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TARGETED MEMORY REACTIVATION FOR ENHANCING EXPOSURE THERAPY

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Targeted Memory Reactivation For Enhancing Exposure Therapy

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

August 2020

Acknowledgements

This dissertation is the result of collective efforts from a number of individuals and institutions, and I am incredibly appreciative of the extensive assistance that I have received. First, I am very grateful for project support that was provided through the Ira Iscoe Fellowship. I would like to recognize my graduate mentor, Michael Telch, for his exceptional insights and guidance that have been indispensible during this process and throughout graduate school. Thank you to my dissertation committee, Joey Dunsmoor, Holly Lapota, and Marie Monfils for their flexibility and for their feedback that has shaped and improved this experiment. I am fortunate to have been able to work with dedicated research assistants that have spent many nights collecting data and weekend mornings in project meetings, especially Lauren Enten, Catherine Gebhardt, John Limbaugh, and Alysse Wiggins. Priya Thomas deserves special recognition for her extraordinary work ethic and project coordination that made this dissertation so much easier. I would also like to extend my appreciation to all of my wonderful graduate colleagues for their support and assistance not only on this project but also during my time at UT Austin. To my amazing friends that have provided so much encouragement and stability during this period of COVID-19, thank you. Finally, I am incredibly grateful to my family, whose support and love has allowed me to pursue my goals.

Abstract

Targeted Memory Reactivation For Enhancing Exposure Therapy

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The University of Texas at Austin, 2020

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Prior research has demonstrated that memory consolidation can be enhanced by coupling learning with an olfactory or auditory contextual cue, then presenting that cue again during subsequent sleep. This process, known as targeted memory reactivation (TMR), has been investigated in basic research but has not been translated into clinical application. The current study investigated whether TMR could be used to augment exposure therapy by promoting consolidation of extinction learning. 109 participants with marked fear of spiders, contamination, or enclosed spaces were given standardized in-vivo exposure therapy in the presence of a contextual odor. Following treatment, they were randomized to one of three conditions: (1) EXPCUE, involving sleep in the presence of the contextual odor previously presented during exposure, (2) NOVCUE, involving sleep in the presence of a novel odor, or (3) CNTL, involving sleep without any odor. Electrodermal and fear responding to behavioral approach tests, as well as self-reported anxiety and disgust, were assessed at baseline, post-treatment, one-week, and one-month follow-up visits. We predicted that at follow-up the EXPCUE condition would exhibit lower anxiety than the NOVCUE and CNTL conditions, and that self-reported peak anxiety during the last exposure trial would moderate the relationship

between condition and anxiety at follow-up. These hypotheses were not supported, as there were no between-group differences in primary outcomes and the predicted moderation effects were not observed. In contrast to hypothesis, the EXPCUE group exhibited a reduced rate of anxiety decrease in comparison to the NOVCUE or CNTL conditions as measured by self-report questionnaires. Results suggest that TMR does not enhance consolidation of extinction learning during exposure therapy.

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CHAPTER 1: INTRODUCTION

Anxiety Disorders: Scope and Significance

EPIDEMIOLOGY

Anxiety disorders are thought to be the most common mental illness in the U.S. Although precise estimates of anxiety disorder prevalence differ somewhat across epidemiological studies, findings consistently demonstrate its pervasive nature. Estimates from the National Comorbidity Survey Replication (NCS-R) placed the lifetime prevalence rate of DSM-IV anxiety disorders at 28.8%, and projected a 31.5% lifetime risk of acquiring any anxiety disorder by age 75 (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005a). Results from this study were consistent with findings from the National Comorbidity Survey (NCS) conducted a decade earlier, which suggested a 24.9% lifetime prevalence rate of anxiety meeting criteria for a DSM-III-R disorder. Meanwhile, the Epidemiologic Catchment Area Survey (ECA), conducted in the early 1980s, found a 14.6% lifetime prevalence of DSM-III anxiety disorders (Bourdon, Rae, Locke, Narrow, & Regier, 1992).

Epidemiological studies that have examined anxiety disorders over shorter timeframes have also found widespread prevalence. The NCS-R, NCS, and ECA reported that during a 1-year period, the percentage of individuals meeting criteria for any anxiety disorder was 18.1%, 17.2%, and 10.1%, respectively (Bourdon et al., 1992; Kessler, Chiu, Demler, Merikangas, & Walters, 2005b; Kessler et al., 1994). Similarly, the National Epidemiologic Survey on Alcohol and Related Conditions found an 11.08% 1-year prevalence rate for any DSM-IV anxiety disorder.

IMPACT AND CONSEQUENCES

Anxiety disorders by definition involve distress or impairment, but they are also associated with a staggering array of secondary consequences. Individuals with anxiety disorders contend with far-reaching negative outcomes relevant to general functioning and well-being, affecting areas such as quality of life, occupational impairment, social functioning, and comorbidity with other mental health disorders.

Mendlowicz and Stein (2000) suggested that regardless of which anxiety subtype is examined, or which experimental methodologies or assessment tools are deployed, anxiety disorders are highly correlated with marked reductions in quality of life and psychosocial functioning. They examined both epidemiologic and clinical studies involving patients with posttraumatic stress disorder (PTSD), social anxiety, obsessive-compulsive disorder (OCD), panic disorder, and generalized anxiety disorder (GAD). The authors concluded that anxiety disorders in general (and especially PTSD and panic) were all strongly tied with decreased quality of life, defined broadly, and that these impairments extended to individuals with subthreshold anxiety disorders.

Additional research has indicated that anxiety disorders are linked to disability across multiple domains of functioning (Greenberg et al., 1999; Kroenke, Spitzer, Williams, Monahan, & Lowe, 2007). Kroenke et al. (2007) assessed anxiety prevalence and functional status at primary care clinics in the U.S., finding that anxiety disorders were highly correlated with impairment in domains of mental health, social functioning, role functioning, general health, bodily pain, and physical functioning. Other studies have determined that anxiety contributes to deficits in occupational performance, manifesting primarily as decreased productivity but also including workplace absenteeism (Greenberg et al., 1999).

Furthermore, anxiety disorders have been linked to comorbidity with other mental illnesses and substance use disorders, future mental illness, and suicidal behavior (Bourdon et al., 1992; Grant et al., 2004; Kasteenpohja et al., 2017; Kessler, Chiu, Demler, Merikangas, & Walters, 2005b). Bourdon, Rae, Locke, Narrow, and Regier (1992) found that 25% of individuals with a DSM-III disorder during a 6-month period had at least one other comorbid disorder. Kessler et al. (2005b) found high rates of comorbidity as well, determining that during a given 12-month period, 22% of individuals with a DSM-IV diagnosis had two diagnoses, and 23% had three or more diagnoses. Other studies have found that individuals with PTSD had significantly elevated probabilities of lifetime suicidal ideation and lifetime suicide attempts, even while controlling for mood and other disorders (Sareen, Houlahan, Cox, & Asmundson, 2005).

Finally, anxiety disorders come at an enormous economic burden to both individuals and society as a whole. Greenberg et al. (1999) estimated that anxiety disorders in the U.S. cost $42.3 billion annually, adjusted to $63.1 billion in 1998 dollars. The authors found that 54% of this cost was attributable to direct nonpsychiatric medical treatment, with an additional 31% attributable to direct psychiatric medical costs. Furthermore, Greenberg et al. determined that 10% of the total economic burden from anxiety disorders stemmed from workplace costs, of which 88% could be traced to decreased workplace productivity.

Taken together, the literature paints a picture of anxiety as a debilitating mental illness that is not only distressing in and of itself, but that also results in a severe impairment across multiple aspects of functioning, increases risk of additional mental and physical problems, leads to significant economic burden, and is responsible for overall reductions in quality of life.

Exposure Therapy

Exposure-based therapies have emerged as an extensively researched and efficacious treatment for anxiety disorders (Deacon & Abramowitz, 2004; Hofmann & Smits, 2008; Norton & Price, 2007; Otte, 2011; Telch, Cobb, & Lancaster, 2014b). The primary component of exposure therapy involves deliberate and repeated approach toward a patient's fear-eliciting stimuli (Arch & Craske, 2009). For example, exposure therapy for ophidiophobia (snake phobia) might involve having a patient approach a snake and remain in close proximity to the animal for an extended duration, while treatment of social anxiety disorder might involve having a patient repeatedly engage in feared social interactions. Both are examples of *in vivo* exposure, in which the patient confronts anxiety-eliciting stimuli in real life. Exposure therapy can also take the form of imaginal exposure, in which the patient deliberately engages with feared thoughts or memories, or interoceptive exposure, in which the patient approaches feared internal bodily sensations such as a racing heart or dizziness (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). Other variants for delivering exposure-based therapy involve the use of writing interventions (D. Sloan, Marx, Bovin, Feinstein, & Gallagher, 2012) or virtual reality (Opriş et al., 2011). Although each therapy modality may differ in their delivery approach, all promote engaging with the patient's feared stimuli or situations.

Efficacy

The efficacy of exposure therapy for the treatment of anxiety disorders is strongly supported by research literature (Deacon & Abramowitz, 2004; Otte, 2011; Telch, Cobb, & Lancaster, 2014b). Evidence suggests that exposure has beneficial effects not only on anxiety symptomology but also on quality of life (Hofmann, Wu, & Boettcher, 2014b).

Norton and Price (2007) conducted a meta-analysis of CBT interventions for anxiety disorders, including 108 studies that had an experimental condition involving exposure, cognitive therapy, or some combination of exposure, cognitive therapy, and relaxation. The study concluded that CBT had a large, beneficial within-group effect on anxiety outcomes, and that these benefits did not differ between treatment components. Furthermore, CBT seemed to be effective for treating all types of anxiety disorders, although marginal evidence suggested that effect sizes for GAD and PTSD might be larger than for social anxiety disorder. Results indicated that all treatment conditions outperformed control conditions. However, these comparisons included no-treatment and expectancy control conditions.

Other studies with more stringent comparison conditions have determined that CBT and behavioral therapies are superior to placebo controls (Hofmann & Smits, 2008). Hofmann and Smits (2008) conducted a meta-analysis of CBT for anxiety disorders that included only randomized, placebo-controlled trials. The study found a pooled effect size of g=0.73 favoring CBT interventions over placebo for anxiety disorder treatment, although an intent-to-treat analysis yielded a smaller effect (g=0.33). The authors found that the greatest benefits were seen in individuals with diagnoses of acute stress disorder and OCD, although controlled trials involving CBT for specific phobias were not included. Neither session count nor type of placebo exhibited a moderating effect on outcomes.

A meta-analysis by Wolitzky-Taylor, Horowitz, Powers, and Telch (2008) examining randomized treatment studies for specific phobias determined that exposure-based treatments offered a large advantage over placebo at post-treatment and at follow-up (d = 0.68). Post-treatment effect sizes were larger when assessed with questionnaires (d = 0.61) as opposed to behavioral assessments (d = 0.42). The study further determined

that exposure therapy outperformed active, non-exposure treatments at post-treatment (d = 0.44) and follow-up (d = 0.35), and the authors found a large effect size for exposure-based treatments over wait-list control (d = 1.05).

Other studies examining the efficacy of exposure-based therapies for specific anxiety disorders have produced similar findings. These have included meta-analyses of studies involving exposure-based treatments for panic (van Balkom et al., 1997), social anxiety (Gould, Buckminster, Pollack, Otto, & Yap, 1997a), GAD (Gould, Otto, Pollack, & Yap, 1997b), OCD (Abramowitz, Franklin, & Foa, 2002), PTSD (Sherman, 1998), and specific phobias (Wolitzky-Taylor et al., 2008). Overall, empirical research strongly supports the efficacy of exposure-based therapies for anxiety disorder treatment.

BEHAVIORAL MODELS OF FEAR EXTINCTION

Because behavioral models of fear acquisition assume that disorders stem from associations between neutral stimuli and aversive responses, it stands to reason that individuals who learn to associate previously feared stimuli with benign responses instead will exhibit attenuated anxiety. The procedural method for accomplishing this involves repeatedly presenting the conditioned stimulus (CS) without the unconditioned stimulus (UCS), which eventually extinguishes the conditioned response (CR) to the CS. In humans, this extinction process is referred to as exposure.

Researchers believe that exposure does not erase the original associations between the stimuli and danger, but instead generates new associations in which the previously feared stimuli now signal safety (Craske, Liao, Brown, & Vervliet, 2012). These new inhibitory memories are thought to outcompete original associations of danger, while leaving previous memories intact. Support for this inhibitory learning account of extinction is evidenced by accelerated reacquisition of fear even after extinction (Napier,

Macrae, & Kehoe, 1992), as well as post-extinction return of fear accompanying a change in context (renewal; Bouton & Bolles, 1979), presentation of the UCS (reinstatement; Rescorla & Heth, 1975), or with the passage of time (spontaneous recovery; Pavlov, 1927)

CRITICISMS OF BEHAVIORAL MODELS

Purely behavioral models of anxiety disorders cannot account for several phenomena observed in fear acquisition and extinction. Researchers have demonstrated that phobias can develop even in the absence of conditioning events, and that individuals with anxiety disorders do not necessarily have a more extensive history of aversive conditioning events than individuals without an anxiety disorder (Menzies & Clarke, 1995). For example, researchers have found that a history of injury-inducing falls does not prospectively predict later fear of heights, and may actually exert a protective effect that decreases the probability of receiving an acrophobia diagnoses later in life (Poulton, Davies, Menzies, Langley, & Silva, 1998). Associative-learning models of fear also do not readily explain why exposure to traumatic or aversive events only lead to subsequent anxiety disorders for a subset of exposed individuals, such as in PTSD (LeardMann et al., 2009).

Conditioning models have also been criticized on grounds that associative learning should lead to fear of a diverse array of stimuli and situations, whereas anxieties observed in the real world are disproportionately concentrated on a select number of fears (Rachman, 1977). Furthermore, fear can be acquired indirectly through social transmission (Rachman, 1977), even in the absence of exposure to the feared stimulus. Dunne and Askew (2013) found that modeling fear or happiness could be used to either

condition or extinguish fear of novel animals in a sample of children, demonstrating that vicarious learning can be a pathway by which fear is acquired.

COGNITIVE-BEHAVIORAL MODELS

Cognitive models of anxiety disorders address many of these criticisms. These models emphasize the role of cognitions in anxiety, under the assumption that anxiety disorders are driven by exaggerated threat appraisals and maladaptive perception and processing of events (Beck & Clark, 1997). In this way, anxiety disorders are more broadly conceptualized to incorporate mental processes and cognitions, instead of singularly focusing on behavioral components. However, cognitive and behavioral approaches are often difficult to disentangle both in theory and practice (Deacon & Abramowitz, 2004). Even interventions involving only ostensibly behavioral components may actually reduce anxiety through cognitive mechanisms in which faulty threat appraisals are challenged and corrected. As such, many models of fear acquisition and extinction are characterized as cognitive-behavioral in nature.

Emotional Processing Theory

Emotional processing theory (EPT) is one such theory, which offers a description of putative fear reduction processes in exposure therapy. EPT has its origins in Lang's (1979) bio-information theory, which provided a conceptual framework for the organization of emotional imagery. This framework was used by Rachman (1980) to provide an account of emotional processing, and was later refined by Foa and Kozak (1986) and applied specifically as an explanation for fear reduction. Emotional processing theory proposes that fear is based on the activation of an information structure comprised of three elements: the feared stimulus, the responses that it elicits (verbal,

physiological, and behavioral), and the meanings associated with these representations. In this view, pathological anxiety is characterized by distorted associations between elements of the fear structure, as well as exaggerated response elements and resistance to structure modification.

EPT asserts that exposure facilitates reduction of fear through modification of the fear structure (Foa & Kozak, 1986), or by inhibition from a newly learned non-fear structure (Foa & McNally, 1996). Initially, exposure to the feared stimulus activates the fear network, with such activation being a necessary component for processing to occur. Following this, incorporation of new information that is incompatible with the existing structure serves to weaken the fear network associations. As an illustration of how this might be realized in practice, within-session habituation (fear decline during a single session) might provide new information that the feared stimulus does not lead to physiological fear responding. This information would challenge the previously held association between the stimulus and resulting physiological fear, leading to fear structure modification such that the stimulus and its previous response were no longer coupled. Repeated exposures might also change the meaning associated with stimulus and response elements, such that an individual would no longer exaggerate the probability or valence of their feared outcome. Foa and Kozak (1986) indicated that emotional processing would be characterized by markers of fear structure activation, within-session habituation, and between-session habituation (fear decline between distinct sessions over an extended period of time).

EPT enjoys widespread endorsement, but more recent evidence has called into question the original model's accounting of exposure-based fear reduction (A. Baker et al., 2010). A review by Craske et al. (2008) not only suggests that within-session habituation fails to predict long term treatment outcomes, but also calls into question the

importance of initial fear activation and possibly between-session habituation on long-term fear reduction. Taking new experimental findings into account, Foa, Huppert, and Cahill (2006) offered an update to EPT that de-emphasizes the importance of within-session habituation.

Expectancy Theories

Expectancy models of fear propose that anticipation of aversive outcomes is central to anxiety disorders, and that these expectations can be acquired through a host of potential learning pathways including observation of others, cognitive learning, or associative learning (Reiss, 1980). These theories also recognize that fear can derive from negative expectations related to multiple aspects of a situation, such as the potential for objective harm, presence of anxiety, social embarrassment, and sensitivity to anxiety itself or its perceived negative consequences (Reiss, 1991; Reiss & McNally, 1985). From this perspective, an individual's fear of flying, for example, might be motivated by an expectation that their plane will crash, but could also be motivated by the expectation of having a panic attack in public (coupled with sensitivity to such anxiety). In this way, expectancy theories highlight the role of cognitive appraisal in the onset, maintenance, and modification of pathological fear.

Bandura (1988) postulated that pathological anxiety derives from perceived inability to cope with environmental threats. Individuals possessing self-efficacy in their ability to control threats arising from situational events do not experience anxious arousal, whereas those who believe that they are unable to manage potential threats will experience anxiety in the face of these perceived threats. Thus, Bandura's self-efficacy theory posits that an individual's degree of coping self-efficacy is of primary importance in determining the presence of anxiety disorders, and experimental evidence has

supported this claim (Bandura, Adams, & Beyer, 1977; Valentiner, Telch, Ilai, & Hehmsoth, 1993).

