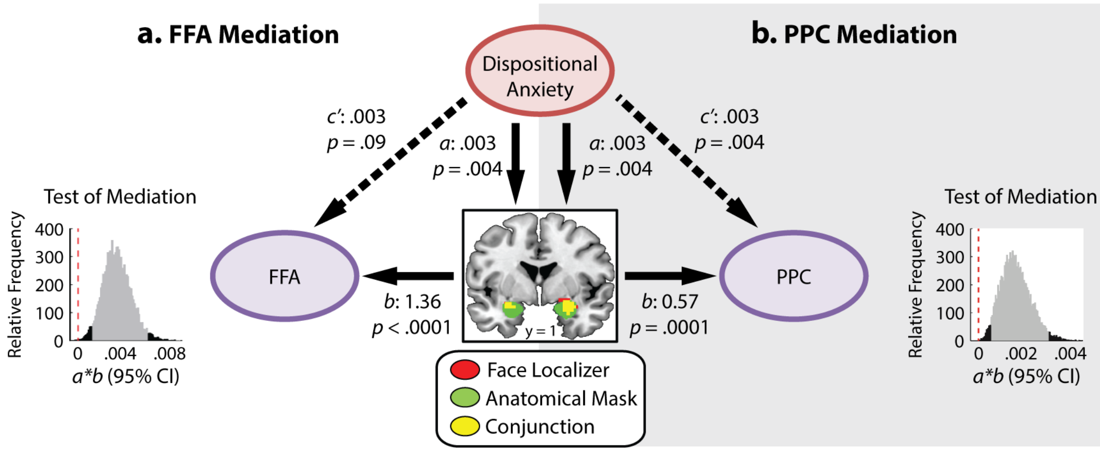

Figure 5. Amygdala-based circuit promotes impaired filtering of task-irrelevant threat. **a**) Mediation analysis testing the hypothesis that amygdala activation mediates the relationship between dispositional anxiety and unnecessary storage in the FFA. A significant mediation was found (*a*b* bootstrapped 95% confidence interval (CI) did not cross zero). Specifically, after controlling for amygdala activity, the relationship between dispositional anxiety and FFA unnecessary storage for threat distracters was no longer significant (path *c′*). **b**) Mediation analysis testing the hypothesis that amygdala activation mediates the relationship between dispositional anxiety and unnecessary storage in the PPC. After controlling for amygdala activity, the relationship between dispositional anxiety and unnecessary storage of threat distracers in the PPC was significantly reduced (path *c′*). Dotted lines denote that the path was significantly reduced. Frequency plots display the boostrapped 95% CI (10,000 samples) for the test of mediation (product of paths *a* and *b*).

Secondary analysis results

I conducted two additional analyses that were not included as part of the primary hypotheses described above, but were important for characterizing the neurocognitive deficits associated with promoting unnecessary storage of distracters in working memory.

Preparatory gating mediation. To test the hypothesis that dispositional anxiety may be characterized by a deficit in the preparatory working memory gating system, I performed a whole-brain mediation search analysis (Wager et al., 2008). For this analysis, I entered self-reported dispositional anxiety as the predictor variable and the significant FFA/PPC unnecessary storage activity for threat distracters as the dependent variable. I performed a whole-brain mediation search on the preparatory cue activity to identify significant voxels that statistically mediate the relationship between dispositional anxiety

and unnecessary storage of threat-distracters in the FFA. No voxels were identified for this analysis in either the FFA or the PPC, suggesting that the anxiety-related unnecessary storage of threat- distracters observed in the current study is unrelated to a preparatory filtering deficit.

Compensatory frontoparietal recruitment. To successfully overcome emotional distraction, increased recruitment of the frontoparietal network is critical (Dolcos & McCarthy, 2006; Clarke & Johnstone, 2013). Taking this into consideration, I examined, at the whole-brain, the difference between threat and neutral distracters (1 Neutral Target + Threat Distracter) > (1 Neutral Target + Neutral Distracter). Results indicate that threat-distracters are indeed associated with enhanced frontoparietal activity (See **Table 2**). Specifically, bilateral inferior frontal gyri (rIFG) (see **Figure 6a**) and right posterior parietal cortex were significantly enhanced for threat-distracters compared to neutral distracters. No clusters displayed greater activity for neutral over threat distracters.

Table 2. Increased frontoparietal activity for threat versus neutral distracters

1 Neutral Target + Threat Distracter > 1 Neutral Target + Neutral Distracter

Region	**Cluster size (in**	**X**	**Y**	**Z**	**T-Value**
Right DLPFC	180	54	19	27	4.45
Right PPC	163	40	-40	41	3.89
Visual cortex	143	-6	-82	3	4.43
Left DLPFC	107	-44	19	17	4.16
Right Middle Temporal Gyrus	63	50	-40	6	3.98
Left Middle Temporal Gyrus	54	-62	-58	3	4.07
Right Precuneus	38	5	-65	48	3.77

$p < .05$ whole-brain corrected

I next examined whether variation in dispositional anxiety is related to this pattern of activity. Consistent with predictions by neurocognitive theories of anxiety (i.e., ACT;

Eysenck & Derakshan, 2011; Eysenck et al., 2007), higher levels of dispositional anxiety were positively associated with increased recruitment of the right rIFG, $r = .27$, $p = .015$ (see **Figure 6b**). Anxiety was not related to activity in any other region in this contrast (*p*s > .05). This pattern of neural activity found in elevated dispositional anxiety, with the lack of behavioral differences, may suggest a compensatory recruitment of prefrontal activity to overcome the emotional distraction by threat-distracters and perform equivalent to their non-anxious peers (Basten et al., 2012; Berggren & Derakshan, 2013; Fales et al., 2008).

