Mechanisms and effects of acute stress on extinction learning: Two randomised-controlled trials of stress-enhanced CBT for spider phobia

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Statement of Originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

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Abstract

Despite years of progress, there remains a need for new therapeutic approaches to anxiety and fear-based disorders, as more than one third of patients experience a relapse within the first year following successful exposure-based treatment. Studies have shown that stress levels influence the learning and memory underlying these exposure-based treatments, and thus can be manipulated during therapy as a way of improving outcomes. This thesis investigated the application of acute stress as a pathway to reduce different relapse phenomena and the mechanisms by which this may occur. To address these aims, a systematic review, a pilot (N=18) and a follow-up randomised-control study (RCT) (N=37) were conducted. The systematic review focused on 1) evaluating the evidence that stress-adjuncts to therapy can reduce relapse and 2) exploring when and how stress exerts its effects on treatment to inform mechanisms. Review findings indicated that stress exerts its effects in the short and long term, generally leading to enhanced extinction learning (short-term) and greater treatment outcomes (long-term) (4-6 weeks). An Integrated Model of Stress-Augmentation was developed and used to synthesise findings and suggest neural and cognitive mechanisms for investigation. The pilot and RCT studies extended previous findings by investigating the potential for stress to reduce relapse associated with a change in context (renewal) and following an extended period of time (spontaneous recovery) within clinical samples. The role of interacting stress hormones (cortisol and noradrenaline), expectancy of harm and attention were explored as mediators of these effects. Study 1 and 2 included participants aged 18-60, with a clinically significant fear of spiders, who were randomly allocated to receive a behavioural stress (socially evaluated cold presser task) or control task 25 minutes prior to two virtual-reality exposure sessions. Renewal of fear was assessed at post-treatment with the presentation of a spider in a novel context, and

spontaneous recovery of fear at 3-month- (in the RCT) and 7-month- follow up (in the pilot study) with the presentation of a spider in the treatment context. Findings revealed stress improved treatment outcomes at post-treatment, 3-month and 7-month follow-up periods, as measured by spider phobic questionnaires. No effect of stress on renewal of fear was found following test in a novel context. During exposure, stress enhanced initial expectancy of harm, but had no effect on participants engagement with the spider. Mediation analysis revealed cortisol partially mediated the long-term, but not the short-term, benefits of stress on treatment outcomes, confirming previous research on the memory-enhancing effect of stress. Noradrenaline, expectancy of harm and attention did not account for the findings. Together, results illustrate stress has the potential to reduce spontaneous recovery of fear, partially accounted for by cortisol, but does not affect renewal of fear assessed in the short-term. This body of research suggests stress-enhancing agents are a promising approach to improve symptom remission and reduce relapse rates. Larger randomised control trials and further research into the mechanisms underlying the effects of stress on extinction learning and relapse phenomena are required.

Table of Contents

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4.

List of Tables

Chapter 2

Chapter 3

Chapter 4.

Abbreviations

ANOVA

ANCOVA

BAT- Behavioural Avoidance Test

CBT- cognitive behavioural therapy

CORT- cortisol

CPT- cold presser task

CR- conditioned response

CS- conditioned stimulus

DASS- Depression Anxiety and Stress Scale

diffSCR- differential skin conductance response

FSQ- Fear of Spider Questionnaire

GR- glucocorticoid receptors

HR- heart rate

HPA- Hypothalamic-pituitary adrenal axis

NE- noradrenaline

sAA- salivary alpha amylase

SECPT- socially evaluated cold pressor task

Sig- significant

SPQ- Spider Phobia Questionnaire

STAIT - State Trait Anxiety Inventory

SUDs- Subjective units of distress

US- unconditioned stimulus

VR- virtual reality

Chapter 1: General Introduction

It's been over 60 years since the science world was introduced to the behavioural approach to treating fear and anxiety disorders. In one of the first experiments, it was shown that a little boys fear towards fluffy white objects could be reduced by gradually bringing a rabbit in a cage closer and closer to the boy (Jones, 1949). Since then, there have been hundreds of books and thousands of peer-reviewed articles developing this approach. However, no CBT protocol has consistently shown a 100% remission rate (Thoma, Pilecki, & McKay, 2015) and there is still a lot of work to be done.

Anxiety, fear and stress-related disorders are characterized by marked, persistent and excessive fear (and avoidance) (DSM–V; American Psychiatric Association, 2013). Together they represent the most common psychiatric disorders (Kessler et al., 2005) with a lifetime prevalence of 29 % (Bandelow & Michaelis, 2015) and are among the most debilitating mental health conditions in the world (Australian Bureau of Statistics, 2008). As such, effectively treating anxiety-based disorders is essential.

Research has shown that exposure-based treatment, commonly occurring within cognitive behaviour therapy (CBT), is the most effective in reducing associated symptoms of distress (Choy, Fyer, & Lipsitz, 2007; Hofmann & Smits, 2008). This form of treatment involves repeatedly exposing individuals to their feared object or situation in the absence of an aversive outcome. Meta-analytic reviews report CBT produces significant improvements in clinical symptoms of a small to large effect size, amongst different anxiety disorders (Hofmann & Smits, 2008; Otte, 2011). However, despite strong empirical evidence for exposure-based treatment, 19-62 % patients with anxiety fail to respond to this treatment or experience a relapse

of symptoms (Craske & Mystkowski, 2006). This has prompted research into new therapeutic approaches which might enhance treatment gains for exposure-based therapies.

One such enhancer has involved the use of acute stress. Human and animal research has demonstrated that acutely elevated levels of stress can strengthen the learning and retrieval ability of memories formed during exposure-based therapy (de Quervain, Schwabe, & Roozendaal, 2017; Maren & Holmes, 2016). Stress is a cognitive, emotional, and biological process in response to emotionally arousing events perceived to be unpredictable and uncontrollable (Epel et al., 2018). It involves the release of stress hormones, noradrenaline (NE) and cortisol, which cause bodily and neural changes to support coping with a stressor. Whilst this avenue of research is still in its early stages, it offers promising developments towards resolving relapse and enhancing treatment outcomes. This thesis investigates the potential for stress-related adjuncts to therapy to attenuate relapse and identify how stress facilitates the learning and memory processes underlying exposure -based treatment.