Bandura argued that there were four primary sources of information by which expectations of self-efficacy could be modified: 1) performance accomplishments, such as increased ability to approach a feared stimulus, 2) vicarious experience, such as seeing another individual approach a feared stimulus without negative consequence, 3) verbal persuasion, serving to increase perceived coping ability through suggestion, and 4) emotional arousal, which an individual might use to appraise their level of vulnerability (Bandura, 1977). Fear reduction in the self-efficacy conception of anxiety disorders is attained by building self-efficacy, for example by gradually mastering an increasingly challenging series of exposure tasks. Bandura further proposed that psychotherapy in general, regardless of form, reduces fear through the common mechanism of increased coping self-efficacy (Bandura, 1977).

Kirsch's response expectancy theory emphasized the importance of anticipation of one's own automatic reactions to cues, and how these response expectancies might shape subjective experience as well as voluntary behavior (Kirsch, 1985). For example, Kirsch and Weixel (1988) showed that experiment participants who consumed decaffeinated coffee experienced changes in alertness, blood pressure, and motor performance, but only if they thought that they were ingesting caffeinated coffee. In contrast to self-efficacy theory, which describes beliefs about one's ability to purposefully respond to potential threats, response expectancy theory highlights the importance of nonvolitional responses (Kirsch, 1985). The model suggests that anxiety disorders are maintained by anxiety expectancies, and that exposure reduces anxiety through modification of these expectancies. Support for response expectancy theory is provided by experiments demonstrating high correlation between expected and actual

improvements in anxiety following exposure (Kirsch, Tennen, Wickless, Saccone, & Cody, 1983; Southworth & Kirsch, 1988; Valentiner et al., 1993), by studies suggesting equivalent anxiety reductions from credible expectancy modification procedures (placebo) and from systematic desensitization (Kirsch & Henry, 1977), and by experiments showing that the benefits of in-vivo exposure only emerge in the presence of therapeutic expectancies (Southworth & Kirsch, 1988).

LIMITATIONS OF EXPOSURE THERAPY

Despite the success of exposure-based therapies in treating anxiety disorders, exposure therapy is not effective for all patients. The commonly used metric of effect size provides a measure of the impact of treatment on an experimental group in aggregate, but does not address effects at an individual level. As such, studies yielding positive findings for treatment efficacy often reflect pooled anxiety reductions for the experimental group as a whole, even as significant percentages of treated participants do not improve. Individuals who undergo exposure-based treatments may fail to respond altogether, maintain residual symptoms, or relapse following treatment termination (Barlow, Gorman, Shear, & Woods, 2000; Wetherell, Gatz, & Craske, 2003).

Loerinc et al. (2015) conducted a review of response rates to CBT for anxiety disorders, determining that 49.5% of individuals responded to CBT at post-treatment and 53.6% responded at follow-up. Percentages of participants characterized as responders were reduced when employing more stringent analyses and classification criteria, including the use of intent-to-treat analyses (resulting in reductions of 8% at post-treatment and 13% at follow-up), utilization of multiple instruments to define response status (reductions of 16% and 15%), and adoption of clinically significant change to define responder status (reduction of 28%), an operationalization that takes into account

significant symptom reduction as well as the presence of subclinical levels of anxiety following the intervention (Jacobson & Truax, 1991). In practice, response rates to exposure-based therapies are likely to be even lower than those suggested by Loerinc et al. (2015), as their review included randomized controlled trials in which therapists had greater access to resources and training than those available in real-world contexts. Clearly, there is significant room for exposure therapy to be improved.

AUGMENTATION STRATEGIES

To remedy these deficits, researchers have explored an variety of strategies for augmenting exposure (Telch, Cobb, & Lancaster, 2014b; Weisman & Rodebaugh, 2018). The augmentation literature is extensive, including treatment additions such as safety behavior fading (Telch & Lancaster, 2012), antagonistic actions that oppose fear-based avoidance tendencies (Wolitzky & Telch, 2009), cognitive restructuring (Bryant et al., 2008), and pharmacological cognitive enhancers (Hofmann, Smits, Asnaani, Gutner, & Otto, 2011). Other strategies have explored optimization of exposure parameters (Foa, Jameson, Turner, & Payne, 1980; Rowe & Craske, 1998a), or manipulation of fear memory reconsolidation (Telch, York, Lancaster, & Monfils, 2017). A brief overview of several exposure augmentation strategies follows.

Safety Behavior Fading

Safety behaviors, defined by Telch and Lancaster (2012) as "unnecessary actions taken to prevent, escape from, or reduce the severity of a perceived threat," are common across all anxiety disorders (Helbig-Lang & Petermann, 2010). An individual with combat PTSD, for example, might avoid watching war movies that remind them of their

trauma, or an individual with social anxiety disorder might attempt to manage their fear of negative evaluation by consuming alcohol before social gatherings.

Experimental evidence indicates that safety behaviors cause and maintain excessive anxiety (Telch & Lancaster, 2012). Olatunji, Etzel, Tomarken, Ciesielski, and Deacon (2011) had undergraduate students engage in a variety of health-related safety behaviors such as consistently washing or disinfecting their hands after handling money. These behaviors led to increased anxiety and avoidance during health-related behavioral tests in comparison to a control group, demonstrating that safety behaviors can causally induce health-related anxiety.

Other studies have suggested that safety behaviors interfere with exposure efficacy. Sloan and Telch (2002) found that individuals who were allowed to engage in safety behaviors during exposure treatment for claustrophobia (such as checking to make sure that the door to the treatment chamber was unlocked, or opening chamber air vents) had significantly greater fear at post-treatment and follow-up than those who were not allowed to use safety behaviors. Powers, Smits, and Telch (2004) further demonstrated that the mere availability of safety aids during therapy interferes with treatment efficacy, even if the safety aids are not actually used. Still, although numerous experiments have suggested that safety behaviors interfere with exposure efficacy (McManus, Sacadura, & Clark, 2008; Powers et al., 2004; Sloan & Telch, 2002), these results have not been consistently replicated across all studies (Meulders, Van Daele, Volders, & Vlaeyen, 2016).

In response to evidence demonstrating an anxiogenic effect of safety behaviors, a number of experiments have investigated whether intentionally fading safety behaviors during exposure improves treatment efficacy. For example, Taylor and Alden (2011) randomly assigned socially anxious individuals to receive either public speaking

exposure only, or exposure with suppression of idiosyncratic safety behaviors. Results indicated that the safety behavior fading group exhibited enhanced outcomes relative to the exposure only group (Taylor & Alden, 2011). Evidence from other experimental studies has corroborated this finding. Telch and Lancaster (2012) reviewed studies that compared regular exposure treatment to an experimental group that faded safety behaviors during exposure. The authors found that all eight experiments meeting this criterion reported enhanced treatment outcomes for the safety behaviors fading group, providing compelling support for safety behavior fading as a treatment augmentation strategy.

Fear Antagonistic Actions

Instead of merely fading safety behaviors during treatment, several studies have examined whether engaging in actions that are in direct opposition to safety behaviors has exposure-enhancing effects. Wolitzky and Telch (2009) investigated the effects of adding fear antagonistic actions to exposure for acrophobia. Researchers instructed individuals in the experimental group to engage in actions such as placing their hands behind their back while looking over a balcony, in opposition to the tendency to grip the railing for safety. The researchers found that adding antagonistic actions to exposure resulted in greater behavioral and subjective fear reduction in comparison to a group that was only given exposure. Wolitzky and Telch reported superiority of the antagonistic actions group at post-treatment and at 1-month follow-up, even in a novel assessment context (Wolitzky & Telch, 2009).

Nelson, Deacon, Lickel, and Sy (2010) obtained similar findings in a sample of individuals with speech anxiety. In this study, undergraduates with elevated public speaking anxiety delivered a series of speeches to experimenter confederates, but were

randomly assigned to deliver the speeches either as competently as possible, or while engaging in potentially embarrassing behaviors such as stuttering. As hypothesized, the group that incorporated fear antagonistic actions into their exposures demonstrated better clinical outcomes than the exposure-only group (Nelson et al., 2010). Although systematic research into antagonistic actions is still nascent, early results suggest that adding fear antagonistic actions to exposure holds promise as an augmentative strategy.

Optimizing Exposure Parameters

Other research strategies have examined whether optimizing various parameters of exposure delivery can enhance treatment outcomes. Parameters have included the temporal spacing between exposure sessions, ordering of exposure trials by level of difficulty, degree of variation in exposure stimuli and contexts, and treatment modality (group or individual therapy).

Temporal Spacing

Early fear extinction studies in animals suggested that massing extinction trials (i.e. minimizing inter-trial intervals) accelerated fear reduction (Mackintosh, 1970). While some researchers have suggested that such effects may be attributed to decreased opportunities for avoidance between trials (Foa et al., 1980), others have noted that the benefits of massed extinction are limited to periods of knowledge acquisition, and that increasing spacing between exposures may enhance long-term fear reduction (R. A. Schmidt & Bjork, 1992) and learning generalization across temporal contexts (Bouton & Swartzentruber, 1991).

As a whole, the literature comparing massed versus spaced exposures has not found clear superiority of one approach over the other. Some studies have reported an

advantage of spaced exposure trials for fear of spiders (Rowe & Craske, 1998b) and public speaking anxiety (Tsao & Craske, 2000), while another found beneficial effects of massing exposure trials for agoraphobia (Foa et al., 1980). However, a majority of experiments across numerous anxiety disorders such as acrophobia (A. J. Lang & Craske, 2000), claustrophobia (Ost, Alm, Brandberg, & Breitholtz, 2001), dental anxiety (Ning & Liddell, 1991), OCD (Abramowitz, Foa, & Franklin, 2003), and panic (Bohni, Spindler, Arendt, Hougaard, & Rosenberg, 2009) have failed to find robust treatment effects resulting from manipulation of inter-trial intervals. Nevertheless, small sample sizes and substantial variance in operational definitions of massed versus spaced trials limit the ability to definitively conclude that the two approaches are equivalent.

Graduated vs Nongraduated

Another parameter of interest is the ordering of exposure trials by difficulty. During graduated exposures, patients are first asked to approach cues that elicit relatively low levels of fear, before confronting cues that successively increase in intensity. In contrast, non-graduated approaches may involve immediate and sustained exposure to an individual's most highly activating fear cues, such as in flooding or implosion therapy. Researchers have also attempted to present fear hierarchy items in a random order, exposing patients to a variety of exposure intensities in a non-linear fashion.

Comparisons of graduated exposures versus flooding have resulted in mixed findings across anxiety disorders. While some experiments have reported superiority of graduated exposure (Boersma, Hengst, Dekker, & Emmelkamp, 1976; De Moor, 1970; Willis & Edwards, 1969), other studies found an opposite effect in which flooding enhanced treatment outcomes (Boulougouris, Marks, & Marset, 1971; Kirsch, Wolpin, & Knutson, 1975). Other experiments reported little difference in treatment outcomes,

regardless of the approach used (Abramowitz, 1996; Crowe, Marks, Agras, & Leitenberg, 1972; Pall M G Emmelkamp, 1974; Everaerd, Rijken, & Emmelkamp, 1973; Gelder et al., 1973). Overall, no obvious advantage for graduated exposures versus flooding techniques has emerged, although future research incorporating larger samples and more stringent methodologies may offer additional clarity.

Researchers have also looked at whether randomizing the order of exposure cue difficulty enhances learning, as opposed to gradually increasing cue intensity or maximizing cue intensity over the entire course of treatment (Kircanski et al., 2012; A. J. Lang & Craske, 2000). However, these manipulations have generally been combined with simultaneous variation in other exposure parameters such as environment and stimulus, making it difficult to examine the isolated effect of randomizing cue intensity.

Variation in Context, Intensity, and Stimuli

Based on principles of inhibitory learning, increasing the variability of exposure enhances an individual's ability to generalize extinction learning beyond the context in which it was originally acquired, and facilitates retrieval of inhibitory associations (Craske et al., 2014). One target for increasing variability is in an individual's emotional state during exposure, which is presumably disrupted by random ordering of fear cue intensities. Some researchers have argued that this approach more closely simulates natural encounters with feared stimuli outside of therapy, and may help individuals build confidence in their capacity to handle unexpected and aversive situations, regardless of intensity and timing (Jacoby & Abramowitz, 2016). Other parameters that may be varied include stimulus type and number, as well as the environmental context in which training is conducted.

Lang and Craske (2000) randomly assigned undergraduates with fear of heights to receive either exposure with constant parameters, or with exposure with varied parameters. For the constant group, height exposure trials were conducted at a single location, in order of sequentially increasing height, and using the same manner of approach toward the feared situation during each trial. Individuals in the varied group conducted exposures at two locations, with each trial conducted at a different height than the previous trial, while using a different approach style. Results indicated that groups did not differ in terms of re-emergence of fear of heights, although the variable exposure group reported reduced general anxiety at follow-up (A. J. Lang & Craske, 2000).

Kircanski and colleagues (2012) simultaneously manipulated variability of exposure duration, stimuli type, and fear intensity in a sample of undergraduates with contamination fear. No general advantage of variable exposure over constant exposure was found between conditions at post-treatment or 2-week follow-up, but the authors reported that greater variability in fear during exposure predicted improved outcomes at follow-up.

Experiments testing the effects of increasing the number and diversity of stimulus targets have focused on fear of spiders. Rowe and Craske (Rowe & Craske, 1998b) and Shiban, Schelhorn, Pauli, and Mühlberger (2015b) both found that using multiple exposure targets resulted in greater fear attenuation than control groups who were exposed to a single target. Shiban et al. (2015b) included additional experimental conditions in which the treatment context was altered. The authors observed that while the use of multiple treatment contexts reduced fear at post-treatment, effects did not persist at follow-up, and that there were also no observed benefits from simultaneously varying stimulus and context (Shiban, Schelhorn, Pauli, & Mühlberger, 2015b).

Studies to date have produced several equivocal findings, and further investigation into the effects of varying exposure parameters is needed before firm conclusions can be drawn. As the field awaits these studies, some researchers have suggested that clinicians should consider incorporating variation during exposures, due to the potential risk of elevated return of fear if they fail to do so (Weisman & Rodebaugh, 2018).

Modality

Exposure therapy conducted in a group format has the advantage of being more cost- and time-efficient than individual therapy, at the expense of reducing the personal attention received by each individual. Several studies investigating the relative efficacies of exposure delivered in group versus individual formats for OCD have found an advantage of individual therapy (Cabedo et al., 2010; O'Connor et al., 2005). However, a small meta-analysis of OCD treatment studies by Jonsson and Hougaard (2010) suggests that even if an advantage exists, the effect size is likely to be small (d = 0.15). Other OCD experiments found no differences in clinical outcome between group or individual modalities (P. Barrett, Healy-Farrell, & March, 2004), including studies that examined long-term outcomes at follow-ups ranging from 1 to 7 years (P. Barrett, Farrell, Dadds, & Boulter, 2005; Jaurrieta et al., 2008; O'Leary, Barrett, & Fjermestad, 2009).

One RCT investigating the effect of group or individual exposure for panic disorder found support for superiority of individual therapy (Sharp, Power, & Swanson, 2004). An additional panic disorder study reported partial support favoring individual therapy, but suffered severe methodological concerns including lack of random assignment and the use of a single therapist to assess outcomes and deliver therapy for both treatment conditions (Néron, Lacroix, & Chaput, 1995). In an randomized controlled

trial investigating treatment for social anxiety disorder, Dogaheh, Mohammadkhani, and Dolatshahi (2011) reported greater efficacy of group therapy than individual therapy, although the two groups achieved equivalent rates of clinically significant response.

Overall, individual therapy may be slightly more effective than group therapy for OCD and panic disorder, but these benefits are likely to be small. For social anxiety disorder, group therapy may be preferable to individual therapy.

Anxiety Management

Researchers have deployed a variety of anxiety management techniques in conjunction with exposure therapy, including strategies such as progressive muscle relaxation, diaphragmatic breathing, self-talk, and distraction. These techniques have been theorized to potentially increase an individual's efficacy and ability to persist during aversive exposures (Butler, Cullington, Munby, Amies, & Gelder, 1984), but also risk being used as maladaptive safety behaviors that might decrease treatment efficacy (N. B. Schmidt et al., 2000).

Most research into treatment augmentation with anxiety management has focused on the effect of adding breathing retraining to exposure-based therapy for panic disorder, or panic disorder with agoraphobia. Such studies have consistently found that anxiety management techniques do not augment exposure-based therapies, as experimental groups utilizing anxiety management exhibited similar outcomes to exposure-only groups (de Ruiter, Rijken, Kraaimaat, & Garssen, 1989; Deacon et al., 2012; Michelson, Marchione, Greenwald, Testa, & Marchione, 1996; N. B. Schmidt et al., 2000). In PTSD treatment studies, one experiment indicated that adding stress inoculation training to prolonged exposure reduced treatment efficacy (Foa et al., 2009). However, several studies using socially anxious samples have found beneficial effects of adding anxiety

management (Borkovec & Sides, 1979; Butler et al., 1984). Overall, anxiety management does not appear to augment exposure for panic disorder and agoraphobia, although further research is needed for other anxiety disorders.

Cognitive Strategies

Efforts to determine whether exposure may be augmented with cognitive restructuring techniques have resulted in divergent findings. Bryant et al. (2008) randomly assigned individuals with PTSD to one of four treatment arms: imaginal exposure (IV), in-vivo exposure (IVE), a combination of imaginal and in-vivo exposure (IE/IVE), or IE/IVE with cognitive restructuring (IE/IVE/CR). At 6-month follow-up, the IE/IVE/CR group had a significantly reduced PTSD rate (31%) in comparison to the exposure only conditions (IE: 75%; IVE: 69%; IE/IVE: 63%). This finding was supported by an additional study that found superiority of imaginal exposure with cognitive restructuring over imaginal exposure alone (Bryant, Moulds, Guthrie, Dang, & Nixon, 2003). Other experiments have found that adding cognitive restructuring to exposure offered no benefit in PTSD outcomes (Foa et al., 2005; Marks, Lovell, Noshirvani, Livanou, & Thrasher, 1998), although methodological differences may account for these discrepant findings. Bryant et al. (2008) noted that exposure protocols often include post-exposure processing that overlaps with elements of cognitive restructuring, potentially masking augmentative effects.