DISCUSSSION

Using an affective adaptation of a well-validated task designed to measure the neural circuitry subserving the attentional capacity of working memory, the current findings demonstrate that dispositional anxiety is associated with the unnecessary storage of distracters in working memory. FFA activity for distracters, particularly threat distracters, was enhanced in highly anxious individuals, suggesting that dispositionally anxious individuals allow task-irrelevant threat access to working memory. In addition, the left PPC further tracked this unnecessary storage for both threat and neutral-related distracters. These results could not be explained by variation in age, sex, maximum working memory capacity, or depressive symptoms. Moreover, these results were specific to distracters — dispositional anxiety was not related to increased storage of threat or neutral task- relevant targets. This indicates that anxious individuals devote limited attentional and working memory resources to information that is irrelevant to the task at hand (Bishop, Jenkins, Lawrence, 2007; Stout et al., 2013).

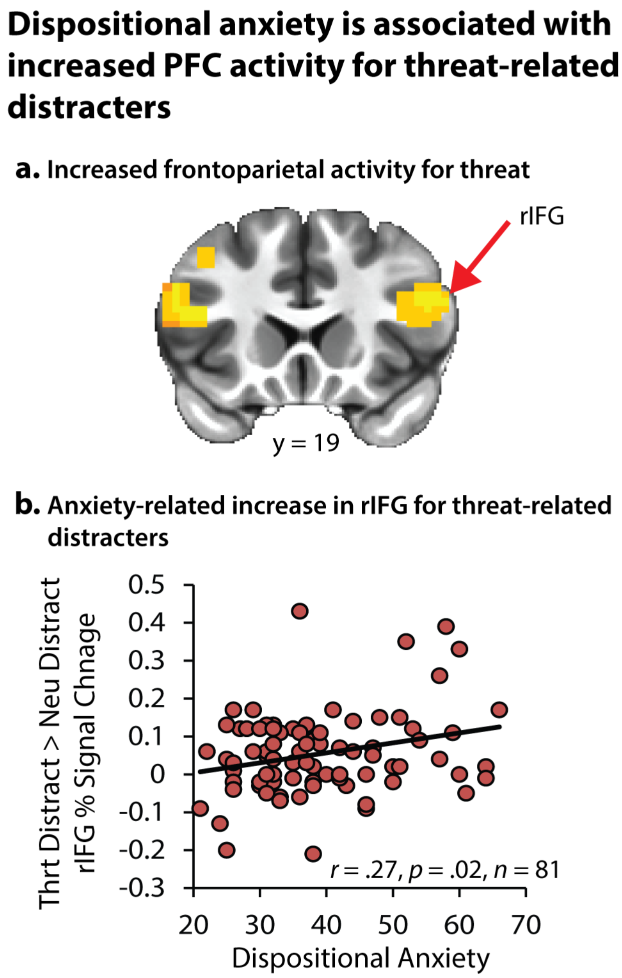

Figure 6. Dispositional anxiety is associated with increased PFC activity for threat-related distracters. **a**) Whole-brain contrast depicting increased PFC activity for threat-related (Neutral Target + Threat Distracter) compared to neutral distracters (Neutral Target + Neutral Distracter) ($p < .05$ corrected). **b**) Correlation analysis depicting the significant positive relationship between dispositional anxiety and increased right inferior frontal gyrus (rIFG; x = 54, y = 19, z = 27).

These findings demonstrate that distracters consume the limited attentional capacity of working memory — and delineate the neural mechanisms by which anxious individuals have difficulty preventing distracters from accessing this important cognitive system. The FFA and the PPC are key regions implicated in the sustained attention and retention of domain-specific and domain-general information in working memory (Druzgal

& D'Esposito, 2003; LaRocque et al., 2013; Lewis-Peacock & Postle, 2012; Ranganath et al., 2004; Postle, 2015). Consistent with this, the results presented here show that the FFA and PPC were sensitive to working memory load, and importantly tracked the unnecessary storage of both threat and neutral distracters (McNab & Klingberg, 2008). Thus, the current findings provide evidence that the FFA and PPC can be used to measure the anxiety-related mis-allocation of working memory resources to task-irrelevant information.

In Stout et al. (2013), I hypothesized that an anxiety-related working memory filtering deficit may reflect the influence of the amygdala on regions important for working memory. The results presented in the current study provide support for this hypothesis. Specifically, I found that the amygdala played an integral role in determining whether threat-related distracters gained access to working memory: (i) amygdala activity was positively associated with both FFA and PPC unnecessary storage activity, and (ii) the amygdala significantly mediated the relationship between dispositional anxiety and unnecessarily storing threat- distracters in working memory. The results from the current study build upon this work by showing that the amygdala is a critical hub in the distributed neural circuit by which threat-related distracters consume the attentional capacity of working memory.