1.1 Conditioning and extinction: Models of the development and treatment of anxiety disorders

Although the etiology of anxiety and fear-based disorders is multi-faceted, the acquisition and maintenance of these fears can be explained, at least in part, by fear conditioning theories. Conditioning theory asserts that phobic stimuli almost always provoke a fear response as a result of the retrieval of a stimulus-associated fear memory (Cuthbert et al., 2003; Lang, 1985). That is, relatively neutral stimuli (conditioned stimuli, CS – such as a dog) are associated with aversive experiences (unconditioned stimulus, US- such as a dog bite) which result in a fear response (conditioned response, CR- such as increased heart rate) when the neutral stimulus (i.e. the dog)

is encountered. These conditioned stimuli and their conditioned fear responses elicit anxiety and distress which persist in the absence of an aversive outcome. In an attempt to mitigate anxiety and fear responses, individuals tend to avoid encounters with their phobic stimuli (e.g., dogs). This serves to alleviate their stimulus-related fear and anxiety but prohibits new learning opportunities which maintain fearful stimulus associations (e.g., dog-danger). Therefore, recovery from fear conditioning involves exposure to phobic stimuli (CS) in the absence of harm (US), such that it inhibits automatic fear responding (CR) to the CS. This is known as extinction learning.

Exposure-based treatments for anxiety and fear-related disorders are currently understood and explored with the use of laboratory fear extinction paradigms. They define extinction as the form of new learning that underlies exposure therapy, where a new safe association with the feared stimulus is made. Extinction occurs when the feared response diminishes as a result of repeated presentations of the phobic stimulus in the absence of an aversive outcome. For example, during exposure therapy an individual may be repeatedly exposed to a dog (CS) in the absence of a dangerous outcome (US) in order to learn that the dog does not signal danger, forming a new dog-no danger association (CS-no US). Thus, exposure therapy can be understood as a learning process in which new non-fearful memory associations (extinction memories) are established (Hermans, Craske, Mineka, & Lovibond, 2006).

However, extinction memories compete with, but do not erase the original fear memory associations, leaving extinction memories susceptible to retrieval deficits that enable the recovery of fear (Quirk & Mueller, 2008b). This failure to retrieve extinction memories is believed to be the cause of the return of fear symptoms (i.e. relapse) following exposure-based treatments (Bouton, 2004; Vervliet, Craske, & Hermans, 2013). Animal and human research has

demonstrated that failure to retrieve extinction memories can occur as a result of the passage of time (spontaneous recovery), after a change in context (renewal), or after exposure to an aversive event (reinstatement) (Bouton, 2004). For example, following repeated exposure to a phobic object such as a dog in the clinic, fear towards dogs may recover if: 1) a dog is encountered outside the clinic (renewal), 2) a dog has not been encountered for some time (spontaneous recovery), or 3) an aversive event such as an animal bite unrelated to a dog prompts the return of fear (reinstatement). These relapse phenomena have been studied extensively using clinical analogue studies in the laboratory, offering a controlled environment for the investigation of relapse mechanisms. These procedures are presented in Figure 1.

Similarly, exposure to stress or the experience of stressful life events appear to trigger the recovery of fear symptoms and render extinction memories more resistant to retrieval (Shin & Liberzon, 2009; Vervliet et al., 2013). Notably, the neuronal structures involved in supporting extinction learning and retrieval overlap with those that modulate the stress response, making extinction processes vulnerable to the effects of stress (Stockhorst & Antov, 2016; Vervliet et al., 2013).

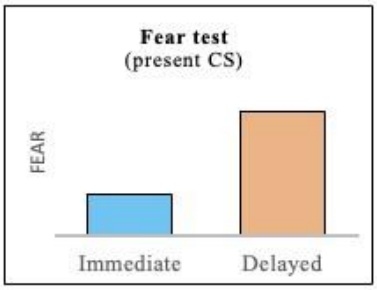
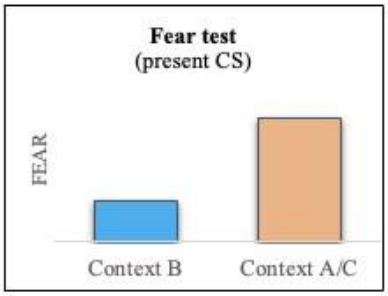
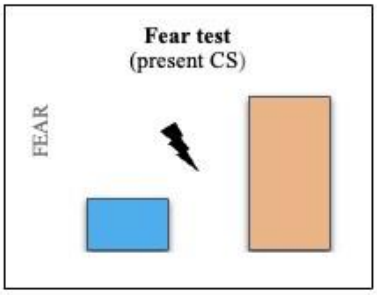
Phenomenon	Description	Retrieval Test
Spontaneous recovery	Recovery of fear that occurs when the phobic stimulus (CS) is presented after some time has passed following extinction learning. To observe this effect, fear is assessed by presenting the CS immediately after extinction and then at a delay.	
Renewal	Recovery of fear that occurs when the CS is presented in a physical context that is different to the extinction one. To observe this effect, an ABA renewal or ABC renewal paradigm is often used; Fear conditioning occurs in context A, extinction in context B and fear testing in context A(ABA renewal) or in a novel context C (ABC renewal).	
Reinstatement	Recovery of fear that occurs when the individual/animal is exposed to an aversive event (US) after extinction. To observe this effect, the US (e.g., shock) is presented to the individual/animal prior to presenting the CS.	

*Figure 1.*Different forms of relapse and their assessment in the laboratory. Adapted from Bouton (2002) and Vervliet, Craske & Hermans (2013).

1.2 Effects of stress on fear extinction learning and memory

Stress involves the activation of hormonal and brain systems which cause physiological, behavioural and neurological changes in the body aimed to support coping with a stressor. In acutely stressful situations, two systems are activated in a time-dependent way. The first is the rapid activation of the sympathetic nervous system including the release of adrenaline and noradrenaline. The second is the slow acting Hypothalamic-Pituitary-Adrenal axis (HPA) involving the delayed secretion of glucocorticoids (i.e., cortisol in humans and corticosterone in animals) (Joëls & Baram, 2009; Wolf, 2003). These systems are known to modulate extinction learning and memory by acting on the brain systems involved in the fear response, namely the amygdala and hippocampus. Whilst these stress hormones are commonly thought to have a detrimental impact on fear extinction, under certain conditions they can improve learning and memory (McEwen & Lupien, 2002; Schwabe et al., 2010). This could make extinction memories less susceptible to the circumstances which promote the return of fear (change in context, passage of time or an aversive experience) and potentially solve the problem of relapse.

1.2.1 Acute vs chronic stress

Stress can vary in its intensity and duration, influencing learning and memory in different ways. Acute stress is short-term stress which is caused by a one-off short-lived event, whilst chronic stress is long-term stress that occurs as a result of prolonged or repetitive exposure to stressful events. Chronic stress is associated with structural changes in the brain and often linked to cognitive decline (McEwen & Sapolsky, 1995) and impairing effects on extinction (Wellman & Moench, 2019). This is because chronic activation of the HPA axis is known to result in reduced neurogenesis, dendritic spines and synaptic plasticity (Joëls et al., 2004; McEwen, 2004; Roozendaal, McEwen, & Chattarji, 2009). In contrast, acute stress can facilitate learning and

synaptic plasticity to strengthen memory, when stress is limited to and experienced around the time of an emotionally arousing event. Therefore, the positive effects of stress on learning and memory will be explored below within the context of acute stress, as the effects of chronic stress are beyond the scope of this thesis.