Several studies have investigated exposure augmentation with guided threat reappraisal (GTR), which involves identification of the participant's specific fear-relevant threats, attentional focus on core threats during exposure, and examination of evidence to disconfirm these perceived threats (Kamphuis & Telch, 2000; T. Sloan & Telch, 2002). Kamphuis and Telch (2000) conducted a randomized claustrophobia treatment study in

which exposure alone was compared to exposure with GTR. Two additional treatment arms included a cognitively demanding task, for the purpose of investigating the effects of distraction. Results indicated that combining GTR with exposure resulted in significant fear reduction compared to exposure alone, regardless of whether distraction was present. Findings also suggested that the distractor task interfered with fear reduction, regardless of the presence of GTR (Kamphuis & Telch, 2000). In support of these findings, Sloan and Telch (2002) randomized claustrophobic participants to receive either exposure with GTR, exposure with safety behavior usage, or exposure alone, and found that the exposure with GTR condition exhibited the greatest fear reductions of any group.

In treatment studies of SAD, several studies have reported benefits of adding cognitive techniques to exposure therapy (Mattick & Peters, 1988; Mattick, Peters, & Clarke, 1989), while one meta-analysis found no advantage of combining exposure with cognitive therapy (Powers, Sigmarsson, & Emmelkamp, 2008). Studies of PDA have similarly resulted in mixed findings, with various studies providing support for (Michelson et al., 1996) or against (Ost, Thulin, & Ramnero, 2004; S. Williams & Falbo, 1996) the efficacy of cognitive add-ons. Although there is not consistent evidence that cognitive strategies augment exposure therapy, it is likely that specific methodological considerations (such as the use of "purely" behavioral exposure conditions with limited or no cognitive components) need to be satisfied in order for treatment effects to be observed (Telch, Cobb, & Lancaster, 2014b).

Cognitive Enhancers

While numerous processes are likely to drive any improvements realized from these augmentation strategies or from psychotherapy more generally, all non-

pharmacological psychotherapies share a dependence on some form of new learning to achieve therapeutic progress. Regardless of whether this learning involves acquisition of inhibitory safety associations in response to a stimulus, modification of cognitive interpretations of an individual's fear response, shifts in expectations of threat, development of self-efficacy, or acquisition of new knowledge from other mechanisms, any approach that enhances psychotherapy-based learning will presumably lead to improved treatment outcomes as well. As such, researchers have also attempted to facilitate acquisition and retention of learning that occurs during existing exposure treatments, rather than modifying parameters of the exposure itself (Davis, Barad, Otto, & Southwick, 2006).

D-Cycloserine

Recent efforts in this domain have turned to the use of pharmaceutical agents known as cognitive enhancers for improving learning and consolidation of exposure-based learning (Hofmann et al., 2011). The most heavily researched pharmacological agent of this class is D-cycloserine (DCS). DCS promotes activity of *N*-methyl-D-aspartate (NMDA) protein receptors, which have been implicated in extinction learning in rodents and humans (Davis, 2011). Walker, Ressler, Lu, and Davis (2002b) showed that DCS facilitated fear reduction in rats who were dosed with the agent during extinction training, but not in rats who did not undergo extinction. This demonstrated that DCS does not function as a general anxiolytic, but rather acts upon fear learning specifically. Following this, Ledgerwood, Richardson, and Cranney (2003) showed that DCS enhances fear reduction in a dose-dependent fashion even when administered post-extinction, supporting the notion that DCS promotes learning consolidation. In human trials for anxiety and related disorders, results have also been promising. A recent meta-

analysis of 22 double-blind, randomized clinical trials examining augmentative effects of DCS for CBT found that individuals who were given DCS showed greater symptom reduction and lower severity at posttreatment than individuals who were given placebo (Mataix-Cols et al., 2017). However, this effect size was small (d=0.25) and it decreased further at follow-up (d=0.19).

Yohimbine

Another substance being studied as a cognitive enhancer is yohimbine, an α2-adrenoreceptor antagonist that acts to increase extracellular norepinephrine levels in neural areas related to fear and extinction, and which has been linked to facilitation of emotional memory consolidation (Holmes & Quirk, 2010; Kaplan & Moore, 2011). Several rodent studies have demonstrated that yohimbine administration promotes extinction learning (Cain, Blouin, & Barad, 2004; Hefner et al., 2008), although others have failed to find such as effect (Mueller, Olivera-Figueroa, Pine, & Quirk, 2009), and open questions remain as to the context-dependency of yohimbine augmentation (Morris & Bouton, 2007).

Human studies suggest that yohimbine may be an effective adjunct to exposure therapy. Powers, Smits, Otto, Sanders, and Emmelkamp (2009) randomly assigned 24 claustrophobic participants to receive either yohimbine or placebo prior to exposure. Results indicated that participants in the yohimbine group experienced greater fear reduction than the placebo group at one-week follow-up but not at posttreatment, consistent with a memory-enhancing mechanism of action. Smits et al. (2014) conducted an RCT examining yohimbine-augmented exposure for social anxiety disorder. The authors found moderate support for augmentative effects of yohimbine, with the yohimbine group demonstrating better outcomes than the placebo control group on self-

report measures but not on clinician-rated measures. Notably, yohimbine's beneficial effects were moderated by low end-fear after exposure, suggesting the presence of exposure-based learning consolidation.

Methylene Blue

Methylene blue (methylthioninium chloride) is a synthetic compound that enhances mitochondrial oxidative metabolism and improves memory consolidation when administered at low doses (Martinez, Jensen, Vasquez, McGuinness, & McGaugh, 1978; Rojas, Bruchey, & Gonzalez-Lima, 2012). It is thought to interact with the mitochondrial enzyme cytochrome oxidase and increase brain oxygen consumption, mediating enhancements in memory (Rojas et al., 2012). In rodents, the use of methylene blue has been shown to improve various forms of learning (Riha, Bruchey, Echevarria, & Gonzalez-Lima, 2005), including enhanced retention of safety memories following extinction of conditioned fear (Gonzalez-Lima & Bruchey, 2004; Wrubel, Barrett, Shumake, Johnson, & Gonzalez-Lima, 2007). Telch et al. (2014a) conducted the only study to examine methylene blue as an exposure augmentation in humans. In this study, claustrophobic participants were randomly assigned to receive either methylene blue or placebo immediately following exposure therapy. Results indicated that for the methylene blue group, posttraining fear level moderated fear exhibited at one-month follow-up, while no moderating effect was present for the placebo group. Participants who had been given methylene blue and who demonstrated low posttraining levels of fear exhibited improved outcomes relative to participants who had been given placebo. Meanwhile, methylene blue participants who exhibited high levels of posttraining fear reported elevated fear at follow-up, demonstrating that methylene blue broadly promotes

learning retention and suggesting that it may be most effective when administration is reserved for successful exposure sessions.

Limitations of Cognitive Enhancers

Findings regarding the use of pharmacological cognitive enhancers as an adjunct to exposure therapy suggest that this is a promising area of research. Still, it is important to recognize that a majority of patients prefer to receive non-pharmacological approaches when treating psychiatric disorders (McHugh, Whitton, Peckham, Welge, & Otto, 2013; Roy-Byrne, Berliner, Russo, Zatzick, & Pitman, 2003). This is particularly relevant in light of the fact that many individuals actively avoid seeking professional help for emotional problems (Mojtabai, Evans-Lacko, Schomerus, & Thornicroft, 2016), or do not receive treatment for anxiety disorders at all (Kroenke et al., 2007). Using data from the National Comorbidity Survey (Kessler et al., 1994), Mojtabai, Evans-Lacko, Schomerus, and Thornicroft (2016) found that over 20% of respondents reported that they would "definitely not" or "probably not" seek professional help for a serious emotional problem. Additionally, pharmacological interventions involve other difficulties including availability of medication prescribers, drug tolerance (Parnas, Weber, & Richardson, 2005) and unwanted side effects (Vasa et al., 2009). These considerations motivate exploration of other, nonpharmacological strategies for promoting consolidation.

Reconsolidation Updating

Researchers have also attempted to augment exposure by interfering with the memory reconsolidation process. Newly encoded memories exist in a labile, unstable state before they are transformed into more durable form during consolidation (McGaugh, 2000). Evidence suggests that reactivating fear memories temporarily returns

them to a state of lability for a period lasting no longer than six hours, after which they reconsolidate once more (Nader & Hardt, 2009; Nader, Schafe, & Le Doux, 2000). Some treatment augmentation research has involved briefly reactivating fear memories prior to exposure. Conducting treatment during the reconsolidation window ostensibly eliminates fear associations and leads to more durable fear reduction than inhibitory learning alone (Agren, 2014). In a landmark study, Monfils, Cowansage, Klann, and LeDoux (2009) demonstrated that reactivating a conditioned fear memory prior to extinction training reduced spontaneous recovery, renewal, reinstatement, and susceptibility to reconditioning in a rodent model. These benefits were only observed when extinction was conducted within the post-retrieval reconsolidation updating window (for example, 10 minutes after retrieval), and not when extinction was conducted 6 hours or more after retrieval, or when retrieval was withheld altogether (Monfils et al., 2009).

Augmentation studies involving reconsolidation interference in humans have primarily involved extinction of conditioned fear (Schiller et al., 2010), while other studies have used pharmacological agents (Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2010) to disrupt reconsolidation. Although some studies reported an augmentative effect of fear memory reactivation (E. L. James et al., 2015; Oyarzún et al., 2012; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013), these results have not consistently been replicated (Chan, Leung, Westbrook, & McNally, 2010; Golkar, Bellander, Olsson, & Öhman, 2012; Kindt & Soeter, 2013; Schroyens, Beckers, & Kindt, 2017).

Several experiments have used clinical samples to investigate exposure augmentation by manipulation of reconsolidation. Telch, York, Lancaster, and Monfils (2017) randomized participants with fear of spiders or snakes to one of two conditions: a brief fear reactivation applied thirty minutes prior to exposure therapy, or an identical fear reactivation applied after exposure therapy. Results indicated that the group

receiving fear reactivation before exposure exhibited accelerated fear reduction during treatment, and reduced phobic responding at 1-month follow-up, relative to the control group (Telch et al., 2017). In contrast, Shiban, Brütting, Pauli, and Mühlberger found no advantage of fear reactivation prior to virtual exposure therapy for fear of spiders (Shiban, Brütting, Pauli, & Mühlberger, 2015a), although procedural differences may account for these disparate findings. Examination of reconsolidation interference as an augmentative strategy for exposure therapy is still at an early stage, and additional research is underway to further evaluate the efficacy of this approach.

Enhancing Memory Consolidation

Basic research into the neuroscience of learning and memory may provide insight into alternative methods for augmenting consolidation of exposure-based learning. Advances in understanding the nature of memory consolidation have led to the discovery that specific memories may be preferentially selected for consolidation during sleep (Rasch, Büchel, Gais, & Born, 2007). The development of this technique, which is known as targeted memory reactivation, opens the possibility of applying this method to clinical interventions for anxiety and other disorders. By intentionally promoting consolidation of learning specifically acquired during therapy, it may be possible increase the potency of exposure and improve retention of therapeutic gains. The remainder of this chapter reviews contemporary knowledge on memory consolidation, followed by an overview of recent efforts to promote consolidation of specific memories during sleep.

CONSOLIDATION AND SLEEP

Each day we are exposed to a vast quantity of information and experiences, creating innumerable opportunities for new learning and memory formation. However, newly acquired knowledge exists in a transient, labile state that is susceptible to decay and disruption, and most of these new experiences are quickly forgotten (Paller, 2017). Nevertheless, some memories persist beyond the initial period of transience and are incorporated into long-term storage. The process by which newly encoded memory traces are stabilized into a more permanent form and integrated into existing long-term memory networks is known as consolidation (Stickgold, 2013).

Sleep is thought to play an essential role in the process of memory consolidation (Diekelmann & Born, 2010; Rasch & Born, 2013a). Research has indicated that sleep promotes stabilization of memories, as evidenced by decreased interference from

subsequent acquisition of competing information (Marshall & Born, 2007). Studies involving a period of declarative learning (e.g. memorization of paired word associates) and subsequent sleep or wakefulness demonstrate that sleep increases recall accuracy (Ellenbogen, Hulbert, Jiang, & Stickgold, 2009; Gais, Lucas, & Born, 2006; Lahl, Wispel, Willigens, & Pietrowsky, 2008; Plihal & Born, 1997) and reduces interference-induced memory loss (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006). Early proposals suggested that sleep offers respite from encoding of new information, leading to the conclusion that its memory-stabilizing effects are a function of decreased interference from subsequent acquisition of information (Jenkins & Dallenbach, 1924). However, sleep's protective effect cannot be attributed to decreased opportunity for retroactive memory interference, as similar results are seen even when associative interference tasks are introduced following sleep, and when the duration of post-sleep wakefulness is extended to match periods wakefulness without sleep (Ellenbogen et al., 2006; 2009). Beyond affording increased memory durability, it has also been suggested that sleep can result in absolute improvement in newly acquired skills, even without the benefit of additional practice (Gaab, Paetzold, Becker, Walker, & Schlaug, 2004; Stickgold, James, & Hobson, 2000; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002a).

Numerous studies have demonstrated that the benefits of sleep on memory retention apply not only to declarative learning, but also to procedural (Fischer, 2005; Fischer, Hallschmid, Elsner, & Born, 2002; Korman et al., 2007; Walker et al., 2003; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005) and emotional (Chambers & Payne, 2014; Hu, Stylos-Allan, & Walker, 2006; Nishida, Pearsall, Buckner, & Walker, 2009; Payne & Kensinger, 2018; Wagner, 2001) memory. For example, Fischer, Hallschmid, Elsner, and Born (2002) showed that post-practice sleep resulted in increased speed and

accuracy of a learned finger tapping sequence, and that these performance improvements were specific to the learned sequence. Similar findings have been obtained from experiments on emotional memory, such as a study by Hu, Stylos-Allan, and Walker (2006) that demonstrated a facilitative effect of sleep on recall accuracy of emotionally valenced pictures. Results from this study suggested that sleep favors consolidation of emotional over neutral content, in line with other findings in this area (Payne, Stickgold, Swanberg, & Kensinger, 2008). For patients with naturally acquired fear of spiders, post-exposure sleep has been shown to decrease behavioral, subjective, and physiological fear responding in comparison to sustained wakefulness following exposure (Kleim et al., 2013; Pace-Schott, Verga, Bennett, & Spencer, 2012). Overall, studies uniformly indicate that sleep offers beneficial effects for consolidation and learning retention across a broad range of memory content.

Mechanisms

Although precise mechanisms by which sleep fosters memory consolidation are still unclear, a number of theories have been proposed to describe the underlying processes. The dual process hypothesis and the sequential hypothesis each describe the influence of different sleep stages on various memory systems, while the synaptic homeostasis and active system consolidation hypotheses provide more detailed accounts of consolidation mechanisms occurring during sleep.

The dual process hypothesis suggests that the rapid eye movement (REM) stage of sleep is essential for consolidation of procedural and emotional memories, whereas non-REM (NREM) sleep, including slow-wave sleep (SWS) in particular, is primarily responsible for consolidation of declarative learning (Rasch & Born, 2013a). This hypothesis is supported by a number of studies indicating that periods of sleep containing

SWS-rich activity are associated with improved learning retention for declarative tasks such as word recall (T. R. Barrett & Ekstrand, 1972; Plihal & Born, 1997), whereas REM sleep is linked to enhanced retention of procedural or emotional memory, as assessed by tasks such as mirror tracing or recall of emotional texts (Plihal & Born, 1997; Wagner, 2001). Experiments often employ the "night-half" paradigm, which capitalizes on the fact that nocturnal sleep is dominated by SWS during its first half, and by REM during its second half (Fowler, Sullivan, & Ekstrand, 1973). To test the effects of SWS, participants are typically administered a memory task, and then allowed to sleep for 3-4 hours before recall testing. To assess the effects of REM sleep, participants sleep for 3 hours, are awakened for the memory task, and then are allowed to return to sleep before recall testing.

The sequential hypothesis, on the other hand, proposes that SWS and REM sleep both contribute to consolidation of declarative and non-declarative learning, and that the cyclic pattern of these sleep stages should occur sequentially for optimal benefits (Gais, Plihal, Wagner, & Born, 2000; Giuditta et al., 1995). The model proposes that memories are selected for either strengthening or weakening during SWS, followed by integration into existing networks during REM (Rasch & Born, 2013a). The sequential hypothesis accounts for observed crossover between benefits of REM and NREM on declarative and non-declarative memories, and also explains findings that organization of NREM-REM sleep cycles more accurately predicts depth of consolidation than duration of REM or NREM sleep in isolation (Ficca & Salzarulo, 2004).

Synaptic Homeostasis Hypothesis

It is widely believed that information is encoded and stored at a neuronal level via Hebbian plasticity, a process by which synaptic efficiency is strengthened as a result of

repeated stimulation of a postsynaptic neuron by presynaptic activity (Hebb, 1949). During wakefulness, encoding of new information via synaptic potentiation is thought to result in a global increase in synaptic strength (Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008). However, synaptic potentiation cannot increase indefinitely due to limitations on energy usage and other resources (Attwell & Laughlin, 2001). According to the synaptic homeostasis hypothesis, the body manages these limitations by alternating between periods of net synaptic strengthening during wakefulness, and global synaptic downscaling during sleep (Diekelmann & Born, 2010). During synaptic downscaling, overall synaptic strength is decreased through global depotentiation. As part of this process, weak connections are lost entirely, boosting the signal to noise ratio of the remaining connections. In this way, new learning is preserved through synaptic potentiation during wakefulness, and neural efficiency is maintained through pruning of weak synaptic connections during sleep-based global synaptic downscaling.

Active System Consolidation Hypothesis

The active system consolidation hypothesis posits that newly acquired memory traces encoded during wakefulness are spontaneously re-activated during sleep, mediating redistribution of fresh memory representations into long-term storage areas and integrating them into pre-existing memory networks (Diekelmann & Born, 2010). It is thought that this replay-induced transfer provides a mechanism for transforming and preserving initially unstable engrams, which can be further strengthened by synaptic potentiation.