From a translational perspective, the results of the present study provide a novel neurocognitive model that extends the role of the amygdala beyond the well- validated relationship between anxiety and the attention bias to threat cues (Bishop et al., 2007; Etkin et al., 2004; Rauch, Shin, & Wright, 2003). Many of the cardinal symptoms of dispositional anxiety and the anxiety disorders (e.g., worry, rumination, intrusive memories) occur when threat-related information is absent from the immediate

environment (Barlow, 2004; Beck, Emery, & Greenberg, 2005; Grupe & Nitschke, 2013; Newman, Llera, Erickson, Przeworski, & Castonguay, 2013; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Yet, the neural circuitry underlying these debilitating and transdiagnostic symptoms remains elusive, and is not addressed by the attentional bias literature (Blair & Blair, 2012). Here and in other work (Stout et al., 2013; 2015), I propose that these symptoms reflect difficulty controlling the access of information to working memory, resulting in sustained processing and retention of task-irrelevant threat, long after it has been removed from the environment. From a cognitive neuroscience perspective, information in working memory is in a privileged place to bias subsequent information processing (Cowan, 2005; Jonides et al., 2008; Oberaurer, 2002; Postle, 2006). Therefore, if irrelevant threat is occupying this important cognitive system, attention is more likely to be biased toward potential future threat, and guide long-term memory retrieval toward mood-congruent memories (Catarino, Küpper, Werner-Seidler, Dalgleish, & Anderson, 2015). Accordingly, the cognitive symptoms of anxiety (i.e., worry, intrusive memories, and uncertainty) may then reflect mis-allocation of the working memory system for irrelevant threat-related information. In other words, anxious individuals are overtaxing the working memory network by retaining irrelevant and threat-related information in an accessible state, to anticipate and plan for potential negative outcomes. This hypothesis is consistent with work showing that patients with generalized anxiety disorder, characterized by excessive worry, display increased coupling between the executive network and the amygdala (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009), and that the cognitive symptoms of anxiety show strong functional connectivity within the frontoparietal network that supports working memory and attentional control

(Bijsterbosch et al., 2014). Collectively, there is a growing body of research suggesting that anxious individuals are aberrantly utilizing neural systems important for attentional control and working memory; setting the stage for understanding the neural circuitry instantiating the debilitating and maladaptive cognitive symptom profile of dispositional anxiety and internalizing disorders.

One prominent theory that has specifically highlighted the importance of working memory in anxiety is the attentional control theory (ACT; Eysenck et al., 2007; Eysenck & Derakshan, 2011). According to ACT, anxious individuals often have task-irrelevant, intrusive, and task-interfering cognitions active in working memory. Because of this unnecessary load to working memory, compensatory recruitment of attentional control is required to perform effectively, often resulting in increased PFC activity but no behavioral differences between anxious and non- anxious individuals (Basten et al., 2012; Berggren & Derakshan, 2013; Fales et al., 2008). Results from the current study are consistent with this prediction, and more importantly, provide the first neural evidence underlying the increased unnecessary storage of task-irrelevant distracters in working memory. These data also support the compensatory prediction of ACT. Dispositional anxiety was associated with increased PFC activity to threat compared to neutral distracters, despite a lack of association between anxiety and behavioral measures of working memory performance. This finding suggests anxious individuals are recruiting the PFC to overcome the effects of unnecessary storage by threat-related distracters (Eyesenck & Derakshan, 2011).

In addition to the primary findings I also conducted an analysis that further attempted to clarify the mechanisms by which anxious individuals have difficulty filtering

irrelevant information. In Stout et al. (2013), I made a hypothesis that the anxiety-related unnecessary storage of threat in working memory may reflect a deficit in the corticostriatal working memory gating system. Previous work has shown that signals emanating from the basal ganglia serve as the gatekeeper of working memory (Awh & Vogel, Baier et al., 2010; Chatham et al., 2014). However, results of the current whole-brain mediation analysis (Wager et al., 2008) did not support this hypothesis; suggesting that preparing to filter irrelevant information may be unrelated to whether anxious individuals unnecessarily store task-irrelevant information in working memory.

From a clinical perspective, identifying treatments that target the neural circuitry associated with unnecessarily storing irrelevant information in working memory may prove fruitful in ameliorating the negative cognitive symptoms in anxiety and comorbid disorders. Such interventions might target either the initial amygdala-driven attentional capture, or deficient attentional control and working memory gating systems (Britton et al., in-press; Browning, Holmes, & Harmer, 2010). Pharmacological interventions, such as selective serotonin reuptake inhibitors (SSRIs) reduce amygdala activity to threat (Phan et al., 2013), which would be expected to decrease hypervigilance and in turn diminish subsequent unnecessary storage of threat. Computerized attention bias modification (ABM) regimens aim to improve attentional control via the frontoparietal network (Bar-Haim, 2010; Hakamata, et al., 2010; MacLeod & Clarke, 2015; MacLeod, C., & Mathews, 2012), which may improve the ability to prevent irrelevant threat from gaining access to working memory. Alternatively, cognitive training designed to bolster working memory capacity itself may also reduce the cognitive symptoms of anxiety and other internalizing disorders (Bomyea & Amir, 2011; Cohen, Nilly, & Avishai, 2015; Owens, Koster, &

Derakshan, 2013).