1.2.2 Acute stress enhances memory consolidation

In general, stress is shown to enhance the consolidation of emotional memories, and this is consistent with the notion that trauma memories are 'over-consolidated' and strengthened under the influence of stress hormones stimulated by traumatic events. Indeed, both stress hormones have been implicated in the enhancing effects on memory consolidation and have a unique and synergic role to play.

Role of NE: Extensive evidence indicates that noradrenergic activation, which is involved in emotional arousal and is a part of the body's emergency response to danger, enhances the consolidation and recall of emotionally arousing experiences, including fear extinction (Bahtiyar, Gulmez Karaca, Henckens, & Roozendaal, 2020). Previous animal studies using rats or mice have shown that administration of NE leads to greater long-term retention and this is proposed to occur via b-adrenergic signalling that promotes neuroplasticity and amygdala- hippocampal connections to strengthen memory. Conversely, infusions of b-adrenergic receptor antagonist, which block the release of NE abolish its memory-enhancing effects (Roozendaal, Okuda, Van der Zee, & McGaugh, 2006) and this has been replicated in human studies **(**Cahill et al. 1994; Berlau & McGaugh, 2006).

Role of Cortisol: Similarly, optimal levels of the second stress hormone, cortisol, have been shown to predict memory enhancement (Roozendaal, 2002). Endogenous and exogenous

cortisol administration shortly prior to or after extinction learning can reliably facilitate memory in both animals and humans (Goldfarb, 2019; Wolf, 2009). However, the memory-enhancing effects of cortisol follow an inverted U-shaped dose-relationship, where moderate doses enhance memory, whereas lower or higher doses typically impair memory consolidation (Roozendaal, 2002). These memory consolidation effects also depend on glucocorticoid receptor (GR) and noradrenergic activation, as blockade of these receptors and NE signalling impair memory performance (Roozendaal, Okuda, Van der Zee, & McGaugh, 2006). This suggests NE and cortisol are both associated with the memory enhancing effects of stress and have a role to play in memory consolidation.

1.2.3 Acute stress promotes learning

Exposure to stress during encoding has also been shown to facilitate learning. This has been supported by animal studies demonstrating NE release induced by footshock or a conditioned stimulus promotes the subsequent enhancement of learning (Rau & Fanselow, 2009). Similarly, corticosterone administration in animals and acute stress exposure in humans improves performance on learning tasks (Akirav et al., 2004; Duncko, Cornwell, Cui, Merikangas, & Grillon, 2007). Animal studies show that corticosterone induced by acute stress potentiates learning via its effects on acid-sensing ion channels (ASICS), which are important modulators of synaptic plasticity, learning and memory (Ye et al., 2018). Moreover, clinical studies demonstrate acute stress reduces differential fear responding during extinction learning (Antov, Melicherová, & Stockhorst, 2015; Bentz et al., 2013) and higher levels of cortisol are related to enhanced extinction learning in clinical patients (Meuret et al., 2015).

1.2.4 Acute stress abolishes context-dependent memory

Stress also changes the nature and quality of memory by reducing the dependency of the hippocampus, which is critical for extinction. Specifically, the hippocampus is responsible for integrating and processing complex representations of the environment during extinction learning. This processing of the context is believed to be essential in supporting extinction memory retrieval as organisms learn to suppress fear responding to the CS only in the context where extinction occurred (Bouton, Garcia-Gutierrez, Zilski, & Moody, 2006; Vogel & Schwabe, 2016). This makes extinction memories susceptible to changes in context (Bouton, 2002, 2004). Several laboratory studies have demonstrated stress administered prior to encoding of an emotional task, impairs the contextualisation of memory (Drexler, Merz, & Wolf, 2018; Lars Schwabe, Böhringer, & Wolf, 2009; van Ast, Cornelisse, Meeter, Joëls, & Kindt, 2013). This means memories formed following stress exposure are not bound to the context and more easily generalise across contexts. Interestingly, animal literature reveals this occurs as a result of the suppression of hippocampal spine plasticity (Diamond et al. 1999), via stress and its effect on other processes such as long-term potentiation in the hippocampus (Diamond et al., 2007). These effects on the contextualisation of memory have been shown to be mediated by cortisol. Thus, it is plausible acute stress also has a positive impact on the generalisation of extinction memory.

Together, acute stress can exert learning and memory-enhancing effects and there is preliminary evidence stress hormones can be used to optimise extinction processes. However, these effects are time-dependent and require careful consideration for optimal outcomes of extinction learning.

1.3 Time-dependent effects of acute stress on Fear Extinction

Whilst stress is known to play a critical role in the modulation of emotional memory and its contextualization (see reviews de Quervain et al., 2017; Maren & Holmes, 2016; Stockhorst & Antov, 2016; Wolf, Atsak, de Quervain, Roozendaal, & Wingenfeld, 2016), recent evidence has shown acute stress hinders or facilitates extinction depending on the timing of the stressor relative to the extinction memory phases of encoding (before extinction learning), consolidation (after extinction learning), and retrieval (before extinction recall).

1.3.1 Stress before extinction recall

In most cases, stress before extinction retrieval testing is reported to impair extinction memory, resulting in the return of fear responding in humans (Raio et al., 2014; Hamacher Dan et al., 2013; Kinner et al., 2016; Kinner et al., 2018) and animals (Deschaux et al., 2013). In these human studies stress effects on retrieval were examined using a preditcive learning task or fear conditiong paradigm, involving conditioning, subsequent extinction learning, and 24 hours later a stress or cortisol manipulation prior to extinction retrieval testing. Findings revealed stress leads to a stronger recovery of fear in the orginal learning context, relative to a control group, indicating acute stress promotes the renewal of fear. Similalry, stress has been shown to enhance the return of fear after reinstatement (Kinner et al., 2018). This is because stress is posited to enhance amygdala activation and promote fear expression (Raio et al., 2014). Alternatively, stress is believed to suppress the retrieval of recently acquired emotional memories, in this case suppresisng extinction memories that are acquired prior to extinction retrieval.