The hypothesis was driven by the discovery that patterns of neuronal activity observed in rodents during wakeful learning re-occur during subsequent sleep. In a pioneering study, Pavlides and Winson (1989) used rats to observe neural signatures of

hippocampal place cells, which are known to selectively fire in response to the animal entering a specific environmental location (O'Keefe & Conway, 1978). The authors observed that place cell activity (e.g. firing rate, firing burst frequency, temporal burst signature) during environmental exploration predicted increased neuronal activity during subsequent SWS. Activity was simultaneously recorded in pairs of cells, allowing the authors to observe that place cell activity during sleep was limited to cells that were activated during prior periods of wakefulness. Other studies have replicated these findings in humans (Deuker et al., 2013; Peigneux et al., 2004), and have demonstrated that the temporal order of firing patterns occurring during learning is preserved during SWS replay (Wilson & McNaughton, 1994), that reactivation can occur in multiple brain areas, and that firing patterns during sleep may be temporally compressed (Euston, Tatsuno, & McNaughton, 2007; Wilson & McNaughton, 1994).

Active system consolidation theory builds upon the assumption that two types of memory storage are used to simultaneously encode new learning. Temporary storage is involved in rapid consolidation of new information at the expense of durability, and long-term storage uses a gradual process to more permanently house information (Frankland & Bontempi, 2005). For declarative memories, the hippocampus is implicated in rapid knowledge acquisition, and neocortical areas are used for more permanent storage (McClelland, McNaughton, & O'Reilly, 1995). During SWS, it is thought that repeated reactivation of newly learned acquired memory traces in short term storage prompts simultaneous reactivation of the corresponding memory traces in long term storage sites. Through coordinated repetitions of neural replay, initially unstable memory engrams are mapped onto more durable storage sites, and are gradually adapted into pre-existing networks within long-term storage (Diekelmann & Born, 2010). The process of redistributing rapidly encoded memory traces into enduring cortical networks is known as

system consolidation. It is thought that further strengthening of the transferred memory traces is accomplished via synaptic consolidation occurring during subsequent REM sleep (Rasch & Born, 2013b).

TARGETED MEMORY REACTIVATION

Re-activation of recently formed memory traces occurs naturally and spontaneously during sleep. However, researchers have begun to artificially induce neuronal replay in an attempt to promote consolidation of specific learning, and to determine whether memory reactivation is causally implicated in consolidation (Oudiette & Paller, 2013). This technique, known as targeted memory reactivation (TMR), typically involves a period of initial learning in the presence of an olfactory or auditory contextual cue, coupled with later presentation of the cue during sleep to ostensibly facilitate memory reactivation and consolidation (Rasch et al., 2007; Rudoy, Voss, Westerberg, & Paller, 2009).

Rasch, Büchel, Gais, and Born (Rasch et al., 2007) were the first to employ the TMR paradigm. In their study, participants were given a spatial-location memorization task in the presence of a rose odor, followed by sleep. During sleep, the rose odor or an odorless control was re-introduced. Retrieval testing conducted upon waking, in the absence of odor, indicated that re-presenting the odor during sleep facilitated memory retention. Follow-up experiments demonstrated that sleep-based odor exposure alone did not enhance learning if the odor was absent during the learning period, and that odor presentation enhanced learning only during SWS presentation, but not during REM or wakefulness (Rasch et al., 2007). Other studies have built upon this work, showing that TMR performance enhancements and the induction of neural reactivations that mediate

them (as measured by EEG signatures during sleep), are specific to the cue presented during learning (Rihm, Diekelmann, Born, & Rasch, 2014).

TMR has been shown to be effective in promoting consolidation of both declarative (Diekelmann, Biggel, Rasch, & Born, 2012; Diekelmann, Büchel, Born, & Rasch, 2011; Rasch et al., 2007; Rihm et al., 2014; Rudoy et al., 2009; Schreiner & Rasch, 2015) and procedural (Antony, Gobel, O'Hare, Reber, & Paller, 2012; Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2014; Schönauer, Geisler, & Gais, 2014) memories, with numerous studies finding evidence of improved task performance subsequent to cue-induced neuronal replay. To a more limited extent, research has also suggested that TMR can enhance creativity (Ritter, Strick, Bos, van Baaren, & Dijksterhuis, 2012) and the effects of implicit bias training (Hu et al., 2015). Attempts to apply TMR to emotional learning have resulted in mixed findings, which may be explained by methodological diversity (Schouten, Pereira, Tops, & Louzada, 2017). While some human studies found evidence that TMR procedures enhanced consolidation of emotionally valenced information (Cairney, Durrant, Hulleman, & Lewis, 2014) or promoted extinction of laboratory-conditioned fear (Hauner, Howard, Zelano, & Gottfried, 2013; He et al., 2015), others found no effect of TMR in altering emotional memory strength (Rihm & Rasch, 2015). Additionally, several studies of conditioned fear in rodents found enhanced fear responding after cue-induced reactivation (Barnes & Wilson, 2014; Rolls et al., 2013).

Clinical Applications

To the best of our knowledge, only one study (Rihm, Sollberger, Soravia, & Rasch, 2016) has attempted to use TMR as a treatment augmentation for naturally acquired, clinically significant fear. In this experiment, sixty individuals with spider

phobia received in-vivo group exposure therapy. Afterwards, participants recalled their positive treatment experiences and feelings of self-efficacy while in the presence of a contextual odor. Subject were then randomized to three groups: 90 minutes of sleep cued with the odor, 90 minutes of sleep in the presence of an odorless control vehicle, or wakefulness without odor. Results revealed no between-group differences on indices of fear reduction, even though polysomnograph recordings suggested that memory traces were successfully re-activated during cued sleep.

Although the Rihm et al. (2016) study represents the first application of TMR procedures to clinically significant fear, methodological considerations preclude the ability to draw valid conclusions about the usefulness of this technique for anxiety disorder treatment. The authors correctly noted that treatment ceiling effects may have masked potential additive benefits of TMR. However, a more pressing concern is that their procedure involved providing a contextual odor cue during a positive feedback session in which participants verbalized feelings of treatment success. No odor cues were present during actual exposure, calling into question the content and relevance of the neural representations that were re-activated during sleep. A core component of fear extinction involves new learning in response to systematic exposure to feared cues (Craske et al., 2012). However, Rihm and colleagues' (2016) experimental design did not allow such learning to be directly associated with the olfactory cue, because the odor was only present while participants retrospectively reflected upon treatment. It is likely that presenting an odor during exposure trials, and then re-presenting that odor during sleep, would have been far more potent than indirect cueing of secondary associations.

CHAPTER 2: PRESENT STUDY

Rationale

Given the widespread nature of anxiety disorders, the extent to which they produce distress and impairment, and the limitations of current exposure-based treatments, it is clear that there is a pressing need for development of new exposure augmentation strategies. Targeted memory reactivation represents a potentially untapped approach that has largely remained within the confines of basic research. Although one research group has attempted to use TMR for clinical purposes (Rihm et al., 2016), deficiencies in design considerations render results uninterpretable.

The present study attempted to address these methodological weaknesses and provide a rigorous test of TMR's efficacy as an augmentative strategy for exposure therapy. Participants with marked fear of spiders, contamination, or enclosed spaces, as measured by behavioral approach tests and self-report measures, went through standardized in-vivo exposure therapy in the presence of a contextual odor. Following treatment, they were randomized to one of three conditions: (1) EXPCUE, involving sleep in the presence of the contextual odor previously presented during exposure, (2) NOVCUE, involving sleep in the presence of a novel odor, or (3) CNTL, involving sleep without any odor. At one-week and one-month follow-up assessments, fear was reassessed in the absence of odor, to determine whether TMR enhanced consolidation of learning acquired during exposure treatment. Primary outcomes of interest were self-reported anxiety and physiological arousal in response to behavioral approach tests (BATs) conducted at pretreatment, post-treatment, 1-week follow-up, and 1-month follow-up. These BATs were conducted in the context used for treatment, as well as in a novel context, allowing for a check on treatment generalizability. Questionnaires

assessing intensity of arachnophobia, claustrophobia, and OCD-related fears were administered at baseline and at follow-up assessments as a secondary outcome of interest.

Hypotheses

Hypotheses were as follows:

(1) All three conditions will exhibit within-group, pre- to post-treatment reductions in self-reported peak anxiety, anticipated anxiety, and electrodermal response during BATs. There will be no significant between-group differences on primary outcomes at post-treatment.

(2) At follow-up, the EXPCUE condition will exhibit lower anxiety than the NOVCUE and CNTL conditions, as measured by self-reported peak anxiety, anticipated anxiety, and electrodermal response during BATs, as well as secondary outcome questionnaires.

(3) Self-reported peak anxiety during the last exposure trial will moderate the relationship between condition and anxiety at follow-up.

   a. Participants in the EXPCUE condition who report low anxiety at exposure termination will display enhanced outcome at follow-up relative to those in the CNTL or NOVCUE conditions.

   b. Participants in the EXPCUE condition who report moderate to high anxiety at exposure termination will display poorer outcome at follow-up relative to those in the CNTL or NOVCUE conditions.

Method

PARTICIPANTS

Participants (N=109) with significant fear of spiders, contamination, or enclosed spaces were recruited from the Austin community as well as from the pool of undergraduate psychology students at the University of Texas at Austin. The study was advertised using flyers, postings to social media and Craigslist, and direct emails to participants in the UT Austin psychology study pool. Participants were screened for anxiety level, olfactory sensitivity, disordered sleep, and concurrent anxiety treatment using the following criteria:

Inclusion Criteria

(a) Marked anxiety in at least one fear domain (spiders, contamination, or enclosed spaces), as determined by the presence of both (1) self-reported peak anxiety of at least 50 on a 100 point scale in response to two behavioral approach tasks and (2) self-report measures meeting the following cutoffs for the target fear:

- Fear of Spiders Questionnaire ≥ 50 (Szymanski & O'Donohue, 1995)
- Obsessive-Compulsive Inventory-Revised (Washing Subscale) ≥ 4 (Foa et al., 2002)
- Claustrophobia Screener ≥ 2

(b) Between ages of 18-65

Exclusion Criteria

(a) Diagnosed sleep disorder

(b) Current sleep medication or benzodiazepine usage

(c) Inability to identify odor from an indoor scent diffuser delivering two 4-second sprays, located 4.5 m (14.8') from the participant in an enclosed room

(d) Current treatment for fear of spiders, enclosed spaces, or contamination

(e) Current use of air fresheners or scented candles

Participants from UT Austin were given course credit for their participation, and community participants were compensated $25.

EXPERIMENTAL DESIGN

The current experiment used a double-blind, randomized controlled design in which all participants conducted exposure therapy in the presence of a contextual odor. Following treatment, participants were randomly assigned to sleep in the presence of one of three scents: the odor present during exposure, a novel odor, or a non-scented control.

Baseline anxiety assessments were conducted using a series of self-report questionnaires, two behavioral approach tests (BATs), and physiological measurements (see "Assessments" section). Following initial assessment, all participants underwent exposure treatment for their target fear, while in the presence of a distinctive odor. Therapy consisted of psychoeducation and a series of *in vivo* exposure trials specific to the participant's fear domain. A post-treatment assessment battery was administered, and participants were stratified upon fear domain and fear extinction rate. Random assignment to one of three experimental conditions occured: (a) sleep in the presence of the exposure scent (EXPCUE), (b) sleep in the presence of a novel cue (NOVCUE), or (c) sleep in the absence of scent (CNTL). Participants were given a scent diffuser system loaded with the appropriate odor for their assigned experimental condition (or loaded with non-scented liquid in the control condition), which they were instructed to place next to their bed and turn on for one night immediately before sleeping. To assess sleep

quantity and quality, participants wore wear a sleep monitoring device at night and completed an online measure of sleep quality the next morning. They returned to the lab one week and one month later for follow-up assessment batteries. See Figure 1 for a participant flow diagram.

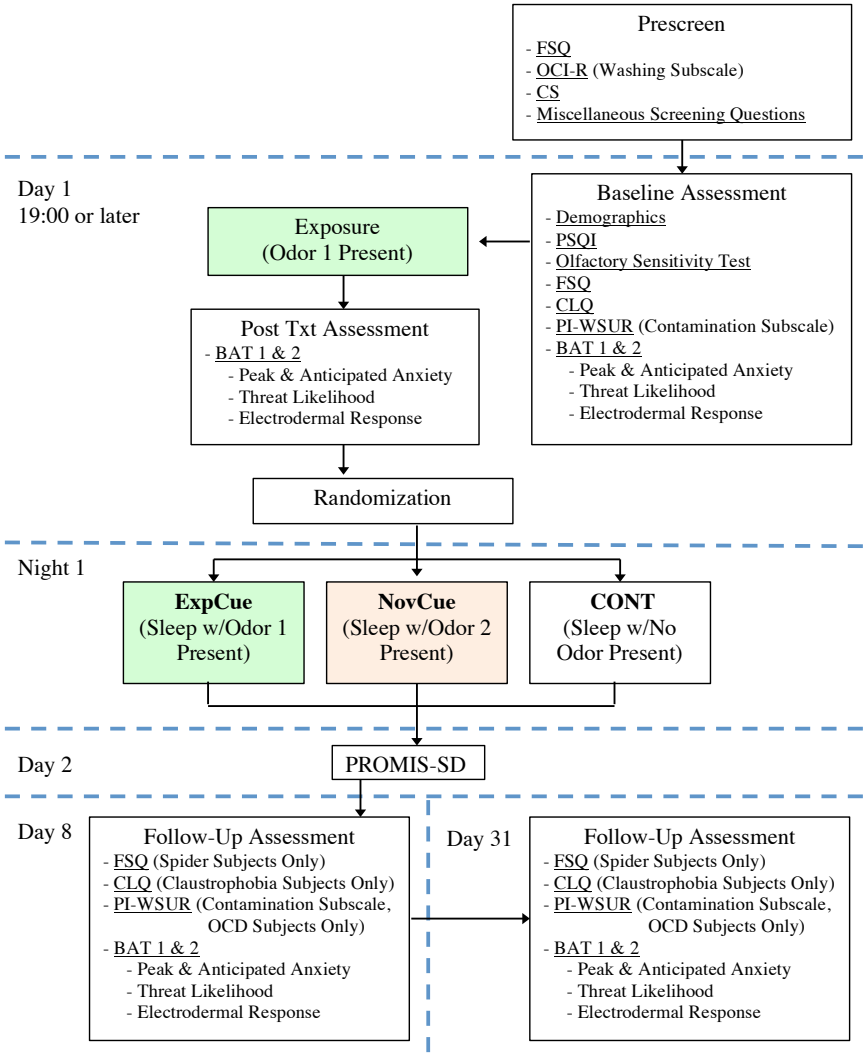


Figure 1: Participant Flow Diagram

PSQI=Pittsburgh Sleep Quality Inventory, FSQ=Fear of Snakes/Spiders Questionnaire, CLQ=Claustrophobia Questionnaire, CS=Claustrophobia Screener, OCI-R=Obsessive-Compulsive Inventory-Revised, PI-WSUR=Padua Inventory-Washington State University Revision, BAT=Behavioral Approach Test, PROMIS-SD= Patient-Reported Outcomes Measurement Information System for Sleep Disturbance- Short Form

ASSESSMENTS

Self-Report Measures

Fear of Spiders Questionnaire

The Fear of Spiders Questionnaire (Szymanski & O'Donohue, 1995) is an 18-item instrument assessing spider phobia. Items are answered on a 7-point Likert scale ranging from 0 (Strongly Disagree) to 6 (Strongly Agree), and are designed to assess spider phobia across a number of dimensions including cognitions, behaviors, and physiological response. The FSQ has demonstrated the ability to discriminate between individuals with and without spider phobia, and is also sensitive to treatment effects (O'Donohue & Szymanski, 1993). The FSQ has adequate convergent validity, as shown by its correlation with the Spider Phobia Questionnaire (r = .65), as well as adequate internal consistency (Cronbach's α = .92) and split-half reliability (r = .89) (Szymanski & O'Donohue, 1995).

Claustrophobia Questionnaire

The Claustrophobia Questionnaire (Radomsky, Rachman, Thordarson, McIsaac, & Teachman, 2001) is a self-report instrument assessing claustrophobic severity. The instrument is comprised of 26-items tapping two main factors: fear of suffocation and fear of restriction (Rachman & Taylor, 1993). Participants are asked to rate their predicted anxiety in a variety of situations (e.g. "Handcuffed for 15 min"), using a 5-point Likert scale ranging from 0 (not at all anxious) to 4 (extremely anxious). The CLQ has exhibited strong psychometric properties during validation studies with undergraduate and community adults, including high predictive validity (assessed using correlations with reported fear during a behavioral task [r = .64]), high internal consistency (Cronbach's α = .92), strong test-retest reliability over a two-week period (r

= .89), high discriminant validity when compared to reported fear of heights (r = .17) and snakes (r = .01), and the ability to differentiate between claustrophobic groups and healthy groups (Radomsky et al., 2001).

Claustrophobia Screener

The Claustrophobia Screener (CS) is a self-report item generated for the current study. The CS is intended to rapidly screen out individuals with insufficient levels of claustrophobic fear, prior to administration of a more stringent behavioral approach test. Individuals must score a 2 or higher on the CS to be considered for study enrollment. The CS and its response options are listed below:

How anxious would you feel if you were locked in a small, dark chamber for several minutes? Select the most appropriate answer:

0	*1*	*2*	*3*	*4*
Not at all anxious	*Slightly anxious*	*Moderately anxious*	*Very anxious*	*Extremely Anxious*

Padua Inventory- Washington State University Revision, Contamination Subscale

The Padua Inventory- Washington State University Revision (Burns, Keortge, Formea, & Sternberger, 1996) is a 39-item instrument designed to measure obsessions and compulsions. The PI-WSUR is adapted from the earlier Padua Inventory (Sanavio, 1988), with revisions designed to allow for greater distinction between obsessions that are specific to OCD, and worries derived from GAD (Burns et al., 1996). The

contamination subscale of the PI-WSUR is comprised of 10 questions assessing contamination-related obsessions and compulsions (e.g. "I find it difficult to touch garbage or other dirty things;" "If I touch something I think is 'contaminated', I immediately have to wash myself or change my clothing"). Responses are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). A recent meta-analysis by Rubio-Aparicio et al. (2018) reported that the contamination subscale of the PI-WSUR has high test-retest reliability (r = .79) and strong internal consistency (α = .89), which increases further when using clinical samples (α = .95). Furthermore, the PI-WSUR's contamination subscale has demonstrated discriminant validity with the full instrument's four other subscales, and factor analyses have provided additional support for a 5-factor scale structure (Burns et al., 1996).