The data from the current study highlights a potential neural mechanism underlying the debilitating cognitive symptoms characteristic of dispositional anxiety and the anxiety disorders. Although, it is clear that more work is required, the results of the current study provide a conceptual framework for better understanding these symptoms. Given that the results are based on sub-clinical levels of dispositional anxiety, it will be critical to test this hypothesis in a clinical sample, and examine whether unnecessary storage of distracters is associated with severity of symptoms, or is consistent across internalizing disorders. Since I found threat-specificity in the FFA, but not the PPC, identifying whether anxiety-related unnecessary storage of distracters is threat-specific (Stout et al., 2013) vs. general (Owens et al., 2012; Qi et al., 2014), and under what situations threat-specificity manifests, will be important (Berggren & Derakshan, 2013). It may be that dissociable neurocognitive processes and neural circuits underlie threat vs. general working memory filtering deficits. Methodologically, adapting the paradigm to include a longer delay interval may prove helpful in determining the chronometry and extent to which threat-distracters are maintained in working memory, and how this may influence other key anxiety-related symptoms (e.g., avoidant behavior, emotion dysregulation, and retrieval of negative memories). Related, capitalizing on analytic tools, such as multi-voxel pattern analysis (Lewis-Peacock & Postle, 2012), will help to further decode the information anxious individuals are 'working' on when it is no longer present in the external environment.

Conclusion

The results of the current study provide a compelling argument that dispositional anxiety, a key risk factor for anxiety and comorbid disorders, is associated with problems

governing the access of information to working memory. Once in working memory, irrelevant threat can hijack limited attentional capacity required to maintain focus on goal-related behavior and cognition — potentially promoting intrusive cognitions, memories, and worry long after the threat is removed from the immediate environment. These results set the stage for understanding the neurocognitive mechanisms underlying these debilitating symptoms, and encourage the development of novel interventions that target these mechanisms (Bomyea & Amir, 2011; MacLeod & Clarke, 2015).

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Qi, S., Ding, C., & Li, H. (2014). Neural correlates of inefficient filtering of emotionally neutral distractors from working memory in trait anxiety. *Cognitive, Affective, & Behavioral Neuroscience, 14*, 253-265.

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*, 385-401.

Ranganath, C., DeGutis, J., & D'Esposito, M. (2004). Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. *Cognitive Brain Research, 20*, 37-45.

Rauch, S. L., Shin, L. M., & Wright, C. I. (2003). Neuroimaging studies of amygdala function in

anxiety disorders. *Annals of the New York Academy of Sciences, 985*, 389-410.

Robitaille, N., Marois, R., Todd, J., Grimault, S., Cheyne, D., & Jolicœur, P. (2010). Distinguishing between lateralized and nonlateralized brain activity associated with visual short-term memory: FMRI, MEG, and EEG evidence from the same observers. *Neuroimage, 53*, 1334-1345.

Rouder, J., Morey, R., Morey, C., & Cowan, N. (2011). How to measure working memory capacity in the change detection paradigm. *Psychonomic Bulletin & Review, 18,* 324-330.

Sabatinelli, D., Frank, D. W., Wanger, T. J., Dhamala, M., Adhikari, B. M., & Li, X. (2014). The timing and directional connectivity of human frontoparietal and ventral visual attention networks in emotional scene perception. *Neuroscience, 277*, 229-238.

Sabatinelli, D., Lang, P. J., Bradley, M. M., Costa, V. D., & Keil, A. (2009). The timing of emotional discrimination in human amygdala and ventral visual cortex. *The Journal of Neuroscience, 29*, 14864-14868.

Sessa, P., Luria, R., Gotler, A., Jolicœur, P., & Dell'acqua, R. (2011). Interhemispheric ERP asymmetries over inferior parietal cortex reveal differential visual working memory maintenance for fearful versus neutral facial identities. *Psychophysiology, 48*, 187-197.

Shackman, A. J., Fox, A. S., Oler, J. A., Shelton, S. E., Davidson, R. J., & Kalin, N. H. (2013). Neural mechanisms underlying heterogeneity in the presentation of anxious temperament. *Proceedings of the National Academy of Sciences, 110*, 6145-6150.

Shechner, T., Britton, J. C., Pérez-Edgar, K., Bar-Haim, Y., Ernst, M., Fox, N. A., . . . Pine, D. S. (2012). Attention biases, anxiety, and development: Toward or away from threats or

rewards? *Depression & Anxiety, 29*, 282-294.

Sheppes, G., Luria, R., Fukuda, K., & Gross, J. J. (2013). There's more to anxiety than meets the eye: Isolating threat-related attentional engagement and disengagement biases. *Emotion, 3*, 520-528.

Shipstead, Z., Lindsey, D. R. B., Marshall, R. L., & Engle, R. W. (2014). The mechanisms of working memory capacity: Primary memory, secondary memory, and attention control *Journal of Memory and Language, 72*, 116-141.

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Mind Garden.

Stout, D. M., Shackman, A. J., Johnson, J. S., & Larson, C. L. (2015). Worry is associated with impaired gating of threat from working memory. *Emotion, 15*, 6-11.