1.3.2 Stress after extinction learning

Post-extinction stress is generally found to enhance consolidation of extinction memories, but reduce their generalisability across different contexts. Two huamn studies by Hamacher-Dang and colloeagues provide evidence for this using a predictive learning task and fear conditioning paradigm (Hamacher-Dang, Engler, Schedlowski, & Wolf, 2013; Hamacher-Dang, Merz, & Wolf, 2015) . In these studies, stress was adminsitered after extincton and particpants were tested 24 hours later for retrieval in the extinction as well as the original learning context. In one study, the stress group displayed enhanced extinction memory (evident by reduced fear responding), relative to the control group, but this did not generalise to the original learning context (Hamacher-Dang et al., 2013). In the other study similar results were found, except a stronger fear response in the stress group compared to the control group was observed in the original learning context, indicating post-extinction stress enahnced renewal of fear (Hamacher-Dang et al., 2015). This is in line with studies demonstrating cortisol administration after an emotional task enhances memory contextualization in the long-term (i.e. reduces generalization) (van Ast et al., 2013) and animal studies showing corticosterone promotes long-term extinction memory consolidation that is dependent on the context (Pugh, Tremblay, Fleshner, & Rudy, 1997). However, post-extinction stress has also been shown to have no effect on memory (Raeder et al., 2019).

1.3.3 Stress before extinction learning

In contrast, stress exposure before extinction facilitates extinction processes by enhancing the consolidation and retention of extinction memories in a context-independent way. This is supported by animal and human literature demonstrating that stress administration within a short time window before learning (i.e. extinction learning) facilitates subsequent memory (i.e.

extinction memory), promoting the consolidation of non-fearful memories (Rozendaal, 2002). At the same time, it is believed that retrieval of previously stored emotional memories (i.e. fear or trauma memories) is supressed (de Quervain et al., 2017). In several experimental human studies, extinction training is found to enhance extinction memory (i.e. reduce fear responding) (Bentz, et al., 2013) and the generalization of this memory to the original learning context (Drexler, Hamacher-Dang, & Wolf, 2017; Drexler, Merz, & Wolf, 2018), but not to a novel context (Merz, Hamacher-Dang, Stark, Wolf, & Hermann, 2018). Further, some studies demonstrate pre-extinction stress accelerates extinction learning (Bentz, et al., 2013; de Quervain et al., 2011).

A recent model by Drexler and colleagues (2019) describes the relationship between stress exposure timing and relapse (see Figure 2.). In accoridance with the literature, it states that stress before extinction leads to a context-independent extinction memory, while post-exposure stress results in an extinction memory that is bound to the context. Accordingly, Drexler et al. (2019) report that stress restricts attention to contextual cues, increasing the generalisability of the extinction memory across contexts. This renders extinction memories more resistant to relapse following a change in context (i.e. less renewal) and indeed empirical evidence from their laboratory studies have supported this model (Drexler et al., 2017; Drexler et al., 2018). However, it remains unclear whether this stress-related attenuation of renewal is observed in clinical populations and whether these benefits extend to other forms of relapse (such as spontaneous recovery and reinstatement). Thus, one of the aims of this thesis will be to investigate whether stress-related adjuncts to therapy can attenuate specific relapse phenomena.

Together, this evidence suggests that exposure to stress *before* extinctin learning is most optimal for clinical use as it promotes extinctiom learning and memory that generalizes across

contexts (Drexler, Merz, Jentsch, & Wolf, 2019). However, the mechanisms of stress prior to extinction that lead to potentially enhanced extinction learning and memory consolidation are not entirely clear.

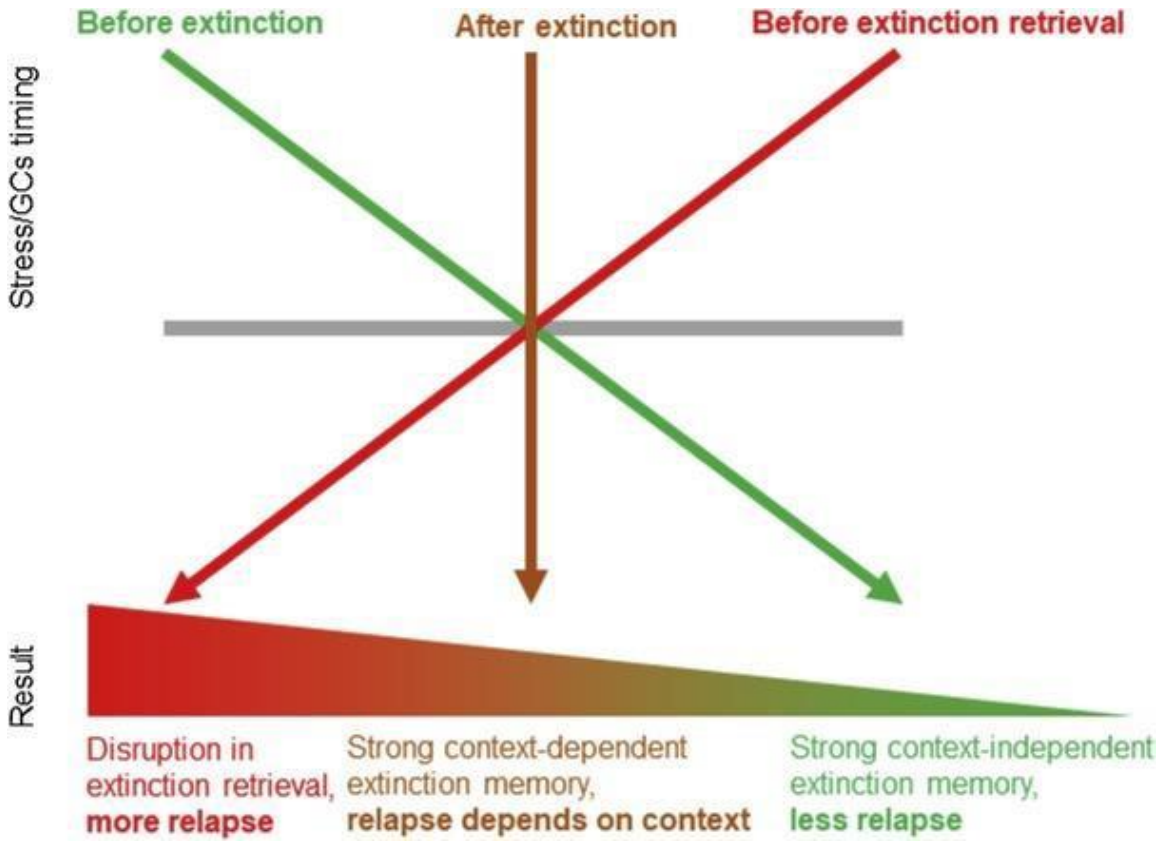


Figure 2. The STAR (Stress Timing affects Relapse) model. Retrieved from Drexler et al. (2019).