Obsessive-Compulsive Inventory-Revised, Washing Subscale

The Obsessive-Compulsive Inventory-Revised (Foa et al., 2002) is an 18-item questionnaire adapted from an earlier 42-item OCI (Foa et al., 1998). The OCI-R contains 6 subscales that assess OCD severity across 6 factors: washing, checking, ordering, obsessing, hoarding, and neutralizing. Items measure distress caused by OCD-related experiences (e.g. "I find it difficult to touch an object when I know it has been touched by strangers or certain people"), and responses are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). Responses are summed to yield 6 subscale scores ranging from 0-12, as well as a total score ranging from 0-72. The present study used the washing subscale of the OCI-R as a preliminary screen for contamination concerns.

The OCI-R washing subscale and the overall OCI-R both exhibit strong psychometric properties. In a sample of OCD patients, the washing subscale showed

high internal consistency (α = .72) and the ability to differentiate OCD patients from non-anxious controls (*d* = .61), as well as from general social phobia (*d* = .93) and PTSD (*d* = .74) patients (Foa et al., 2002). The same study also indicated that the washing subscale has strong two-week test-retest reliability (*r* = .91) and strong convergent validity, as measured with correlation to the corresponding subscale of the Maudsley Obsessional-Compulsive Inventory (*r* = .78). Other psychometric research has suggested that the OCI-R's subscales are valid assessments of OCD subtypes, as the subscales mapped well to primary symptoms in a clinical sample of OCD patients (Huppert et al., 2007).

Pittsburgh Sleep Quality Inventory

The Pittsburgh Sleep Quality Inventory (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is a widely used instrument for measuring sleep quality, that was originally developed to distinguish between "good" and "poor" sleepers. A recent meta-analysis conducted by Mollayeva et al. (2016) found over 1512 articles relating to the term "Pittsburgh sleep quality inventory," reflecting its widespread usage across a range of populations and presentations. The PSQI consists of 19 items that are used to calculate seven "component" scores: sleep quality, latency, duration, efficiency, disturbance, sleep medication use, and daytime dysfunction. These component scores are summed to yield a total score of 0-21, in which elevated scores are indicative of poorer sleep quality. The review by Mollayeva et al. (2016) found that the PSQI has high internal consistency (α ranging from .7 to .83), adequate test-retest reliability (all ICCs > .7), adequate convergent validity with sleep-related measures such as DSM-IV insomnia diagnoses, and divergent validity with other constructs such as psychopathology and bladder dysfunction. Additionally, the PSQI was able to distinguish between groups with known

sleep-quality differences, regardless of whether clinical or non-clinical populations were examined.

Patient-Reported Outcomes Measurement Information System (PROMIS™) Sleep Disturbance - Short Form

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a National Institutes of Health initiative to develop highly reliable question banks for patient-reported health outcomes, that can be used across a range of diseases (see www.nihpromis.org). The 27-item PROMIS sleep disturbance question bank was developed as part of this initiative (Buysse et al., 2010), and was further refined and abbreviated into a shortened version in 2012 (Yu et al., 2012).

The short form of the PROMIS sleep disturbance item bank (PROMIS-SD) consists of 8 questions assessing global sleep quality over the last 7 days (e.g. "In the past 7 days my sleep was restless"). Items are rated on a 5-point Likert scale ranging from 1 (not at all) to 5 (very much), with 4 reverse-coded items. Item Response Theory analysis using data from a clinical samples and online participants has suggested that PROMIS-SD is a more precise measurement instrument than the PSQI (Yu et al., 2012). Other research has indicated that the PROMIS-SD is negatively correlated with actigraphy-measured total sleep time in adolescents, and that is significantly correlated with the related measures such as the Cleveland Adolescent Sleepiness Questionnaire (r = .77) (Hanish, Lin-Dyken, & Han, 2017).

For the present study, wording of PROMIS-SD items was adapted to reflect sleep quality over the previous night instead of the previous 7 days. Item prompts beginning with "In the past seven (7) days…" were replaced with the phrase "Last night…" Item response options to three questions were adapted to range from "Not At All" to "Very

Much" instead of from "Never" to "Always." The instrument was administered the morning following exposure treatment, to assess quality of sleep during the experimental manipulation. This data complemented biometric sleep quality data obtained from a Fitbit Flex 2 device.

Prescreening Items and Demographics

Participants were given Qualtrics prescreening questionnaires about age, sleep disorder diagnoses, sleep medication or benzodiazepine usage, current psychotherapy for fear of spiders, enclosed spaces, or contamination, and current use of air fresheners, scented candles, or other items with odors related to apple cinnamon or mandarin orange scents. At baseline, participants completed a self-report questionnaire to acquire demographic information such as gender, ethnicity, and socioeconomic status.

Behavioral Approach Tests (BATs)

General Overview

Behavioral approach tests (BATs) were used to assess phobic responding to in-vivo fear stimuli. Two BATs relevant to each participant's most prominent fear domain were administered at baseline, post-treatment, 1-week follow-up, and 1-month follow-up. Each BAT involved brief engagement with a feared stimulus, for example by having participants with claustrophobic concerns remain in a closed container for up to two minutes (see subsections below for procedural details and stimuli specific to each fear domain). Participants were encouraged to engage with the stimulus for as long as possible, but had the option of ending the test at any point. Participants were not informed of the BAT duration beforehand, however were stopped by the experimenter after engaging with the feared stimulus for 30 seconds. Anticipated and peak anxiety

ratings were taken immediately before and after engaging with the stimulus, using a scale ranging from "0- No Anxiety" to "100- Extreme Anxiety." Threat likelihood ratings were also taken prior to each BAT, on a scale ranging from 0 to 100. Electrodermal response was continuously measured to assess physiological arousal during the BAT, and 60 seconds of quiescent electrodermal activity were recorded prior to each BAT in order to differentiate background noise from fear responding.

Within each fear domain, two BATs were administered at each assessment point: BAT 1, which assessed fear in the treatment context, and BAT 2, which assessed fear in a generalization context. BAT 1 assessed phobic responding to the same stimulus used during exposure treatment (e.g. a brown spider). BAT 2 assessed phobic responding to a different stimulus used exclusively during assessments (e.g. a multi-colored spider). Inclusion of BAT 2 allowed for a more robust examination of whether treatment effects generalize to novel stimuli and situations.

Spider BATs

BAT 1 (treatment context) for arachnophobia used a Chilean rose hair tarantula (species: *Grammostola rosea*; length approximately 10.2 cm; width approximately 7.6 cm) with grey and brown coloring as a stimulus. Procedural elements were similar to those used by Telch, York, Lancaster, and Monfils (2017). Participants were given a detailed overview of the BAT procedure, and were asked to remove their shoes and stand outside the BAT room. The experimenter positioned the spider on the floor of the BAT room, in the center of visual floor grid comprised squares measuring 30.48 cm (12 in) per side. Participants were instructed open the door to the room for 5 seconds and observe the spider from a distance of 3 meters. Then, the room door was closed and participants rated their anticipated anxiety and threat likelihood from 0 to 100. Following this,

participants were instructed to enter the room and approach the spider, maintaining a constant distance of 1 square grid from the animal's head and holding eye contact. Participants were instructed to remain in this position for as long as they possible until they were told to stop, however were not be told a specific test duration in advance of the BAT. After a maximum of 30 seconds, participants were instructed to exit the room and provide peak anxiety ratings from 0 to 100.

BAT 2 (generalization context) used the same procedure as BAT 1, with the exception of the stimulus used. Instead of using BAT 1's grey and brown spider that was also used for exposure treatment, a Pink Zebra Beauty tarantula was used instead (species: *Eupalaestrus campestratus*; length approximately 10.2 cm; width approximately 7.6 cm) that was colored grey with distinctive white stripes on its appendages.

Contamination BATs

In the contamination fear domain, BAT 1 (treatment context) involved behavioral approach toward a pile of soiled laundry, a stimulus which has previously been used in contamination exposure studies (Cougle, Wolitzky-Taylor, Lee, & Telch, 2007). Socks, rags, crumpled tissues, and old clothing were smeared with potting soil, then placed into a cardboard box with an open top. Outside of the BAT room, participants were provided with a detailed procedural overview of the task and were told, "some of the items in the box may have been in contact with bodily fluids." Participants were instructed open the door to the room for 5 seconds and observe the laundry from a distance of 3 meters. Then, the room door was closed and participants rated their anticipated anxiety, anticipated disgust, and threat likelihood from 0 to 100. Following this, participants were instructed to enter the room and touch the laundry with their palm, keeping their hand fully open and maintaining physical and visual contact with the laundry. Participants

were instructed to remain in this position for as long as they can until they were told to stop, and they were not told a specific duration in advance of the test. After a maximum of 30 seconds had elapsed, participants were instructed to exit the room and provide peak anxiety and disgust ratings from 0 to 100.

BAT 2 (generalization context) involved a similar procedure to BAT 1, except that a non-functional, porcelain toilet containing potting soil smears was used as the stimulus. Participants were instructed to touch the toilet seat with the palm of their hand while maintaining physical and visual contact with the toilet.

Claustrophobia BATs

BAT 1 (treatment context) in the claustrophobia domain used a black, wooden chamber with a lockable door as the stimulus. The chamber dimensions were 183x91x61 cm (72"x36"x24"), requiring participants to lie in a supine position to fit within the chamber. Participants were provided with a detailed procedural overview of the task. Then, they observed the open chamber for 5 seconds before exiting the room and rating their anticipated anxiety and threat likelihood from 0 to 100. Participants were instructed re-enter the room and lie down in the chamber in a supine position. Once the chamber door was closed and locked, participants remained in the chamber for as long as possible until they were told to stop, although they were not be given specific time limits in advance of the test. After a maximum of 30 seconds had elapsed, participants were instructed to exit the BAT room and provide peak anxiety ratings from 0 to 100.

BAT 2 (generalization context) involved the use of a different closeable chamber that was colored yellow, with internal dimensions of 84x117x39 cm (33"x46"x15.5"). Instead of lying in a supine position, participants were instructed to lie on their side in a fetal position. There were no other procedural differences from claustrophobia BAT 1.

Electrodermal Response

Electrodermal response were measured using an eSense Skin Response system (Mindfield Biosystems Ltd., Gronau, Germany) connected to a cell phone and sampling at 1 Hz. Two single-use gel electrodes were attached using one of the positions pictured in Figure 2. Baseline skin conductance level (SCL) was obtained prior to exposure by taking a 60s average SCL with the participant sitting without the target stimulus present (Shiban, Brütting, Pauli, & Mühlberger, 2015a). This baseline value was subtracted from the average SCL during the first 15 seconds of BATs.

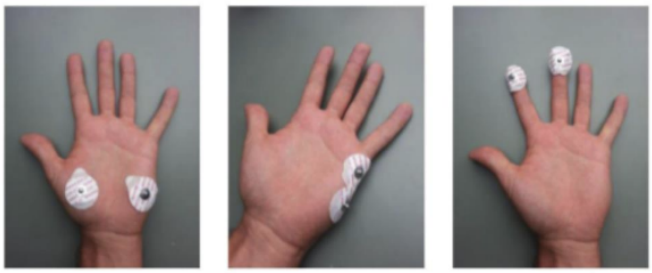


Figure 2: Electrode Positioning

Sleep Quality

Sleep quality was measured using a Fitbit Flex 2 device (FF2, Fitbit Inc., San Francisco, CA, USA), a widely used, commercially available activity and sleep tracker. Prior studies examining the acceptability of commercial sleep trackers for research have produced mixed findings, which are complicated by the use of different device types and versions (Evenson, Goto, & Furberg, 2015). Furthermore, algorithms used to calculate sleep quality indices are often kept proprietary, and it is unclear how or whether these algorithms change between device versions.

However, several studies suggest that commercial sleep trackers can reasonably assess sleep quality indices, particularly total sleep time (de Zambotti, Baker, & Colrain,

2015a; de Zambotti, Claudatos, Inkelis, Colrain, & Baker, 2015b). Seung-Gul Kang et al (2017) compared Fitbit Flex sleep measurements to polysomnography (PSG) in a sample containing good sleepers and individuals with insomnia. Results indicated that in comparison to PSG, the Fitbit Flex assessed total sleep time with high reliability for both good sleepers (ICC = 0.97) and individuals with insomnia (ICC = 0.89), and that measures of sleep onset latency and sleep efficiency were fair to good. Other Fitbit studies using adult and adolescent samples have suggested that sleep tracking devices significantly overestimate total sleep time, but it is possible that these results are attributable to using earlier device models such as Fitbit Ultra and Fitbit Classic (Meltzer, Hiruma, Avis, Montgomery-Downs, & Valentin, 2015; Montgomery-Downs, Insana, & Bond, 2011).

In the current study, participants wore a Fitbit Flex 2 device on their wrist during sleep to measure total sleep time.

Odor Delivery and Detection

Odor was delivered with a commercially available AirWick essential oils diffuser, along with the corresponding AirWick fragrance refills "Mandarin Orange" and "Apple Cinnamon." The device intermittently releases the selected fragrance into the environment, with three settings allowing the device to spray for a duration of 4 seconds every 17 minutes, 5 seconds every 12 minutes, or 6 seconds every 10 minutes. Several considerations were taken into account during device selection: (1) ability to release fragrance intermittently, thus minimizing olfactory fatigue, (2) an extremely quiet scent release mechanism that minimizes potential for sleep disruption or distraction during exposure tasks, (3) portability and ease of use, and (4) widespread accessibility and low

cost, allowing for ease of potential dissemination to a large audience when compared to most laboratory-based olfactometers.

An olfactory sensitivity test was administered at baseline to ensure that participants were able to sufficiently detect odor from the device. Participants sat at one end of a room measuring 7.8 m (25.6') long, 3.4 m (11.2') wide, and 2.9 m (9.5') tall. All windows and doors to the room were closed, and the scent diffuser was placed 4.5 m (14.8') away from the participant, near the center of the room. An experimenter turned on the device and delivered two 4-second scent sprays, and participants were asked to identify the odor within a period of five minutes. Individuals who are unable to detect the scent were excluded from the study. Fragrances were balanced across conditions and tasks so that no single fragrance was exclusively used as the exposure odor, the exposure-incongruent odor presented during sleep, or the olfactory sensitivity task odor.

EXPOSURE TREATMENT

Exposure therapy involved having the participant approach a fear-relevant stimulus in 4-minute trials, separated by approximately 1-minute breaks. Treatment was terminated either when participants achieved fear or disgust reduction of 35 points or greater in comparison to the first trial, using a scale ranging from 0-100, or when total exposure time reached 40 minutes. Previous exposure protocols conducted in this laboratory have found comparable fear reductions after 40 minutes of contamination exposure (Cougle et al., 2007), and greater fear reduction to shorter exposure durations for claustrophobia (Telch, Bruchey, Rosenfield, Cobb, et al., 2014a) and snakes/spiders (Telch et al., 2017). Treatment began with psychoeducation providing information about the adaptive nature of anxiety, the anxiogenic effects of avoidance, the mechanisms by which engaging with feared objects and situations reduces fear, and the benefits of

exposure. Following psychoeducation, participants were given a detailed description of the exposure protocol. The procedure and stimulus used in each trial was identical to the procedure and stimulus used in BAT 1 for each fear domain, with the exception of three modifications. First, two scent diffusers were turned on and set to their maximum odor release setting several minutes before beginning treatment, for the purpose of providing a contextual odor during exposure. Secondly, there were multiple 4-minute exposure trials instead of a single 30-second behavioral assessment. Finally, participants were not asked to observe the stimulus for 5 seconds before every trial, as this step would be redundant. With the exception of these three procedural alterations, each exposure trial involved an identical process of providing an anticipated anxiety and threat likelihood rating on a 0-100 scale, entering the exposure room and engaging with the stimulus, and providing peak fear ratings from 0-100 after the trial was completed. Exposure involved the same stimulus and actions used in BAT 1 (maintaining a distance of 30.48 cm (12 in) from a spider, touching a pile of soiled laundry, or remaining in a closed chamber).

PROCEDURE

An overview of the study flow is provided in Figure 1. Individuals responding to recruitment efforts (via postings to Craigslist and social media, flyers, or direct emails to individuals in the UT Austin psychology research study pool) were sent an online Qualtrics prescreening survey. This questionnaire included the FSQ, CS, the OCI-R Washing Subscale, and five questions assessing age, presence of a sleep disorder, current psychotherapy treatment status, sleep medication usage, and current use of fragrances or fragrant objects. Individuals passing initial inclusion/exclusion criteria on the screener were scheduled for a laboratory visit occurring no earlier than 7:00 pm.

The laboratory visit began with informed consent, at which time participants were given an experimental rationale stating,

> *"We are investigating the effects of odors during anxiety treatment and during sleep. Some research has suggested that applying odors in different ways during sleep and psychotherapy might help reduce fear. We are interested in examining the effects of both strong odors and subtle odors. The subtle odors are present but below detectable levels, so you may or may not always smell the fragrance that our devices are releasing."*

Participants completed the PSQI and the olfactory sensitivity test, and experimenters selected the target fear domain based upon the participant's most severe screening instrument score. Those with claustrophobia or contamination fear completed the CLQ or the contamination subscale of the PI-WSUR, respectively. Next, participants were fitted with electrodermal monitoring equipment, and BATs 1 and 2 were administered for the target fear domain. Participants who qualified for study enrollment based upon sufficient olfactory performance and reported fear during the BATs proceeded to exposure treatment.

Several minutes before beginning exposure, the experimenter turned on two scent delivery devices to provide a contextual odor cue during treatment. Participants were provided with psychoeducation and guided through the exposure trials, and then performed BATs 1 and 2 during a post-treatment assessment. Following this assessment, participants were stratified on fear domain and number of exposure trials required to reach stopping criterion, and were randomly assigned to a treatment condition using an online random number generator available at www.randomizer.org (Urbaniak & Plous,

2014). Randomly assigned treatment conditions included (1) EXPCUE, in which sleep-based memory reactivation was cued by the same odor that was present during exposure, (2) NOVCUE, in which a novel odor was presented during sleep and exposure memory reactivation was not induced, and (3) CNTL, in which participants slept with no odor present. Participants were provided with a Fitbit Flex 2 sleep tracker to monitor total sleep time, as well as a scent delivery device to take home that corresponded to their treatment condition. Double-blind conditions were maintained by (1) labeling scent delivery devices with numbered stickers so that experimenters were unaware of what fragrance participants took home, and (2) not informing participants about the hypothesized effects of using an exposure-congruent scent, an exposure-incongruent scent, or control. Participants were instructed to take their device home and place it as close as possible to the head of their bed. Immediately before sleeping, participants were instructed to turn on the device and set it to the maximum release rate, take a picture of the device in the "on" position (including the bed in the picture frame), and send the picture to the experimenters as a procedural compliance check. The next morning, participants were instructed to turn off the device and fill out an online version of the PROMIS-SD to assess sleep quality. They also were instructed to return the Fitbit Flex 2 to research staff to download biometric sleep data from the device.