Stout, D. M., Shackman, A. J., & Larson, C. L. (2013). Failure to filter: Anxious individuals show inefficient gating of threat from working memory. *Frontiers in Human Neuroscience, 7*:58.

Suzuki, M., & Gottlieb, J. (2013). Distinct neural mechanisms of distractor suppression in the frontal and parietal lobe. *Nature Neuroscience, 16*, 98-104.

Swartz, J., Knodt, A., Radtke, S., & Hariri, A. (2015). A neural biomarker of psychological vulnerability to future life stress. *Neuron, 85*, 505-511.

Thiruchselvam, R., Hajcak, G., & Gross, J. J. (2012). Looking inward: Shifting attention within working memory representations alters emotional responses. *Psychological Science, 23,* 1461-1466.

Todd, J. J., & Marois, R. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature, 428*, 751-754.

Todd, J. J., & Marois, R. (2005). Posterior parietal cortex activity predicts individual differences in visual short-term memory capacity. *Cognitive, Affective, & Behavioral Neuroscience, 5*, 144-155.

Tsubomi, H., Fukuda, K., Watanabe, K., & Vogel, E. K. (2013). Neural limits to representing objects still within view. *The Journal of Neuroscience, 33*, 8257- 8263.

Vogel, E. K., & Machizawa, M. G. (2004). Neural activity predicts individual differences in visual working memory capacity. *Nature, 428*, 748-751.

Vogel, E. K., McCollough, A. W., & Machizawa, M. G. (2005). Neural measures reveal individual differences in controlling access to working memory. *Nature, 438*, 500-503.

Voytek, B., & Knight, R. T. (2010). Prefrontal cortex and basal ganglia contributions to visual working memory. *Proceedings of the National Academy of Sciences, 107*, 18167-18172.

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., & Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nature Neuroscience, 7*, 1271-1278.

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., & Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron, 59*, 1037-1050.

Whalen, P. J. (1998). Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Current Directions in Psychological Science, 7*, 177-188.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., . . . Vos, T. (2013). Global burden of disease attributable to mental and substance use

disorders: Findings from the global burden of disease study 2010. *The Lancet, 382*, 1575-1586.

Xu, Y., & Chun, M. M. (2006). Dissociable neural mechanisms supporting visual short-term memory for objects. *Nature, 440*, 91-95.

Ziaei, M., Peira, N., & Persson, J. (2014). Brain systems underlying attentional control and emotional distraction during working memory encoding. *Neuroimage, 87*, 276-286.

CURRICULUM VITAE

Daniel M. Stout

EDUCATION

2015-2016	Predoctoral Psychology Intern, University of California-San Diego/VA La Jolla, CA
2010-2016	Ph.D., Psychology, University of Wisconsin – Milwaukee Major: Clinical Psychology Minor: Quantitative Methods Advisor: Christine Larson, Ph.D.
2006-2008	M.S., Psychology. North Dakota State University, Fargo, ND Major: Clinical Psychology Advisor: Paul Rokke, Ph.D.
2002-2006	B.S., Psychology, North Dakota State University, Fargo, ND Magna cum Laude

RESEARCH EXPERIENCE

2010 – Current	***Graduate Research Assistant*** Affective Neuroscience Laboratory, University of Wisconsin – Milwaukee Supervisor: Christine Larson, Ph.D.
2006-2008	***Graduate Research Assistant*** Attention and Emotion Laboratory, North Dakota State University Supervisor: Paul D. Rokke, Ph.D.
2004-2006	***Undergraduate Research Assistant*** Attention and Emotion Laboratory, North Dakota State University Supervisor: Paul D. Rokke, Ph.D.

RESEARCH SKILLS

- Neuroimaging analysis (fMRI), primarily in task-based designs and BOLD activity. Extensive use of AFNI for preprocessing and group-level statistics. Responsible for implementing non-linear registration as part of standard preprocessing pipeline using both *AFNI* (3dQwarp) and *FSL* (FNIRT). Additional expertise in context-modulated functional connectivity (e.g., gPPI, beta-series analysis) for event-related designs and whole-brain mediation modeling for fMRI data.
- Design, collection, and analysis of electroencephalography (EEG) and event-related potentials (ERP). Collection experience with *Neuroscan* and *ANT* hardware and software. Data analysis experience primarily through *Matlab*-based toolboxes *EEGLAB* and *ERPLAB*.
- Designing cognition/emotion paradigms. Particular emphasis in attention and working memory paradigms with programming experience using *E-Prime* software.
- Implementation of mood-induction procedures such as threat-of-shock, affective pictures, and music.
- Conducting structured interviews (SCID, MINI) to assess for psychiatric disorders.