1.4 Optimising exposure therapy via acute stress

The above experimental findings have had important implications for the use of stress-related adjuncts to enhance exposure therapy in clinical patients. In recent years, evidence from experimental studies and randomised controlled clinical trials have revealed that pharmacological manipulations of stress (via the consumption of Hydrocortisone tablets) or

behavioural administration of physical or psychosocial stress [via Cold Presser Task (CPT) [1] or Socially-Evaluated Cold Presser Task (SECPT)[2] interventions) can reduce fear responding in a variety of patients with social anxiety, PTSD, and specific phobias, as well as conditioned fear in healthy adults (Sovaria et al., 2014; De Quervain et al., 2011; Yehuda et al., 2015; Soravia et al., 2006; Antov et al., 2015, Hamacher-Dang et al., 2015). For example, in a double-blind, placebo-controlled study, 40 patients with social phobia were administered 20mg of cortisol or placebo, orally, 1 hour prior to a socio-evaluative stressor [the trier social stress test (TSST)]. The cortisol treatment lead to reduced self-reported fear during the anticipiation, exposure and recovery phase of the TSST. In another randomised-controlled study, 20 patients with spider phobia, received 10mg of cortisol 1 hour prior to repeated exposure therapy sessions. This resulted in a greater reduction of fear responding towards spider stimuli during exposure and two days later, relative to placebo (Soravia et al., 2006). Similarly, 20mg of pre-exposure cortisol across repeated exposure sessions was found to enhance symptom improvement up to 1 month post-treatment in patients with height phobia (de Quervain et al., 2011). Therefore both once-off and repeated administration of cortisol can augment exposure-based treatment outcomes. However, at the time of conducting the studies of this thesis, no study had investigated the effects of non-pharmacological manipulations of stress (i.e. behavioural interventions to elevate endogenous cortisol) on exposure therapy in clinical patients**.** Notably, after the present studies were conducted, one researcher used a behavioural intervention to induce stress in a women only

[1] Cold Presser Task (CPT) is a behavioural intervention used for the efficient induction of stress in humans. It involves the participant immersing one hand into a metal basin filled with ice-cold water for 3 minutes.

[2] Socially Evaluated Cold Presser Task (SECPT) involves the same physiological challenge as the CPT (hand immersion into ice water) but also includes a socio-evaluative component which involves the participant being recorded by a video camera and observed by a researcher.

sample. This study found pre-expousre stress reduced fear and avoidance towards treated stimuli in woman not taking oral contraception (Zlomuzica et al., 2021). This research could offer insights into less invasive alternatives to medication and its side effects.

Moreover, studies have shown that taking advtanage of the circadian ryhtm of endogenous cortisol levels can affect the outcome of exposure therapy. Lass-Hennerman and Michael (2014) found that exposure therapy conducted in the morning when endogenous cortisol levels are highest was more effective (i.e. lead to greater treatment outcomes), than therapy in the evening, when endogenous cortisol levels are lowest. These time of day effects are shown to be mediated by cortisol (Meuret et al., 2016). However, clinical studies have not assessed the role of noradrenaline in the stress-augmentation of therapy.

In summary, there is prelimnary evidence that stress ajduncts to therapy can enhance exposure therapy treatment outcomes. However studies are yet to detremine the long-term effects of stress on treatment outcomes and the effectiveness of behavioural interventions. Moreover, the precise mechanisms by which pre-exposure stress might enhance extinction processes and relapse remain unclear. In the next session potential novel mechanisms of stress-augmentation of therapy are proposed and discussed with reference to supporting literature.

1.5 Proposed mechanisms of Stress

Here it is proposed that stress may aid psychotherapy of fear and anxiety disorders in three ways: 1) by strengthening and enhancing extinction memory via emotional arousal (associated with noradrenaline) and its interaction with cortisol, 2) by acting as an excitatory stimulus to maximise surprise (i.e., increase violation of harm expectancy to amplify learning); and 3) by deepening extinction learning via enhanced attention to phobic stimuli.

1.5.1 Emotional arousal is critical for the effects of stress on memory consolidation and generalization

It is well known that emotionally arousing information is remembered better than neutral events (McGough, 2003), and this is consistent with the proposition that emotional activation is important for the success of exposure-based treatment (Foa & Kozak, 1986). This is because emotional arousal, which activates the amygdala, is known to enhance the long-term consolidation of emotional memories. Converging findings demonstrate that the degree of arousal-induced amygdala activation during encoding is highly associated with subseuqent recall (McGaugh, 2004). In line with this is the notion that trauma memories are 'over consolidated' and context independent as a result of extreme arousal associated with the traumatic event (Ehlers and Clark, 2000). This suggests that stress may enhance consolidation of memories by increasing the emotional arousal of extinction learning. Indeed, animal data strongly suggests that emotional arousal specifically involving the activation of norepinephrine (NE) during the stress response is necessary for the enhancement of memory consolidation (Mueller & Cahill, 2010) and long-term retrieval (Buchanan & Lovallo, 2001). Evidence for this hypothesis is provided by studies demonstrating that memory facilitation is not induced when antagonists of beta-adrenergic receptors (block NE release) or glucocorticoid receptors (block cortisol/corticosterone activity) are administered (Quirarte et al., 1997, Roozendaal et al., 2002). In fact, it is the combination of both arousal systems (NE and cortisol) that is required for memory facilitation as a delay between their activations is reported to block memory enhancement (Roozendaal et al., 2006). Interestingly, both animal and human studies reveal that the interaction between cortisol and noradrenergic activity enhances emotional (but not neutral) memories, suggesting that arousal-induced nordarenergc activity is required for the influence of

cortisol on memory processes. Similarly, only the contextualisation of emotional but not neutral memory is affected by cortisol administration, suggesting the effects of stress on memory generalization is also dependent on arousal and could be mediated by noradrenaline (van Ast et al., 2013)**.** Therefore, there is evidence that noradrenergic mechanisms modulate the stress-related facilitation of extinction memory consolidation and generalization. However, it is surprising that no study has directly measured NE to determine the role of adrenergic activity in the stress-augmentation of extinction (Buchanan & Lovallo, 2001).

1.5.2 Stress-induced arousal and expectancy violation

Emotional arousal associated with stress could also facilitate extinction learning by increasing the change in expectancy of harm which is proposed to explain the strength and rate of contingency learning during extinction. There are two ways in which stress may enhance expectancy of harm to influence learning: 1) via emotional arousal and 2) via perceptions of unpredictability related to the cognitive component of stress. Prior to the exploration of the evidence for this, the role of expectancy of harm in extinction learning is explained.