Participants returned to the laboratory for 1-week and 1-month follow-up assessments, which began with administration of either the FSQ, CLQ, or PI-WSUR, depending on the participant's assigned fear domain. Next, participants were fitted with electrodermal monitoring equipment and conducted BATs 1 and 2 to assess retention of learning during exposure. Finally, participants were debriefed and compensated with research credits or $25.

CHAPTER 3: STATISTICAL ANALYSES

Baseline Equivalence of Experimental Groups

To determine whether randomization resulted in equivalent experimental groups at baseline, we tested for group differences in primary outcome measures (peak and anticipated fear or disgust, threat likelihood, and electrodermal response during pretreatment BATs 1 and 2), secondary outcome measures (self-report questionnaires), general sleep quality in the month prior to the experiment, scent valence, and demographic characteristics using one-way ANOVAs for continuous variables and Chi-square tests for categorical variables.

Manipulation Checks

Mixed design ANOVAs were used to determine whether exposure successfully reduced fear across conditions, using a two-level within-subjects factor of time (Baseline, Post-Treatment), and a three-level between-subjects factor of condition (EXPCUE, NOVCUE, CNTL). We hypothesized that all three conditions would exhibit within-group, pre- to post-treatment reductions in primary outcomes during BATs, with no significant between-group differences. Separate analyses were performed for each outcome measured during BATs 1 and 2 (self-reported peak anxiety, anticipated anxiety, threat likelihood and electrodermal response).

Groups were also checked for comparable levels of compliance in using the home scent diffuser. A chi-square analysis was used to explore potential between-group differences in scent diffuser picture response rates.

Post-Exposure Equivalence of Experimental Groups

Because the primary experimental scent manipulation occurred following exposure treatment, it was necessary to test whether experimental groups were comparable post-exposure and during sleep the night following exposure. Group equivalence post-exposure was examined using one-way ANOVAs for continuous variables and Chi-square tests of independence for categorical variables. The following variables were included in this analysis: exposure end-fear, number of exposure trials, sleep quantity and quality (measured by Fitbit Flex 2 and PROMIS-SD), alcohol consumption status, fear domain, and treatment condition.

Outcome Analyses

Linear mixed models were used to test the primary hypothesis that post-exposure sleep in the presence of an exposure-congruent scent would enhance treatment efficacy. In contrast to more traditional repeated measures approaches, linear mixed models are able to account for correlations between observations, incorporate information from subjects with incomplete data, and decrease Type 1 error rate (Raudenbush & Bryk, 2002).

Each model included a primary outcome measure as the dependent variable, with fixed effects of treatment condition, time, and the time x condition interaction. Models included random effects of participants only, as comparisons to models with random effects of participants and time did not result in better fit when using Akaike's Information Criterion for selection. Baseline outcome variable score was entered as a covariate in each model in order to minimize variance in outcomes and increase power, and therefore time represented assessments from post-treatment, 1-week follow-up, and 1-month follow up. Time was treated as a continuous variable and centered at 1-week follow-up. In order to examine the hypothesis that participants who smelled an exposure-congruent scent would exhibit decreased fear at follow-up in comparison to other groups, we examined the significance of the Time x Condition interaction and also used pairwise comparisons to compare the Exp Cue group to each of the other conditions.

A similar analytic strategy was used to examine secondary outcomes on self-report anxiety questionnaires (FSQ, CLQ, PI-WSUR). However, because these questionnaires were only administered at baseline, 1-week follow-up, and 1-month follow up, they were entered with time representing 1-week and 1-month follow-up assessments, with baseline scores as covariates.

Models were fitted using restricted maximum likelihood estimation, with Akiake's Information Criterion used to select among sixteen candidate covariance structures. The first-order autoregressive [AR(1)] structure resulted in the best fit and was used for all models. The Satterthwaite approximation was used to determine degrees of freedom, and effect sizes were derived using the formula $r = (t^2/(df + t^2))^{1/2}$. Statistical analyses used two-tailed tests with an alpha criterion of 0.05. All analyses were conducted with IBM SPSS 22.0.

Moderator Analyses

Possible moderators of treatment outcome were examined using guidelines proposed by Kraemer, Wilson, Fairburn, and Agras (2002). Moderator x Time x Condition interactions were used to predict peak anxiety and electrodermal response, while controlling for baseline scores as well as self-reported sleep quantity and quality (PROMIS-SD score). Potential moderator variables of end fear (peak fear during final exposure trial), exposure quantity (i.e. learning rate), and fear domain were examined, each of which was measured prior to the experimental manipulation of scent application during sleep. All predictors were mean-centered, and separate analyses were performed for each combination of moderator variable and outcome. The Benjamini-Hochberg procedure was used to control the false discovery rate and provide a more powerful test than approaches controlling the familywise error rate (Benjamini & Hochberg, 1995).

Significant interactions were explored using guidelines from Aiken and West (1991), in which predictors were mean-centered and conditional effects were examined at one standard deviation above the moderator mean, and one standard deviation below the moderator mean.

CHAPTER 4: RESULTS

Attrition and Missing Data

As presented in Figure 3, 109 participants were randomized to either the EXPCUE (n = 36), NOVCUE (n = 37), or CNTL (n = 36) conditions. 4 participants were lost at 1-week follow-up (1 due to family/personal issues and 3 of which gave no reason). 7 participants (6%) failed to complete post-sleep questionnaires assessing sleep quantity. Equipment failure resulted in loss of 8.2% of electrodermal data across all timepoints, as well as 11.9% of Fitbit sleep data.

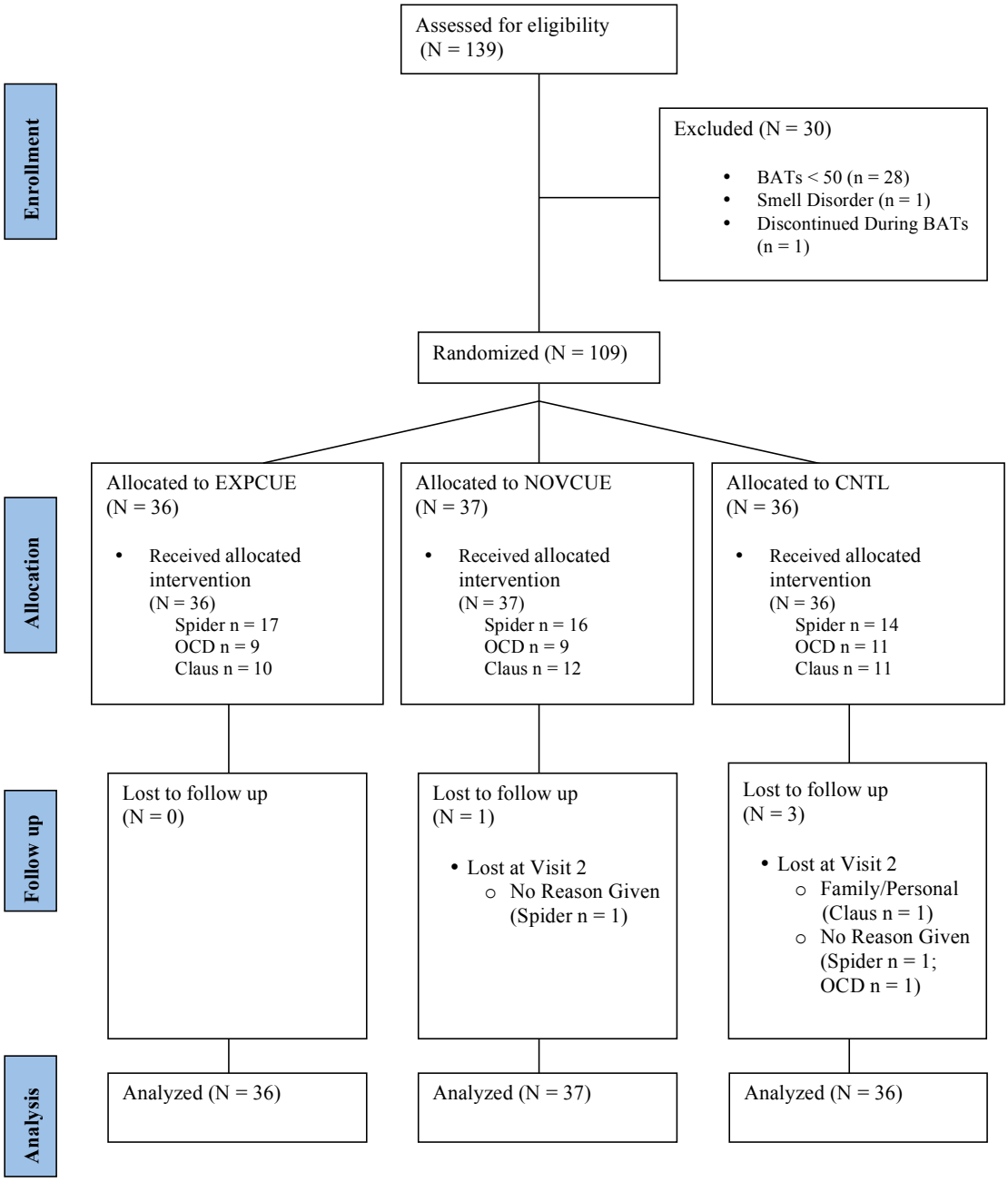


Figure 3: CONSORT Flow Diagram

Baseline Equivalence of Groups

Baseline sample characteristics including demographics, general sleep quality, and scent valence ratings are presented in Table 1. Descriptive statistics for primary and secondary outcome measures are presented in Table 2. Chi-square tests of independence and one-way ANOVAs revealed no significant differences at baseline among any of these variables (all p's > .05).

Scent valence ratings were non-normal (clustered around two Likert scale options), and therefore Kruskal-Wallis H tests were used to explore potential between-group differences in scent preference. These analyses also revealed no significant between-group differences in valence ratings for either the Apple Cinnamon or the Mandarin Orange scents. Participants rated both scents scent highly, with mean valence ratings within each condition falling between 4 ("good") and 5 ("very good").

Mean PSQI score for the overall sample was 8.10 (SD = 3.42), suggesting that participants had "poor" sleep quality in the month preceding the experiment. These scores are in line with previous findings for populations with clinical anxiety (Bush et al., 2012).

Table 1: Baseline sample characteristics by condition

	Exposure Cue (N = 36)	Novel Cue (N = 37)	Control (N=36)
	M (SD)	M (SD)	M (SD)
Demographic Variables			
Gender (% Female)	28 (77.8)	25 (73.0)	28 (77.8)
Race/Ethnicity			
American Indian or Alaska Native	1	1	
Asian	12	17	15
Black or African American	2	4	4
White (European/Middle Eastern/Hispanic)	17	11	24
Other		3	
Employment Status			
Not working/unemployed	6	9	4
Student	24	19	27
Working >30 hours/week	1		2
Working part-time	5	7	3
Scent Valence			
Apple Cinnamon	4.22 (.80)	4.32 (.92)	4.19 (.71)
Mandarin Orange	4.25 (.94)	4.19 (.88)	4.64 (.54)
General Sleep Quality			
PSQI	8.08 (3.29)	9.00 (3.18)	7.19 (3.62)

Note. PSQI = Pittsburgh Sleep Quality Index; EDR = Electrodermal Response; FSQ = Fear of Spiders Questionnaire; CLQ = Claustrophobia Questionnaire; PI-WSUR = Padua Inventory-Washington State University Revision (contamination subscale)

Table 2: Descriptive statistics for primary and secondary outcomes at baseline, post-treatment, 1-week follow-up, and 1-month follow-up

Outcome Variable	Baseline Mean (SD)	Post-Treatment Mean (SD)	1-Week Follow Mean (SD)	1-Month Mean (SD)
BAT 1 Anticipated Anxiety				
Exposure Cue	70.72 (17.91)	31.08 (21.76)	37.69 (23.58)	29.86 (20.97)
Novel Cue	74.03 (14.58)	33.24 (19.19)	42.58 (18.45)	31.14 (17.93)
Control	69.17 (19.44)	27.28 (18.87)	32.70 (20.68)	23.27 (20.01)
BAT 2 Anticipated Anxiety				
Exposure Cue	73.19 (16.68)	39.56 (24.46)	37.89 (25.07)	30.61 (22.25)
Novel Cue	72.43 (17.17)	43.11 (21.84)	39.11 (19.41)	33.47 (22.20)
Control	74.86 (14.89)	39.67 (23.55)	32.27 (22.76)	23.36 (21.05)
BAT 1 Threat Likelihood				
Exposure Cue	37.67 (27.31)	13.03 (17.14)	13.67 (18.53)	10.33 (15.07)
Novel Cue	40.88 (26.88)	15.89 (17.17)	21.06 (18.99)	15.97 (17.17)
Control	45.31 (27.98)	14.72 (20.16)	14.33 (19.98)	9.27 (12.09)
BAT 2 Threat Likelihood				
Exposure Cue	41.63 (32.51)	18.28 (23.73)	16.39 (23.85)	12.00 (16.74)
Novel Cue	45.89 (30.68)	22.05 (23.48)	18.92 (17.94)	16.47 (20.04)
Control	51.42 (32.39)	21.69 (24.99)	14.82 (17.57)	11.18 (15.68)
BAT 1 Peak Anxiety				
Exposure Cue	73.28 (14.03)	22.42 (20.13)	28.58 (21.75)	21.06 (19.00)
Novel Cue	75.00 (14.81)	26.27 (20.96)	31.86 (19.26)	25.94 (18.07)
Control	73.61 (16.67)	20.06 (18.77)	25.24 (20.31)	18.33 (18.89)
BAT 2 Peak Anxiety				
Exposure Cue	75.17 (16.21)	33.64 (26.69)	33.64 (25.39)	27.31 (26.13)
Novel Cue	75.89 (14.45)	37.46 (24.39)	34.83 (20.44)	30.06 (23.04)
Control	76.42 (15.34)	34.81 (27.59)	30.76 (25.00)	21.61 (22.01)
BAT 1 Electrodermal Response				
Exposure Cue	9.17 (10.69)	0.62 (3.39)	4.13 (7.02)	4.30 (3.71)
Novel Cue	7.70 (5.62)	0.23 (6.40)	6.90 (6.10)	4.61 (4.82)
Control	9.72 (14.59)	-0.25 (6.24)	4.58 (6.12)	4.50 (3.32)
BAT 2 Electrodermal Response				
Exposure Cue	8.76 (10.41)	2.70 (8.13)	6.51 (8.41)	5.16 (4.19)
Novel Cue	9.27 (11.60)	0.90 (7.32)	8.62 (10.00)	6.27 (5.93)
Control	9.49 (14.69)	-0.28 (6.41)	3.77 (9.30)	5.16 (3.86)
Fear of Spiders Questionnaire				
Exposure Cue	76.41 (13.40)		42.07 (15.62)	41.65 (21.42)
Novel Cue	80.29 (13.31)		55.83 (26.58)	48.87 (23.36)
Control	76.36 (13.77)		54.43 (17.21)	35.23 (20.08)

Table 2 (continued)

Claustrophobia Questionnaire			
Exposure Cue	47.30 (15.76)	38.40 (12.72)	38.30 (12.53)
Novel Cue	58.33 (13.41)	46.17 (17.66)	40.17 (17.49)
Control	54.09 (21.11)	41.90 (16.64)	28.10 (14.20)
Padua Inventory-Washington State University Revision			
Exposure Cue	19.22 (8.18)	13.36 (7.69)	15.22 (5.61)
Novel Cue	18.56 (7.06)	18.56 (6.29)	12.22 (7.43)
Control	20.64 (6.64)	14.78 (5.45)	11.90 (5.07)

Manipulation Integrity Checks

Peak anxiety at baseline and post-treatment are presented in Figures 4 and 5. Participants reached fear reduction criterion of 35 subjective units of distress after an average of 22.64 minutes (SD = 10.80) of exposure (5.66 trials, SD = 2.70). 15 participants (13.8%) failed to reach fear reduction criterion and stopped exposure after 40 minutes. Within this subset, average fear reduction during exposure was 15.8 subjective units of distress.

Results from mixed design ANOVAs examining exposure integrity across conditions are presented in Table 3. Analyses revealed a significant effect of time across treatment conditions in both exposure and generalization contexts as measured by multiple indices (anticipated anxiety, peak anxiety, and electrodermal response), suggesting that exposure successfully reduced anxiety across all groups. Exposure effect size was large across all fear indices, exceeding partial eta squared values of 0.34 when measured by electrodermal response and 0.683 when measured by self-reported peak anxiety or anticipated anxiety. As expected, there were no significant effects of condition or Time x Condition, indicating that all groups showed equivalent reductions in post-exposure fear.

89.8% of the sample sent a picture of the scent diffuser next to their bed following exposure. A chi-squared test indicated that diffuser compliance did not significantly differ between conditions, $\chi^2(2, N=109) = 0.50, p = 0.78$.

Figure 4: BAT 1 peak anxiety at baseline and post-treatment. Exp Cue = Exposure Cue, Nov Cue = Novel Cue, Cntl = Control. Error bars represent +/- 1 standard error.