PEER-REVIEWED PUBLICATIONS

Stout, D.M., Shackman, A.J., Johnson, J.S., & Larson, C.L. (2015). Worry is associated with impaired gating of threat from working memory. *Emotion*, *15,* 6-11. doi:10.1037/emo0000015

Larson, C.L., Baskin-Sommers, A.R., **Stout, D.M.**, Balderston, N.L., Schultz, D.H., Curtin, J.J., Kiehl, K.A., & Newman, J.P. (2013). The interplay of attention and emotion: Top-down attention modulates amygdala activation in psychopathy. *Cognitive, Affective, & Behavioral Neuroscience*, *13*, 757- 770. doi: 10.3758/s13415-013-0172-8

Stout, D.M., Shackman, A.J., & Larson, C.L. (2013). Failure to filter: Anxious individuals show inefficient gating of threat from working memory. *Frontiers in Human Neuroscience,* 7**:**58. doi: 10.3389/fnhum.2013.00058

Baskin-Sommers, A.R., Curtin, J.J., Larson, C.L., **Stout, D.**, Kiehl, K.A., & Newman, J.P. (2012). *Characterizing the anomalous cognition-emotion interactions in externalizing. Biological Psychology, 91,* 48-58. doi: 10.1016/j.biopsycho.2012.05.001

Stout, D.M., & Rokke, P.D. (2010).Components of working memory predict levels of distress. *Cognition and Emotion,* 24, 1293-1303. doi:10.1080/02699930903309334

Lystad, C., Rokke, P.D., & **Stout, D.M.** (2009). Emotion congruent facilitation of attention when processing anxious stimuli. *Cognitive Therapy and Research*, *33,* 499-510.

BOOK CHAPTERS

Stout, D.M., & Rokke, P.D. (2009). Self-Efficacy. In R.E. Ingram (Eds.) *The International Encyclopedia of Depression* (pp. 494-495). New York: Springer.

MANUSCRIPTS UNDER REVIEW OR IN PREPARATION

Miskovich, T.A., Baskin-Sommers, A.R., Newman, J.P., Hanson, J.L., **Stout, D.M.**, Koenigs, M., Kiehl, K.A., … Lisdahl, K.M. (under review). Abnormal anterior midcingulate cortex gyrification in males with psychopathy.

Stout, D.M., Shackman, A.J., Pedersen, W.S., Miskovich, T., & Larson, C.L. (in preparation). Neural circuitry governing anxious individuals' failure to prevent threat from working memory.

Stout, D.M., Sheppes, G., Luria, R., Shackman, A.J., & Larson, C.L. (in preparation). Electrophysiological evidence for the failure to recover from attentional capture to threat in anxiety.

SYMPOSIUM & TALKS:

National/International:

Stout, D.M., & Larson, C.L. (2014). *Neural circuitry underlying the intrusion of threat into working memory in anxiety.* Symposium presentation given at the annual meeting of Anxiety and Depression Association of America, March 27-30, Chicago, IL. Symposium co-chair with Dr. Christine L. Larson.

Stout, D.M., Shackman, A.J., Miskovich, T., & Larson, C.L. (2013). *Neural measures of the access of threat to working memory in anxiety*. Symposium presentation given at the annual meeting of the Society for Psychophysiological Research, October 2-6, Florence, Italy. Symposium co-chair with Dr. Christine L. Larson.

Regional/Local:

Stout, D.M. (2014). *How anxiety affects your attention and memory*. Presented at the Upward Bound Math and Science Data Blitz and Demo Day, University of Wisconsin-Milwaukee, July 15th, Milwaukee, WI.

Stout, D.M. (2014). *Neural circuitry underlying the intrusion of threat into working memory in anxiety*. Presented at the University of Wisconsin—Milwaukee Association of Graduate Students in Psychology's 16th Annual Psychology Graduate Student Research Symposium. *Awarded 1st place for best student presentation.*

Stout, D.M. (2012). *Neural measures reveal threat's access to working memory results from reduced attentional filtering*. Presented at the University of Wisconsin—Milwaukee Association of Graduate Students in Psychology's 14th Annual Psychology Graduate Student Research Symposium.

Stout, D.M. (2008). *Do working memory and attentional control predict dysphoria?* Thesis presented at the North Dakota State University Psychology Department's 2008 Spring Colloquium Series, Fargo, ND.

POSTER PRESENTATIONS

Gorgas, J., Larson, C.L., Speech, C., & **Stout, D.M.** (2015). Failure of visual attention to recover from threat distracters. Poster presented at the 2015 University of Wisconsin-Milwaukee Undergraduate Research Symposium, Milwaukee, WI.

Stout, D.M., Shackman, A.J., Johnson, J.S., Miskovich, T.A., Larson, C.L. (2014). Deficits gating threat from working memory in anxiety. Poster presented at the 28th annual meeting of the Society for Research in Psychopathology, Evanston, IL.

Miskovich, T.A., Hanson, J., Newman, J.P., Baskin-Sommers, A.R., Koenigs, M., **Stout, D.M.,** Balderston, N.L., Kiehl, K.A., Larson, C.L. (2013). Abnormal gyrification and white matter integrity in psychopathy. Poster presented at the 28th annual meeting of the Society for Research in Psychopathology, Evanston, IL.

Stout, D.M., Shackman, A.J., Johnson, J.S., Miskovich, T.A., Larson, C.L. (2014). Unnecessary storage of threat in working memory: A proximal mechanism underlying anxiety and worry. Poster presented at the 2014 Milwaukee Chapter of the Society for Neuroscience, Milwaukee, WI.