1.5.2.A Role of expectancy of harm in extinction learning.

According to the Rescorla Wagner model (1972), learning can be maximised when there is a greater discrepancy between what is expected (an aversive outcome), and what actually occurs (no aversive outcome). That is, for example, the more surprised an animal or human is by the absence of harm (i.e., no danger) during exposure to their phobic object (i.e., dog), the greater their learning of the non-fearful contingency (dog-no danger). Thus, the greater the mismatch (i.e., expectancy violation), the greater the learning (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). This is because expectancy violation is believed to promote new

learning and plasticity during encoding (Greve, Cooper, Kaula, Anderson, & Henson, 2017; Rescorla, Wagner, Black, & Prokasy, 1972). This approach using one trial of exposure has been found to yield long-term benefits that are equivalent to daily repeated trials of exposure in patients with spider phobia (Baker et al., 2010). Reviews of animal and human literature suggest that reduction in expectancy of harm mediates extinction-based therapy rather than reduction of fear expression (Hofmann, 2004, 2008). This is consistent with human and animal research demonstrating the magnitude of fear reduction at the end of exposure is not predicted by the level of fear expressed at follow-up (i.e. habituation) (Craske, Liao, Brown, & Vervliet, 2012). Interestingly, sustained arousal throughout exposure has been shown to be more beneficial than the habituation of arousal (Quirk & Mueller, 2008a). Therefore, the greater memory for arousing events may be due to the expectancy violation associated with these events**.** Thus, a key approach to enhancing extinction learning and memory involves maximizing expectancy violations of harm which could be influenced by arousal

1.5.2.B Emotional arousal affects expectancy of harm

According to Rescolar (2000), one way to maximise expectancy violations is to increase the expectation of harm with the addition of an excitatory stimulus during extinction-based therapy. This has been shown to enhance fear responding during extinction but reduce spontaneous recovery of fear (i.e., attenuate fear responding at follow-up). There is evidence that the excitation from one stimulus (e.g. sympathetic activation from exercise) can intensify emotional responding to another stimulus (Zillmann, Katcher, & Milavsky, 1972). According to the emotion-transfer theory, congruency between the type of emotional arousal associated with two excitatory stimuli (e.g. both unpleasant or pleasant excited emotional reactions) is not necessary for the amplification of an excitatory response (Zillmann, 2006). This implies that

emotional arousal associated with stress can transfer and amplify phobic fear in order to increase the violation of harm expectancy during extinction/exposure. Importantly, there is evidence that noradrenergic activity (NE release) stimulated by emotional arousal (including stress induction) enhances intrinsic excitability in the amygdala (Tully, Li, Tsvetkov, & Bolshakov, 2007) and this is also evoked following the presentation of a phobic object (Cassens, Roffman, Kuruc, Orsulak, & Schildkraut, 1980; Hugues, Garcia, & Léna, 2007). Similarly, arousal induced by exercise prior to exposure therapy has been shown to enhance treatment outcomes, possibly due to its effect on expectancies (Keyan & Bryant, 2019). This could suggest that stress and phobic fear activate the same type of emotional excitatory response which can result in heightened fear and greater expectancy of harm during extinction.

1.5.2.C Cognitive properties of stress affect expectancy of harm

Consistent with the physiological (i.e., arousal) impact of stress on expectancy violations, the cognitive components of stress (i.e., perceptions of uncontrollability and unpredictability) have also been posited to enhance extinction learning. Extinction learning is believed to involve high-order cognitive processes that are modulated by changes in perceptions of controllability and predictability (Hofmann, 2008), suggesting cognitive aspects of stress could influence extinction processes. Trapp, O'Doherty, and Schwabe (2018) speculate that the unpredictability associated with the stress response may elicit a greater prediction error (expectancy violation) to facilitate and deepen extinction learning. Preliminary evidence supports this view, demonstrating the faciliatory effects of stress on memory are impaired when stress-induced changes in expectancy of harm are reduced (Kalbe, Bange, Lutz, & Schwabe, 2020). Another study found that mood and arousal enhanced US expectancy biases, such that individuals with experimentally-induced positive and negative moods significantly overestimated the likelihood

of an aversive outcome, relative to a neutral control condition (Cavanagh & Davey, 2001). This suggests emotional arousal (regardless of valence) can amplify fear expectancy, which in fact could underpin the effects of stress on extinction-based learning. Moreover, stress is known to impact attentional processes (including selective attention and the salience network) which facilitate and amplify expectancy of harm violations. This is discussed in greater detail below.

Together, this research illustrates the importance of expectancy violations in the success of exposure therapy and highlights the possible role of stress in augmenting extinction learning via its effects on expectancy of harm. However, expectancy of harm has not been examined as a potential mediator of the enhancing effects of stress. Understanding the role of stress in influencing expectancy of harm will hold promise for targeting underlying mechanisms and assist clinicians in their assessment of successful trajectories of stress augmentation of therapy.

1.5.3 Emotional arousal, cortisol and attentional processes

Another possibility that has not been investigated and could account for the impact of stress on extinction, is the role of noradrenergic arousal and cortisol in inducing alertness, focused attention, enhanced encoding and reduced contextualization of memory.

1.5.3.A Role of attention in extinction learning

According to expectancy violation models, attention towards the phobic object (CS) and awareness of the non-occurrence of an aversive outcome (US) is critical for the formation of new non-harmful contingencies and expectancy violations (Rescorla, 1972). This means that greater awareness of the CS-no US contingency will result in a faster rate of extinction. Moreover, expectancy violation models state that the salience of the CS enhances the strength of the CS-noUS contingency (Mackintosh, 1975; Pearce & Hall, 1980; Rescorla, 1972), that is believed to

determine the intensity of the fear response. In support of this, greater expectancy violations (amount of surprise affecting the rate of learning) have been shown to be associated with longer eye gaze in a predictive learning task (Wills, Lavric, Croft & Hodgson, 2007). Indeed, there is evidence that selective attention or prolonged engagement with the phobic stimulus promotes learning during exposure therapy. A number of studies assessing the impact of attentional biases during exposure therapy have shown attentional bias towards threat predicts improved treatment response and greater reductions in anxiety following treatment (Barry, Sewart, Arch, & Craske, 2015; Barry, Vervliet, & Hermans, 2015). Individual differences in attention have also been shown to moderate the rate of fear extinction and the extent fear returns after extinction (Barry, Vervliet, & Hermans, 2016). Thus, strategies that enhance attention and increase salience of the phobic object can be used to augment extinction learning.