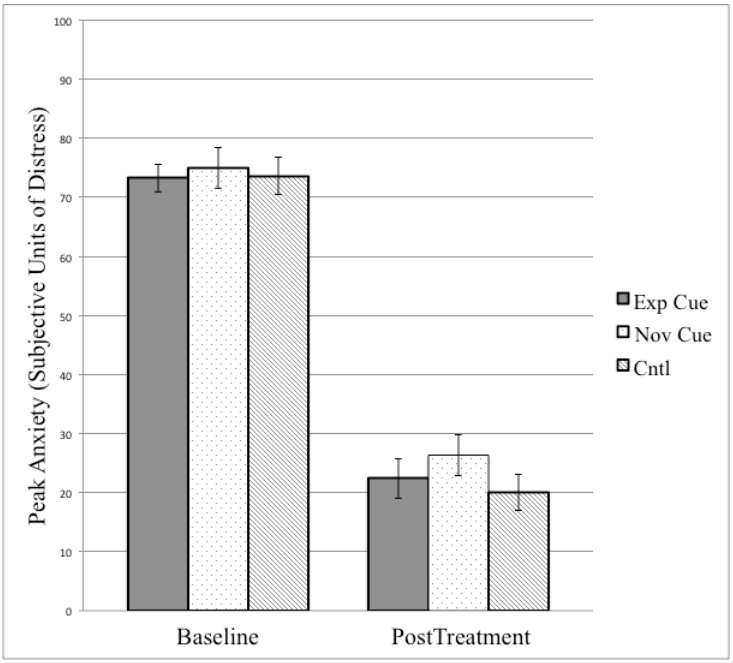


Figure 5: BAT 2 peak anxiety at baseline and post-treatment. Exp Cue = Exposure Cue, Nov Cue = Novel Cue, Cntl = Control. Error bars represent +/- 1 standard error.

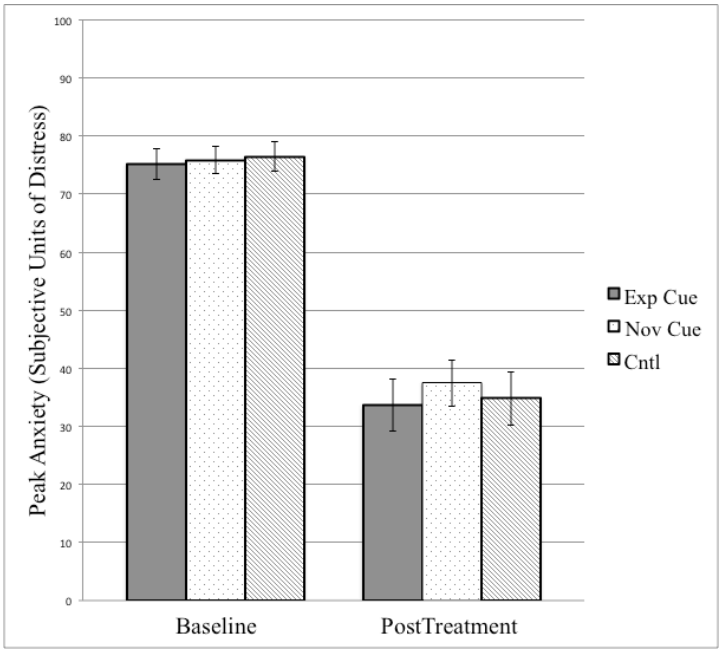


Table 3: Mixed ANOVAs testing effects of exposure therapy from pre- to post-treatment

Variable	Effect	*F*	*P*	η_p^2
BAT 1 Anticipated Anxiety	Time	344.410	<.001*	.765
	Condition	1.218	.300	.022
	Time x Condition	.087	.917	.002
BAT 1 Peak Anxiety	Time	698.439	<.001*	.868
	Condition	.664	.517	.012
	Time x Condition	.524	.593	.011
BAT 1 Electrodermal	Time	47.448	<.001*	.343
Response	Condition	.328	.721	.007
	Time x Condition	.317	.729	.007
BAT 2 Anticipated Anxiety	Time	228.714	<.001*	.683
	Condition	.066	.936	.001
	Time x Condition	.664	.517	.012
BAT 2 Peak Anxiety	Time	323.038	<.001*	.756
	Condition	.145	.865	.003
	Time x Condition	.221	.802	.004
BAT 2 Electrodermal	Time	56.695	<.001*	.374
Response	Condition	.070	.932	.001
	Time x Condition	1.590	.209	.032

Post-Exposure Equivalence of Groups

Descriptive statistics of post-exposure sleep characteristics are shown in Table 4. Mean sleep time for the sample was 7.54 hours as measured by Fitbit, which closely matched self-reported sleep time (7.51 hours). Fitbit data indicated that participants woke an average of 1.40 times during the night and spent an average of 26.77 minutes either awake or "restless" after sleep onset. Mean PROMIS-SD score was 17.14, which can be interpreted as sleep disturbance in the none to slight range (Yu et al., 2012). Two participants reported that they were under the influence of alcohol during post-exposure sleep.

No differences in experimental groups were revealed during or following exposure, or during subsequent sleep. This was explored using one way ANOVAs and chi-squares analyses examining variables of exposure end-fear ($F(2,106) = 0.50$, $p = 0.61$), total exposure trials ($F(2,106) = 0.21$, $p = .81$), total sleep quantity as measured by Fitbit ($F(2,93) = 0.27$, $p = 0.77$), total sleep quantity as measured by self-report ($F(2,99) = 1.71$, $p = 0.19$), PROMIS-SD total score ($F(2,102) = 0.57$, $p = 0.57$), number of times awake after sleep onset ($F(2,93) = 0.63$, $p = 0.53$), number of times restless after sleep onset ($F(2,93) = 1.86$, $p = 0.16$), total time awake or restless after sleep onset ($F(2,93) = 2.09$, $p = 0.13$), alcohol consumption status $\chi^2(2, N=99) = 0.98$, $p = 0.61$, or fear domain $\chi^2(4, N=109) = 0.74$, $p = 0.95$.

Table 4: Post-exposure sleep characteristics

	Exposure Cue (N = 31)	Novel Cue (N = 31)	Control (N=34)
	M (SD)	M (SD)	M (SD)
Fitbit Variables			
Total sleep time (minutes)	441.32 (99.83)	454.45 (123.53)	460.76 (101.13)
Number of times awake	1.19 (1.30)	1.65 (2.07)	1.35 (1.35)
Number of times restless	10.84 (7.12)	14.32 (7.41)	14.03 (9.04)
Total Time Awake or Restless (minutes)	21.65 (15.91)	30.48 (17.99)	28.06 (18.77)
Self-Reported Total Sleep Time (minutes)	441.57 (95.82)	436.68 (101.88)	474.09 (67.22)
PROMIS-SD Total Score	17.53 (7.05)	17.69 (6.76)	16.12 (6.16)

Primary Outcome Analyses

Results from linear mixed models showing fixed effects of Time, Condition, and Time x Condition interactions are presented in Table 5. Table 6 shows pairwise comparisons of the Time x Condition interaction that directly compare rates of anxiety reduction between the EXPCUE condition versus the Cntl condition, and between the EXPCUE condition versus the NOVCUE condition. Significant main effects of time were found for BAT 2 outcomes of peak anxiety (B = -3.17, se = 1.36, 95% CI = [-5.86, -0.47], t = -2.33, p = 0.02, r = 0.21), anticipated anxiety (B = -4.47, se = 1.67; 95% CI = [-7.78, -1.16], t = -2.68, p = 0.01, r = 0.24), and threat likelihood (B = -3.30, se = 1.22, 95% CI = [-5.73, -0.87], t = -2.70, p = 0.01, r = 0.25), indicating that fear responding in the generalization context decreased from post-treatment through 1-month follow-up. However, there were no significant Time x Condition interactions for BAT 2. In contrast to hypothesis, groups did not differ in fear responding over time in the generalization context, when controlling for fear at baseline. Effect sizes for the main effect of time were small per guidelines put forth by Cohen (1992).

No corresponding main effect of time was found on BAT 1 outcomes of peak anxiety (B = -0.68, se = 1.45, 95% CI = [-3.56, 2.19], t = -0.47, p = 0.64, r = 0.05), anticipated anxiety (B = -0.61, se = 1.57, 95% CI = [-3.73, 2.51], t = -0.39, p = 0.70, r = 0.04), or threat likelihood (B = -1.35, se = 0.98, 95% CI = [-3.29, 0.60] t = -1.38, p = 0.17, r = 0.14). Furthermore, no significant interaction of Time x Condition was found for BAT 1, indicating that the primary hypothesis was not supported. These findings suggest that fear responding within the exposure training context remained stable from post-treatment through 1-month follow-up, controlling for baseline fear.

Linear mixed models examining electrodermal response revealed a main effect of time for both BAT 1 (B = 1.81, se = 0.51, 95% CI = [0.81, 2.81] t = 3.56, $p < 0.001$, r =

0.22) and BAT 2 (B = 1.65, se = 0.60, 95% CI = [0.48, 2.82] t = 2.77, p < 0.01, r = 0.17), suggesting that skin conductance in response to BATs increased slightly from post-treatment through 1-month follow-up in both the exposure and the generalization contexts. Effect sizes indicated that this observed main effect of time was small. Main effects of Condition and the Time x Condition interactions were not significant, meaning that change in electrodermal activity did not differ between treatment groups across assessment points.

To control for potential effects of sleep quantity and quality in addition to baseline outcome measurements, the following covariates were entered separately into each model: total sleep time as measured by self-report, total sleep time as measured by Fitbit, sleep quality as measured by PROMIS-SD, and general sleep quality as measured by PSQI. When controlling for Fitbit total sleep time, the main effect of time for the BAT1 threat likelihood outcome became statistically significant (F(1, 85.95) = 4.06, p = 0.047), indicating that estimated threat likelihood decreased over time in the exposure context (consistent with findings from the BAT2 threat likelihood outcome). However, all Time x Condition interactions remained nonsignificant and no meaningful changes were found from the addition of sleep-related covariates.

Table 5: Results from linear mixed models showing fixed effects of time, condition, and time x condition interactions on primary outcome variables

Effect	Numerator df	Denominator df	*F*	*p*
BAT 1 Anticipated Anxiety				
Time	1	102.42	1.23	0.27
Condition	2	103.69	1.10	0.34
Time x Condition	2	102.40	0.07	0.93
BAT 2 Anticipated Anxiety				
Time	1	114.20	32.03	<0.001*
Condition	2	103.91	1.22	0.30
Time x Condition	2	114.18	0.79	0.46
BAT 1 Threat Likelihood				
Time	1	95.39	3.28	0.07
Condition	2	99.85	1.45	0.24
Time x Condition	2	95.34	0.87	0.43
BAT 2 Threat Likelihood				
Time	1	108.86	24.67	<0.001*
Condition	2	98.57	0.84	0.44
Time x Condition	2	108.83	0.46	0.64
BAT 1 Peak Anxiety				
Time	1	100.42	0.23	0.63
Condition	2	105.17	1.02	0.36
Time x Condition	2	100.40	0.035	0.97
BAT 2 Peak Anxiety				
Time	1	113.81	27.09	<0.001*
Condition	2	104.72	0.37	0.69
Time x Condition	2	113.80	0.69	0.51
BAT 1 Electrodermal Response				
Time	1	245.65	44.26	<0.001*
Condition	2	107.86	0.08	0.93
Time x Condition	2	245.61	0.16	0.85
BAT 2 Electrodermal Response				
Time	1	257.90	38.62	<0.001*
Condition	2	132.51	0.87	0.42
Time x Condition	2	257.92	0.63	0.54

* = Significant at p <0.001 level

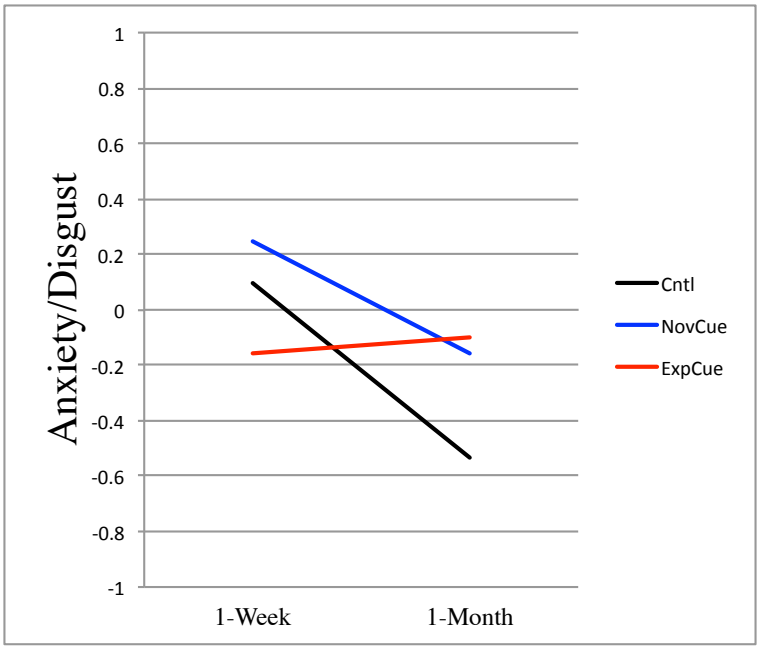
Table 6: Pairwise comparisons from linear mixed models examining the Time x Condition interaction. Comparisons use EXPCUE as as the reference category in order to examine rate of fear reduction for EXPCUE versus CNTL condition, as well as EXPCUE versus NOVCUE condition.

Parameter	*B*	CI	se	df	*t*	*p*	Effect Size
BAT 1 Anticipated Anxiety							
Time x Exp Cue	REF						
Time x Cntl	-0.84	[-5.33, 3.65]	2.26	102.65	-0.37	0.71	0.04
Time x Nov Cue	-0.39	[-4.80, 4.02]	2.22	101.43	-0.18	0.86	0.02
BAT 2 Anticipated Anxiety							
Time x Exp Cue	REF						
Time x Cntl	-2.79	[-7.55, 1.97]	2.40	114.43	-1.16	0.25	0.11
Time x Nov Cue	-0.35	[-5.02, 4.33]	2.36	113.19	-0.15	0.88	0.01
BAT 1 Threat Likelihood							
Time x Exp Cue	REF						
Time x Cntl	-0.41	[-3.21, 2.39]	1.41	95.52	-0.29	0.77	0.03
Time x Nov Cue	1.35	[-1.40, 4.09]	1.38	94.80	0.97	0.33	0.10
BAT 2 Threat Likelihood							
Time x Exp Cue	REF						
Time x Cntl	-1.13	[-4.60, 2.33]	1.75	109.04	-0.65	0.52	0.06
Time x Nov Cue	0.49	[-2.92, 3.89]	1.72	107.97	0.28	0.78	0.03
BAT 1 Peak Anxiety							
Time x Exp Cue	REF						
Time x Cntl	0.27	[-3.86, 4.41]	2.09	100.62	0.13	0.90	0.01
Time x Nov Cue	0.54	[-3.51, 4.60]	2.05	99.50	0.27	0.79	0.03
BAT 2 Peak Anxiety							
Time x Exp Cue	REF						
Time x Cntl	-2.24	[-6.13, 1.64]	1.96	113.95	-1.15	0.26	0.11
Time x Nov Cue	-0.67	[-4.47, 3.14]	1.92	113.14	-0.35	0.73	0.03
BAT 1 Electrodermal Response							
Time x Exp Cue	REF						
Time x Cntl	0.24	[-1.20, 1.67]	0.73	245.67	0.32	0.75	0.02
Time x Nov Cue	0.43	[-1.06, 1.91]	0.75	244.81	0.57	0.57	0.04
BAT 2 Electrodermal Response							
Time x Exp Cue	REF						
Time x Cntl	0.85	[-0.82, 2.52]	0.85	257.91	1.00	0.32	0.06
Time x Nov Cue	0.80	[-0.91, 2.52]	0.87	257.91	0.92	0.36	0.06

Secondary Outcome Analyses

Linear mixed models examining Z-scored self-report measures (FSQ, CLQ, PI-WSUR) at 1-week and 1-month follow-up revealed that Time ($F(1, 95.19) = 10.28$, $p = 0.002$) and the Time x Condition interaction ($F(2, 95.19) = 4.01$, $p = 0.021$) significantly predicted outcome, while controlling for baseline score. The Time x Condition interaction is plotted in Figure 6. Self-reported anxiety and disgust remained stable during the 1-week to 1-month follow-up assessments in the EXPCUE condition ($b = 0.03$, se = 0.08, 95% CI = [0.14, 0.20] $t = 0.34$, $p = 0.74$). In comparison to the EXPCUE condition, the CNTL condition exhibited significantly faster self-reported anxiety reduction ($b = -0.34$, se = 0.12, 95% CI = [-0.59, -0.10] $t = -2.77$, $p = 0.007$), and the NOVCUE condition also demonstrated a more rapid anxiety reduction that was marginally significant ($b = -0.23$, se = 0.12, 95% CI = [-0.48, -0.01] $t = -1.88$, $p = 0.06$). These findings are in contrast to hypothesis, which predicted that the exposure cue condition would exhibit more rapid decline in self-reported anxiety and disgust than the novel cue or control conditions.

Figure 6: Time x Condition interaction predicting self-reported anxiety and disgust, while controlling for baseline score. Cntl = Control, NovCue = Novel Cue, ExpCue = Exposure Cue



Moderator Analyses

Contrary to hypothesis, no significant Time x Condition x End Fear interaction was found for BAT 1, indicating that end fear did not moderate rates of anxiety change between the different experimental conditions. There was a significant 2-way interaction between end-fear (peak anxiety during the final exposure trial) and time when examining BAT 1 peak anxiety as an outcome and controlling for peak anxiety at baseline, self-reported sleep quantity, and PROMIS-SD total score ($F(1, 80.52) = 17.45$, $p < 0.001$). Figure 7 presents conditional effects of time in the exposure context, with end fear centered one standard deviation below its mean and one standard deviation above its mean, and collapsing across conditions. Results indicated that individuals with high end-fear during the final exposure trial exhibited a decrease in anxiety levels from post-treatment through 1-month follow-up ($B = -3.97$, se = 1.16, 95% CI = [-6.28, 1.65] $t = -3.41$, $p = 0.001$), while individuals with low end-fear exhibited an increase in anxiety ($B = 3.15$, se = 1.15, 95% CI = [0.86, 5.43] $t = 2.74$, $p = 0.007$). Individuals with low end fear exhibited lower anxiety across all timepoints than individuals with high end fear ($F(1, 93.51) = 125.44$, $p < 0.001$).

The Time x End Fear interaction was also a significant predictor of BAT 2 peak anxiety in the generalization context ($F(1, 103.90) = 13.11$, $p < 0.001$), controlling for peak anxiety at baseline, self-reported sleep quantity, and PROMIS-SD total score. Figure 8 presents conditional effects of time in the generalization context, with end fear centered one standard deviation above and below its mean value, and collapsing across conditions. Results indicated that individuals with high end-fear exhibited more rapid decreases in anxiety from post-treatment through 1-month follow-up ($B = -7.02$, se = 1.00, 95% CI = [-9.01, -5.03] $t = -7.01$, $p < 0.001$) than individuals with low end-fear ($B = -2.25$, se = 0.99, 95% CI = [-4.21, -0.30] $t = -2.28$, $p = 0.024$). Contrary to hypothesis,

no significant Time x Condition x End Fear interaction was found in the generalization context, indicating that end fear did not moderate rates of anxiety change between the different experimental conditions.