Stout, D.M., Shackman, A.J., Johnson, J.S., Miskovich, T.A., Larson, C.L. (2014). Unnecessary storage of threat in working memory: A proximal mechanism underlying anxiety and worry. Poster presented at the inaugural conference of the Society for Affective Sciences, Bethesda, MD. *Recipient of best poster award.*

Pedersen, W.S., Shackman, A.J., Blaisdell, J.A., Belleau, E.L., **Stout, D.M.,** & Larson, C.L. (2013). Posterior parietal cortex activation predicts working memory capacity for faces. Poster presented at the annual meeting of the Cognitive Neuroscience Society, San Francisco, CA.

Stout, D.M., Shackman, A.J., Wamboldt, M.M., & Larson, C.L. (2013). Neural Measures Indicate That Threat's Privileged Access to Working Memory Reflects Reduced Attentional Filtering. Poster presented at the 2013 Milwaukee Chapter of the Society for Neuroscience, Milwaukee, WI.

Bocinova, A., **Stout, D.M.,** Shackman, A.J., Larson, C.L., & Johnson, J.S. (2013). Do anxious individuals have difficulty gating threat-related information from working memory? Poster presented at the annual Red River Psychology Conference, Fargo, ND.

Stout, D.M., Shackman, A.J., Wamboldt, M.M., & Larson, C.L. (2012). Neural Measures Indicate That Threat's Privileged Access to Working Memory Reflects Reduced Attentional Filtering. Poster presented at the 2012 Society of Psychophysiological Research Conference, New Orleans, LA.

Wamboldt, M.M., **Stout, D.M.,** & Larson, C.L. (2012). Efficient Storage of Fearful Faces in Working Memory. Poster presented at the 2012 University of Wisconsin System Symposium for Undergraduate Research and Creative Activity, Kenosha, WI.

Wamboldt, M.M., **Stout, D.M.,** & Larson, C.L. (2012). Efficient Storage of Fearful Faces in Working Memory. Poster presented at the 2012 University of Wisconsin-Milwaukee Undergraduate Research Symposium, Milwaukee, WI.

Stout, D.M., & Rokke, P.D. (2009). Components of Working Memory Predict Dysphoria. Poster presented at the 2009 Association for Behavioral and Cognitive Therapies Conference, New York City, NY.

Christianson, J., **Stout, D.M.**, & Rokke, P.D. (2007). Cognitive Vulnerability to Depression: A Laboratory Investigation. Poster presented at the 2007 Association for Behavioral and

Cognitive Therapies Conference, Philadelphia, PA.

Lystad, C.M., **Stout, D.M.,** & Rokke, P.D. (2007). Emotion-Congruent Facilitation When Processing Anxious Stimuli. Poster presented at the 2007 Association for Behavioral and Cognitive Therapies Conference, Philadelphia, P.A.

Stout, D.M., Scarski, M., Hochstein, A.A., Allen, J.L., & Rokke, P.D. (2007). Does Anxiety Influence Attention to Body Shape and Weight Words? Poster presented at the 2007 Red River Psychology Conference, Moorhead, MN.

Allen, J.L., Christianson, J., **Stout, D.M.**, Rokke, P.D. (2007). Does Sadness Influence Attention to Body Shape and Weight Words? (2007). Poster presented at the 2007 Red River Psychology Conference, Moorhead, MN.

Randall, A.K., Christianson, J., Scarski, M., **Stout, D.M**., & Rokke, P.D. (2006). State-Trait Anxiety Interactions on Attention. Poster presented at the 2006 Association for Behavioral and Cognitive Therapies Conference, Chicago, IL.

Stout D.M., Randall, A.K., Christianson, J., Mueller, C., Scarski, M., & Rokke, P.D (2006). Individual Differences in Attentional Control on Task Performance. Poster presented at the 2006 Red River Psychology Conference, Fargo, ND.

Randall, A.K., Christianson, J., Scarski, M., **Stout, D.M**., & Rokke, P.D (2006). A Preliminary Investigation of State Trait Anxiety Interactions on Attention. Poster presented at the 2006 Red River Psychology Conference, Fargo, ND.

Christianson, J., Scarski, M., Mueller, C., Randall, A.K., **Stout, D.M**., & Rokke, P.D. (2006). Can the Cognitive Failures Questionnaire Predict Performance on Tasks of Attention? Poster presented at the 2006 Red River Psychology Conference, Fargo, ND.

AD HOC REVIEWER

Cognitive, Affective, and Behavioral Neuroscience; Frontiers in Human Neuroscience; Cognition and Emotion; Psychoneuroendocrinology, Cognitive Neurodynamics

TEACHING EXPERIENCE

Fall 2014	*Graduate Teaching Assistant* Psychology 325, Research Methods University of Wisconsin – Milwaukee Instructor: Dr. Susan Lima
Spring 2012	*Graduate Teaching Assistant* Psychology 325, Research Methods University of Wisconsin – Milwaukee Instructor: Dr. Marcellus Merritt
Fall 2011	*Graduate Teaching Assistant* Psychology 325, Research Methods University of Wisconsin – Milwaukee Instructor: Dr. Susan Lima
Spring 2006	*Undergraduate Teaching Assistant* Human Sexuality North Dakota State University Instructor: Dr. Babette Patton

Spring 2005	*Undergraduate Teaching Assistant* Human Sexuality North Dakota State University Instructor: Dr. Stacy Benson

CLINICAL EXPERIENCE

August 2013-
June 2014

Graduate Student Trainee, *Student Intern Behavior Specialist—Adult Residential OCD Center Rogers Memorial Hospital, Oconomowoc, WI*
Dr. Bradley C. Riemann, Supervisor

- Develop hierarchy and implement exposure and response prevention for OCD-spectrum disorders in a residential setting.
- Implement CBT for a variety of anxiety-related disorders (e.g., GAD, Social Phobia, Panic Disorder) and behavioral activation for depression.