1.5.3.B Role of attention in context-dependency

Attention towards the context during exposure therapy also influences the extent to which fear returns following exposure (Barry et al., 2015). It is believed that narrowed attention during extinction can reduce the context-specificity of extinction memories. This is because narrowed attention towards the CS likely reduces encoding of the surrounding context, decreasing the context-dependency of extinction learning which could influence renewal. In fact, animal studies have shown that administration of the drug scopolamine, which is shown to narrow the focus of attention during extinction, can reduce contextual encoding and renewal of fear (Zelikowsky et al., 2013).

1.5.3.C Acute stress affects attention

Several studies indicate that stress-induced variations in cortisol are related to attentional bias to threat stimuli (Ellenbogen, Carson & Pishva, 2010; McHugh et al., 2010; Pilgrim, Marin, & Lupien, 2010), and as such could impact attentional mechanisms that facilitate extinction learning. There is direct evidence that a causal relationship between stress and selective attention exists, where stress administration has been shown to facilitate attention to threatening stimuli (Roelofs et al., 2005; Rued, Hilmert, Strahm, & Thomas, 2019). This is suggested to occur through engagement with the 'salience network', where acute stress facilitates neural responding to emotionally salient stimuli (Hermans, Henckens, Joels, & Fernandez, 2014) and increases stimulation of brain regions responsible for selective attention (i.e. medial regions of the Prefrontal Cortex) (Lupien & McEwen, 1997**).** In fact, this stress-related enhancement of threat processing is associated with greater long-term memory (Weyar, Schwabe, et al., 2012**).** As such, biases in attentional selection induced by stress may intensify the salience of events and engagement with the phobic stimulus to augment extinction learning and long-term memory. In support of this, a preliminary study investigating eye gaze behaviour during an acute behavioural stressor found participants in the stress group showed longer and more frequent fixations on central objects and enhanced memory for these objects, relative to the control group (Nadja Herten, Otto, & Wolf, 2017). In line with this, manipulating attention towards threat has been shown to enhance cortisol levels, suggesting heightened cortisol is associated with greater attention to the phobic stimulus during exposure therapy (Pilgrim, Ellenbogen, & Paquin, 2014). Moreover, noradrenergic arousal (stimulated by stress) has been shown to be necessary for attention to the phobic object during exposure (Mason, 1983). Thus, there is evidence that acute stress enhances attentional processes underlying emotional learning and memory. However, it

remains unclear whether changes in attention account for the effects of stress on exposure therapy and relapse related to context change.

1.6 Summary of literature

Taken together, there is evidence from human and animal literature that acute stress influences extinction specific aspects of learning (i.e., expectancy violation and attention) and memory (consolidation and context generalization) during extinction procedures and these effects appear to be associated with noradrenergic arousal and cortisol. This literature review highlights the general conclusion that pre-exposure/extinction stress enhances extinction memory consolidation and reduces the context-dependency of memory to promote memory generalization across different contexts. In turn, stress may have the potential to reduce or prevent relapse effects. However, this has not been assessed within a clinical population at longer follow-up periods (to assess spontaneous recovery of fear) or following a shift in context (to assess renewal). Moreover, clinical studies designed to optimise exposure therapy using stress have focused on the use of pharmacological manipulations of cortisol and only measured cortisol as a mechanism. To this point, the results of these studies suggest the release of cortisol is *necessary,* but they do not address whether it is *sufficient* in producing learning and memory-enhancing effects in clinical patients. Considering emotional arousal involving noradrenaline (NE) is proven to be critical for the enhancing effects of stress on learning and memory, it is reasonable to suspect NE mediates the benefit of cortisol on exposure therapy. Additionally, there is some evidence that attention and expectancy of harm which are necessary for extinction learning are positively affected by components of the stress response. However, the role of NE, attention and expectancy of harm in the therapeutic benefit of acute stress has not been investigated or directly measured within clinical studies to date.

These issues of mechanisms underlying extinction and the role of stress are critical to understanding how fears are learned and unlearned, and improvements in our knowledge of these issues have the potential to inform better treatments. Thus, the purpose of the present thesis is to investigate: 1) whether behavioural stress adjuncts to therapy can attenuate two relapse phenomena (spontaneous recovery and renewal); and 2) to examine whether stress may aid psychotherapy of fear and anxiety disorders by its effects on emotional arousal measured by noradrenaline, attentional processes and expectancy of harm to maximise learning and strengthen memory. However, there are methodological considerations for examining stress effects.

1.7 Methodological considerations in the study of stress and extinction-based treatment

1.7.1 Specific timing of stress induction in the present research

As briefly noted earlier, stress hormones, NE and cortisol, are known to have distinct temporal onsets and durations that affect the brain differently depending on the timing of the stressor (Stockhorst & Antov, 2016). Specifically, noradrenaline usually acts within seconds of the onset of the stressor but subsides quickly (about 2- 3 min after). It is known to cause rapid physiological changes to the body including increased heart rate and blood pressure. Whilst the initial NE response dissipates quickly, it has been shown to enhance sensitivity to subsequent stressors shortly after or 24 hours later (Herten et al., 2016), suggesting that stress-induced noradrenergic arousal can have longer-lasting effects, by amplifying responding to emotional stimuli such as the CS during exposure therapy.

In contrast, activation of cortisol following a stressor is delayed, reaching maximal levels 20 -30 min after stressor onset, with its effects considered more long-lasting (hours, days and months) (Joëls & Baram, 2009; Sapolsky, Romero, & Munck, 2000). Research from animal and

human studies suggest that NE plays an important role in enhancing acquisition of information, whilst cortisol is critical for enhancing consolidation. This indicates that the specific timing of the stressor relevant to extinction learning is critical for optimizing the effects of stress. Based on this knowledge from several years of research, stressor exposure should be administered 20- 30 minutes prior to learning (Schwabe, Haddad, & Schachinger, 2008; Schwabe & Schachinger, 2018), to produce the desired effect.

1.7.2 Types of stress induction.

The validity of the type of stressor in releasing both NE and cortisol is imperative to consider when selecting a method of stress induction. Studies typically use pharmacological or behavioural manipulations to elevate stress hormone levels. Pharmacological administration of Hydrocortisone is shown to reliably increase cortisol levels, producing stress effects at various doses, with less variability in individuals stress responses (Harrewijn et al., 2020). However, cortisol administration does not affect noradrenergic arousal. Alternatively, behavioural stressors including the Cold Presser Task (CPT), Socially Evaluated Cold Presser Task (SECPT), and the Trier Social Stress Test (TSST) have been shown to enhance both NE and cortisol concentrations. However, studies report that the CPT, where participants immerse their hand into ice cold water for 3 minutes, increases noradrenergic arousal but does not reliably increase cortisol (Antov et al., 2015; Bentz, de Quervain, et al., 2013). In contrast, stressors with a social-evaluative component including SECPT and TSST are typically seen to more robustly increase both NE and cortisol levels (Dickerson & Kemeny, 2004). Thus, to assess the joint effects of NE and cortisol, psychosocial stressors are required.