End fear did not significantly moderate the relationship between Time x Condition and electrodermal response for either BAT 1 or BAT 2. Examination of extinction rate and fear domain as moderators yielded several interactions with p values less than 0.05, however these effects did not survive Benjamini-Hochberg correction for multiple comparisons, and furthermore were not observed in both the exposure and generalization contexts as would be expected for robust effects. Findings suggested that while end fear may moderate rates of anxiety change following exposure therapy, these effects were non-specific to treatment condition and were not observed in electrodermal response. Extinction rate and fear domain were not observed to be significant moderators for any outcome in either the exposure or the generalization contexts.

Figure 7: Time x End Fear interaction predicting BAT 1 peak anxiety, collapsing across conditions and controlling for baseline peak anxiety, self-reported sleep quantity, and PROMIS-SD total score. End fear is centered at one standard deviation above and below its mean.

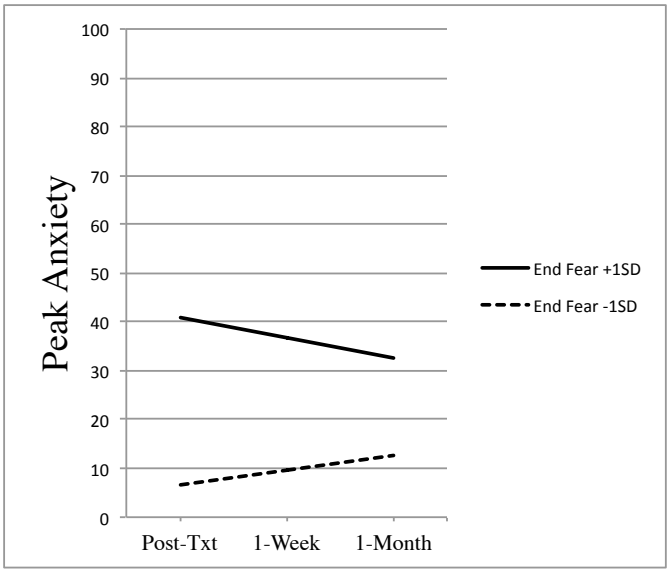
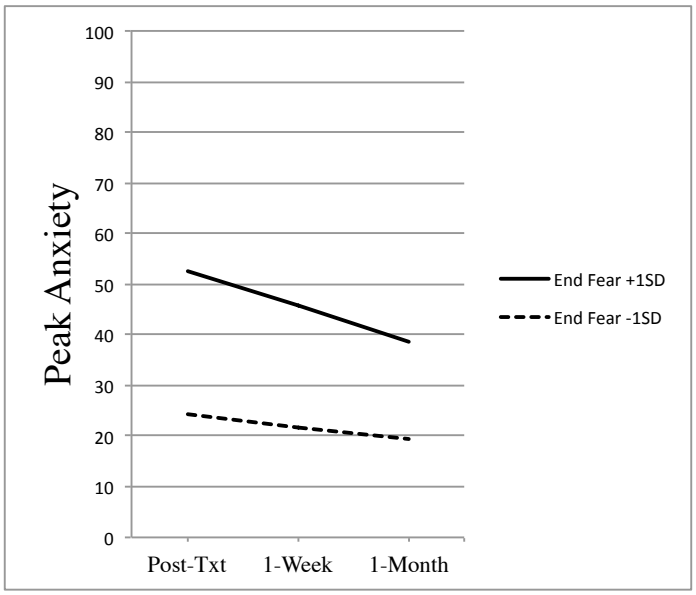


Figure 8: Time x End Fear interaction predicting BAT 2 peak anxiety, collapsing across conditions and controlling for baseline peak anxiety, self-reported sleep quantity, and PROMIS-SD total score. End fear is centered at one standard deviation above and below its mean.



CHAPTER 5: DISCUSSION

The current study was motivated by a need to develop strategies for enhancing exposure-based therapies. The primary goal was to determine whether exposure therapy could be augmented by using targeted memory reactivation (TMR) to enhance consolidation of extinction learning and reduce long-term fear. Participants with marked fear of spiders, contamination, or enclosed spaces received exposure therapy in the presence of a contextual odor cue and were randomly assigned to subsequently sleep either in the presence of the same exposure scent cue (EXPCUE), a novel scent cue (NOVCUE), or an odorless control vehicle (CNTL). We hypothesized that participants would exhibit significantly decreased fear immediately following exposure therapy, and that the magnitude of this fear reduction would be similar across all groups. We also hypothesized that at one-week and one-month follow-up assessments, the EXPCUE condition would exhibit decreased anxiety levels in comparison to the NOVCUE and CNTL conditions. Furthermore, we hypothesized that this effect would be moderated by exposure end-fear, such that EXPCUE participants with low anxiety at exposure termination would demonstrate reduced fear relative to other conditions, and EXPCUE participants reporting high levels of anxiety at exposure termination would demonstrate greater fear than participants in other conditions.

Efficacy

As predicted, exposure resulted in significant pre- to post-exposure reduction in fear responding across all groups, as measured by electrodermal response as well as self-reported fear during behavioral approach tasks (BATs). The effect size of this fear reduction was large regardless of measurement by indices of peak anxiety, anticipated anxiety, threat expectancy rating, or electrodermal response. The effect was also observed regardless of whether measures were obtained in the exposure context (BAT1) or in a generalization context (BAT2) that used novel fear targets to assess phobic responding. Consistent with hypothesis, groups did not differ in magnitude of pre- to post-exposure fear reductions.

In contrast to prediction, no between-group differences were found in fear responding to BATs during follow-up assessments, suggesting that sleeping in the presence of an exposure-congruent scent did not reduce long-term anxiety in comparison to control conditions. This result is inconsistent with prior research suggesting that TMR promotes consolidation of multiple forms of learning, including those involving declarative (Diekelmann et al., 2012; Rudoy et al., 2009; Schreiner & Rasch, 2015; Shimizu et al., 2018) and procedural memories (Antony et al., 2012; Cousins et al., 2014; Schönauer et al., 2014). However, findings in the domain of emotional memory have been more mixed, with some evidence suggesting that emotional memory strength is not affected by TMR (Rihm et al., 2016; Rihm & Rasch, 2015). It is possible that extinction memories are less amenable to consolidation by TMR than other forms of learning.

Several other explanations may account for the failure to reject the null hypothesis. First, the scent manipulation may have failed to induce neuronal replay of extinction learning altogether. Previous TMR experiments have used highly controlled environments for delivering odor cues which included use of olfactometers, nasal masks

worn during sleep, and other specialized equipment to deliver measured quantities of scent as participants slept in a laboratory (Rasch et al., 2007; Rihm et al., 2014). Such equipment is unrealistic for widespread use in clinical practice, as logistical, monetary, and practical constraints would prevent most individuals from accessing such resources.

Instead, the present study emphasized translation of basic research findings into easily disseminable results, and therefore used commonly available commercial scent diffusers to deploy the exposure odor cue. Adoption of these devices came with loss of some experimental control, as participants were responsible for proper nighttime use of the diffuser within their home. While 89.9% of the sample submitted a picture of the diffuser next to their bed, the nature of the scent manipulation meant that participants differed in variables that would impact odor intensity and delivery, such as proximity of the diffuser to their bed, room volume, and airflow. There was also no method for verifying that individuals did not turn off the diffuser after taking a picture of it.

Previous research has used EEG signatures taken during sleep as a marker for whether odor cues induced memory reactivation (Rihm et al., 2014; Rihm et al., 2016). However, because no EEG readings were taken during the current study it is unknown whether or not neuronal replay actually occurred during the present experiment. If the scent cue did not successfully trigger neuronal replay of extinction learning in the current experiment, it would not have led to enhanced memory consolidation even if such a mechanism is viable.

Future studies would benefit from inclusion of tests to verify that TMR can be successfully extended to general clinical settings. The most obvious initial targets might be replication of effects within learning domains that have already demonstrated responsiveness to TMR-induced consolidation. Although results from one study suggest that successful TMR in an uncontrolled home environment is possible (Ritter et al.,

2012), further research is necessary to replicate this finding and to outline the conditions under which it is efficacious.

In the current study, including a declarative learning task in addition to extinction learning tasks would have helped to determine whether TMR was successfully implemented, even if it did not promote extinction learning consolidation specifically (one would expect to see enhanced declarative memory but not enhanced fear extinction at follow-up in this case). If no evidence of either declarative or extinction learning consolidation was observed, null findings could be attributed to failure of the experimental setup to reactivate cued memories during sleep.

We must also account for the possibility that the present study may have failed to detect a treatment augmentation effect that was actually present, due to Type II error from lack of power. However, using GLIMMPSE power analysis software (Kreidler et al., 2013) we estimated that the obtained sample size of 109 participants provided 80% power to detect a medium-sized effect, corresponding to a difference of 11 subjective units of distress at the one-month follow-up period while using the observed standard deviation of 20.

Moderation of Primary Outcomes

The hypothesis that end fear at exposure termination would moderate the effects of treatment condition on rates of anxiety change was not supported. The literature on treatment augmentation with pharmacological enhancers suggests that augmentation of learning during exposures is a double-edged sword. Because learning is indiscriminately boosted with substances such as D-cycloserine or methylene blue, successful extinction sessions will result in reduced fear, but unsuccessful sessions may result in symptom exacerbation through enhanced reconsolidation of fear (Hofmann, 2014; Hofmann, Otto, Pollack, & Smits, 2014a; Telch, Bruchey, Rosenfield, Cobb, et al., 2014a). Using this work to guide hypotheses about moderators in the current study, we predicted that individuals with low end fear during exposure would exhibit anxiety reductions at follow-up relative to the other conditions, whereas individuals with high end fear would exhibit elevated anxiety. Instead, no significant moderator effects were found.

The fact that there were only a small number of unsuccessful exposure cases in the present study may have increased the difficulty of detecting such a moderating effect. This may partially be a function of treatment design. In an effort to reduce the potential for reaching a treatment ceiling (i.e. all groups demonstrating complete fear extinction and precluding the ability to detect further augmentation effects), treatment was terminated once participants achieved fear reduction of 35 subjective units of distress during exposure, regardless of whether this took only several minutes or a full 40 minutes of exposure time.

Almost all participants achieved this stopping criterion: only 15 of 109 total participants failed to achieve full fear reduction of 35 units, and of these participants only 2 reported increased anxiety levels following exposure. BATs to assess fear responding also appeared to serve as additional exposure, despite only lasting 30 seconds each. The

average peak fear reduction from pre- to post-treatment BAT assessments was 51 units in the exposure context, and 41 units in the generalization context.

Given the uniformity of treatment response, it is perhaps unsurprising that significant moderator variables were not detected for primary outcomes. A study design in which exposure duration was identical for all participants may have resulted in greater spread in post-exposure anxiety reduction, and therefore allowed for a more sensitive examination of whether successful extinction learning moderates the relationship between treatment condition and fear decline over time. Nevertheless, the current design provided the opportunity to investigate whether treatment duration would moderate outcomes, although no moderating effect of exposure length was found either.

The emergence of a two-way interaction between end-fear and time, irrespective of condition, was somewhat unexpected. Individuals with high end fear demonstrated more rapid reductions in anxiety than individuals with low end fear from post-treatment through one-month follow-up. It is important to note that individuals with low end fear still demonstrated better outcomes overall than individuals with high end fear, as their anxiety was lower across all follow-up assessments. The Time x End Fear interaction may simply represent a treatment ceiling effect in which individuals with low end fear experienced dramatic post-exposure reductions in anxiety that could not be reduced further, whereas individuals with high end fear experienced reductions in anxiety that still had room to decrease at follow-up visits.

Secondary Outcomes Analysis

In contrast to hypothesis, secondary outcomes of subjective anxiety as measured by self-report instruments suggested that symptoms in the EXPCUE group remained stable through the one-week and one-month follow-up visits, whereas symptoms in the NOVCUE and CNTL conditions declined from the one-week to the one-month visit. The finding that the EXPCUE group exhibited a slower rate of fear decline than other conditions is the opposite of what was predicted. Findings raise two questions regarding interpretation of results:

1) How can the lack of between-group differences from primary outcome analyses be reconciled with secondary outcome findings that the EXPCUE group performed more poorly than other conditions?
2) What mechanisms might account for underperformance of the EXPCUE group relative to other experimental conditions, when measuring self-reported anxiety?

In addressing the first question, it is informative to remember that primary outcome measures assessed fear in response to behavioral approach tests, during which participants directly confronted a feared stimulus by standing 1 foot from a spider, touching a toilet, or being locked in a small container. In contrast, secondary outcome instruments assessed self-reported fear in response to hypothetical scenarios, and were measured in the absence of feared stimuli.

Research has shown that declarative fear memories are not the same as emotional fear responding, and that it is possible to dampen emotional fear responding even while self-declared fear remains intact (Kindt et al., 2009; Soeter & Kindt, 2015). Soeter and Kindt (2015) demonstrated that brief exposure to a spider, followed by application of the

reconsolidation-blocking agent propanalol, resulted in rapid increase in behavioral approach toward spiders even as participants retained declarative knowledge of spider fear. It was not until 3 months later that self-reported spider fear decreased as well. Other work has demonstrated that startle response to feared stimuli can be eliminated even while self-declared fear to those stimuli is retained (Kindt et al., 2009). In the present study, a similar dissociation between self-declared fear and emotional fear responding was observed.

This dissociation does not account for the unexpected underperformance of the EXPCUE group relative to other experimental conditions when examining self-declared fear. One explanation may simply be that TMR does not promote consolidation of extinction learning on an emotional level, but does in fact promote consolidation of declarative knowledge of fear. The act of engaging in a single brief session of exposure treatment, capped at a reduction of 35 subjective units of distress, may have reminded participants about their pre-existing explicit fear without providing ample opportunity to disconfirm this fear on a declarative level. This declarative fear memory may then have been reconsolidated with an exposure-consistent odor cue during sleep. It is possible that extending the exposure cutoff criterion (e.g. not capping the magnitude of anxiety reduction) would provide greater opportunity for participants to disconfirm pre-existing, explicit knowledge of their fear.

Discrepancy Between EDA and Fear Response to BATs

When examining the main effect of time (regardless of treatment condition), an inconsistency between results from electrodermal response and fear in response to BATs was observed. Peak anxiety, anticipated anxiety, and threat expectancy ratings in response to BATs decreased slightly from post-treatment through one-month follow-up in the generalization context. When controlling for total sleep quantity as measured by Fitbit, BAT 1 threat expectancy also decreased slightly over time, while peak and anticipated anxiety in the exposure context were stable. In contrast, electrodermal response for both BAT 1 and BAT 2 showed small increases from post-treatment through one-month follow-up.

It is likely that observed increases in electrodermal fear responding over time were an artifact of experimental procedures, rather than representing a genuine anxiety increase during the follow-up period. Each BAT assessment involved measuring electrodermal activity during a quiescent period in which participants sat in a non-stimulating environment without the presence of any feared stimuli. This quiescent electrodermal activity was subtracted from the electrodermal activity measured during each BAT, at which time participants confronted feared stimuli.

At baseline and at each follow-up assessment, the quiescent measurement period was one of the initial steps of the experimental visit, meaning that participants were unlikely to be experiencing significant stimuli-related anxiety and therefore would not have large values subtracted from total BAT electrodermal response. At the post-exposure assessment, measurement of quiescent electrodermal activity occurred following exposure therapy and before post-exposure BATs. At this point of the procedure, participants had undergone up to 40 minutes of exposure to feared stimuli, and

therefore may have continued to experience residual anxiety despite the immediate absence of feared stimuli in the environment.

Examination of quiescent electrodermal activity at each assessment period revealed that electrodermal activity was indeed greatest prior to post-exposure BATs ($F(3,403) = 28.78$, $p < 0.001$), with mean quiescent electrodermal activity at the post-exposure assessment (16.86 +/- 12.83μS) being more than twice as large as any other quiescent measurement period. Subtracting these inflated measurements would artificially decrease total electrodermal response to post-exposure BATs, and contribute to a time effect in which electrodermal fear responding appeared to increase from post-treatment through follow-up. Increasing the amount of time between exposure termination and the post-exposure BAT may have eliminated the discrepancy between electrodermal response and self-reported anxiety, although it would not be expected to change overall findings.

Limitations

The present study had several limitations that deserve attention. Although participants were screened for significant fear in response to two behavioral approach tests as well as self-report measures, no formal testing for psychiatric diagnoses was conducted. It would be useful to examine whether results are replicated in a sample in which all individuals have a formal diagnoses of OCD or specific phobia of spiders or enclosed spaces. Additionally, despite efforts to recruit from the community the sample was disproportionately comprised of female university students. Replication with a more diverse sample of participants is warranted.

Second, as mentioned previously participants were not strictly monitored in their use of the scent diffuser within their homes, other than asking that they sent a picture of the diffuser next to their bed. This resulted in a degree of uncertainty as to whether all participants received a similar scent manipulation.

Third, no polysomnography was employed to record patterns of neural reactivation during slow wave sleep. Therefore, we were not able to directly assess whether neuronal replay of extinction learning was successfully achieved. Although odors have successfully been used to cue TMR in prior studies, it is not firmly established whether this translates to a home environment.

Fourth, data loss due to equipment failure or participant nonresponse was not ideal, although no pattern of missingness was detected and the statistical methods employed are well-suited to handle missing data.

Finally, the one-month follow-up period may have been too brief to allow for long-term assessment of trends. Future studies would benefit from extended follow-up to determine stability of results.

Conclusion

In summary, results from the current study do not support the use of TMR as an augmentation strategy for enhancing exposure for fear of spiders, enclosed spaces, or contamination. Groups did not differ in fear responding to behavioral approach tests at any point following exposure, and results from self-report instruments indicated that individuals who were given an exposure-congruent scent during sleep experienced less improvement at follow-up visits than individuals in other conditions. Results suggest that extinction learning may not be amenable to enhancement through TMR, although further research is needed.

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