May 2012-
September 2013

Graduate Student Trainee, *Anxiety Disorders Therapist*
NIMH Program of Excellence Training in Scientifically Validated Interventions
University of Wisconsin – Milwaukee, Dr. Shawn Cahill, Supervisor

- Received specialized training and supervision for conducting individual therapy in adults using empirically-based CBT interventions for anxiety disorders (e.g., OCD and Social Anxiety Disorder) at UWM's Psychology Clinic.

June 2012-
September 2013

Graduate Student Trainee, *Student Therapist*
Generalist Team
University of Wisconsin – Milwaukee, Dr. Robyn Ridley, Supervisor

- Conducted individual therapy with adults using CBT and mindfulness-based techniques for generalized anxiety, depression, stress management, and obesity.

September 2011-
May 2012

Graduate Student Trainee, *Anxiety Disorders Assessment*
NIMH Program of Excellence Training in Scientifically Validated Interventions
University of Wisconsin – Milwaukee, Dr. Shawn Cahill, Supervisor

- Received specialized training and supervision for conducting empirically-based assessment for anxiety disorders (e.g., PTSD and OCD).
- Provided comprehensive assessments using structured interviews (SCID, PSS-I, and Y-BOCS) for adults seeking treatment for anxiety disorders.

September 2010-
May 2012

Graduate Student Trainee, *Psychological Assessment Training*
University of Wisconsin – Milwaukee, Dr. Bonnie Klien-Tasman and Dr. Han Joo Lee, Supervisors

- Conducted comprehensive psychological assessments with four adults and one child with integrated reports.
- Administered validated tests of cognitive and academic achievement for assessing learning-related and cognitive difficulties.
- Assessments included structured and semi-structured clinical interviews to formulate DSM diagnostic impressions with recommendations.

- Assessments administered: WAIS-IV, WISC-IV, WIAT-III, Woodcock-Johnson, D-KEFS, CMS, CVLT-II, MMPI-II, and other tests of academic, cognitive, and personality functioning.

July 2008- August 2010	***Needs Assessment Counselor***, Prairie St. John's Psychiatric Hospital Elysia Neubert, MS, LPCC- Supervisor • Worked full-time as triage and intake assessment counselor for adult and child psychiatric and substance abuse treatment center. • Conducted comprehensive assessment and clinical interviews to determine level of care for adults and children. • Coordinated with regional emergency room physicians to transfer patients into psychiatric and substance abuse treatment. • Arranged and coordinated admission process in consultation with admitting psychiatrists for all levels of care (e.g., outpatient, inpatient, and residential treatment).
Fall 2007- 2008	***Graduate Student Intern***, Minnesota State University – Moorhead Spring Counseling Center, Dr. Deb Seaburg and Dr. Sandi Schuette, Supervisors • Worked as student intern conducting individual therapy for mental health and career concerns for university students. • Common concerns presented by students were depression, stress, social anxiety, academic planning, and career concerns. • Administered career assessments for academic and career planning.
Spring 2007	***Graduate Student Intern***, Neuropsychology, Sanford Hospital, Fargo, ND Dr. Paula Bergloff, Supervisor • Observed neuropsychological assessments and feedback at a local outpatient neuropsychology clinic.

HONORS AND AWARDS

2014	Best student poster, inaugural conference of the Society for Affective Science
2013	UWM Graduate Student Travel Award
2013	UWM Department of Psychology Summer Research Fellowship
2012	UWM Graduate Student Travel Award
2011	American Psychological Foundation COGDOP Graduate Research Scholarship
2010-2011	Clinical and Translation Science Institute, Research Fellowship
2010-2011	Chancellor's Graduate Student Award, University of Wisconsin – Milwaukee
2003-2006	Dean's List, North Dakota State University
2004-2006	Chair's List, Psychology Department, North Dakota State University
2004	Psi Chi
2004	The National Society Collegiate Scholars Honor Society
2005	Golden Key International Honour Society
2005	The Honor Society of Phi Kappa Phi
2006	Faculty Excellence Award, Department of Psychology North Dakota State University
2007	Sponsored Program Travel Award to Present Research

MEMBERSHIP IN PROFESSIONAL ORGANIZATIONS

2014-Present	Society for Research in Psychopathology
2014-Present	American Psychological Society
2013-Present	Society for Affective Science

2013-Present	Anxiety and Depression Association of America
2010-Present	American Psychological Association
2010-Present	Society for Psychophysiological Research
2012-Present	Sigma Xi

POSITIONS HELD

2007-2008	*Student Member of Faculty Search Committee* North Dakota State University Department of Psychology
2005-2006	*Psychology Club Officer*, Activity Chair Dr. Chris Kelland Friesen, Faculty Supervisor