1.7.3 Time of day effects

The circadian variation in cortisol throughout the day also modulates the effect of stress on fear extinction learning and memory. In humans, endogenous cortisol levels are shown to be highest in the mornings and lowest in the evenings, influencing the stress response and cognition in different ways. A review by Het and colleagues (2005) reported that cortisol administered in the mornings caused significant memory impairment, whereas cortisol administration in the afternoon lead to an enhancement of memory. These findings are suggested to occur as a result of an overactivation of the cortisol system leading to a potential impairment of the amygdala and hippocampus when exposure to the stressor occurs in the morning (Maheu, Collicutt, Kornik, Moszkowski, & Lupien, 2005). Thus, it is important to control for time-of-day effects when conducting stress experimentation.

1.7.4 Sex effects

There is some evidence that sex hormones influence the stress response and its effects on extinction learning and memory. Compared to woman, men are shown to have a more pronounced stress response (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kirschbaum, Pirke, & Hellhammer, 1993), presumably due to the interaction of sex hormones (namely, estrogen) and fear extinction under stress. Estradiol, which is considerably higher in women than in men, is shown to enhance extinction recall at higher levels when fear acquisition is preceded by stress but attenuates extinction recall in women with lower estradiol levels, and this varies depending on the female's menstrual cycle (Antov & Stockhorst, 2014; Stockhorst & Antov, 2016). Moreover, females using oral contraceptives (OC) (having suppressed estradiol levels) show a blunted cortisol response following stress exposure relative to men and free-cycling women, and this has been linked to diminished effects of stress on extinction learning

and memory (Merz & Wolf, 2017). One explanation for this is that OC users secrete more cortisol-binding globulin (CBG) which reduces the free cortisol response (Kirschbaum et al., 1999). For these reasons, it has been encouraged that stress studies control for estradiol levels in women and/or exclude women on oral contraception.

1.7.5 Other factors interfering with cortisol response

Psychotropic medication can also affect cortisol secretion and is often a confound in research involving stress induction. According to a systematic review by Subramaniam, LoPilato, and Walker (2019), most antipsychotic and antidepressant medication (with the exception of fluoxetine) reduces cortisol secretion, but stimulant medication yields either no change or acute increases in cortisol. Subsequently lifestyle factors including smoking, caffeine, alcohol consumption and intense physical exercise are known to stimulate the HPA axis, and should be considered when assessing cortisol levels (Fukuda & Morimoto, 2001).

Together, this research points towards the complexity of methods and quality assurance in stress research. Given this research is still in its early stages, it is critical to account for confounding variables so that accurate conclusions can be made about the causal impact of stress on extinction processes and its underlying mechanisms. The empirical studies in this thesis will aim to control for these variables whilst optimising ecological validity under these conditions.

1.8 Thesis Plan

This thesis aimed to investigate the effects of pre-exposure stress on different relapse phenomena (specifically spontaneous recovery and renewal of fear) within a clinical population, and examine potential mechanisms (including cortisol, noradrenergic arousal, attention and expectancy of harm) that mediate the therapeutic benefit of stress. Study 1 is a systematic review

of stress-augmentation studies which aimed to first evaluate the evidence that stress-adjuncts to therapy can attenuate relapse. Secondly, it examined the impact of stress on cognitive, behavioural and physiological fear symptoms throughout the treatment process (i.e., during extinction learning, immediately after or in the long-term) in order to better realise the mechanisms of these effects. A testable novel model of stress-augmentation of therapy was proposed to help disentangle the mechanisms at play. Study 2 is a pilot study designed to provide a first examination of the potential for pre-exposure stress to attenuate spontaneous recovery and renewal within clinical patients; and examine the role of emotional arousal indexed by noradrenaline in producing effects on extinction and relapse. In Study 3, stress effects on relapse were examined using a larger sample size and proposed neural (noradrenaline and cortisol) and cognitive (attention and expectancy of harm) mechanisms were tested as meditators of the effects of stress. Finally, this thesis provides a general discussion that reviews the general findings in the context of the proposed model and current stress literature, as well as an exploration of the limitations of the study, future directions, and clinical implications.

1.8.1 Rationale for participants and treatment modality

To address the aims of empirical studies 2 and 3, participants with a specific phobia of spiders were selected as representatives of the general phobic population. This phobia was chosen as a suitable exemplar condition; phobias concerning animals are the most common of all fears (Stinson et al., 2007) and are known to persist for several years and decades in 10-30% of individuals with a specific phobia. In particular, Arachnophobia (specific phobia of spiders) is prevalent in up to 15% of the population and (along with other types of phobias) is strongly predictive of more general anxiety disorders (Eaton, Bienvenu, & Miloyan, 2018). In fact their high comorbidity (50-80%) with anxiety disorders, and the similar neural correlates and

treatment of choice of these disorders (Shin & Liberzon, 2009), suggests successful treatment for phobias may reduce other fear and anxiety disorders present (Eaton et al., 2018).

In addition, as less than 20% of individuals with specific phobias seek treatment (Garcia-Palacios, Hoffman, Kwong See, Tsai, & Botella, 2001; Magee, Eaton, Wittchen, McGonagle, & Kessler, 1996), presumably due to their avoidance, Virtual Reality (VR) exposure therapy was selected as the modality of treatment to investigate the aims of the present thesis. Several trials have demonstrated VR exposure-based treatment is comparable to *in-vivo* (i.e., real life) exposure therapy in its efficacy and superior to control treatments (Carl et al., 2019; Powers & Emmelkamp, 2008). Moreover, VR exposure therapy has proven to be more effective in increasing the proportion of individuals who seek treatment for their phobia (Garcia-Palacios et al., 2001). Offering a standardized and more controlled treatment environment, VR treatment was the operational decision most ideal for clinical research.

It should be noted that Study 2 and 3 were completed during COVID-19 and follow-up periods were affected by periodic government shut-down periods. This meant that face-to-face behavioural data at 3-months follow-up could not be obtained in the pilot study and instead participants were invited back for a 7-months follow-up. Additionally, in Study 3 (RCT), government lockdowns prevented 7-month follow up data to be collected face-to-face, but 3-month follow-up data were able to be obtained.

Chapter 2: Systematic Review

Study 1: A systematic review of the effects of pre-exposure stress on extinction learning, relapse phenomena and potential mechanisms

This chapter is presented as written and submitted for publication. It aimed to evaluate the evidence pre-exposure stress can reduce relapse and examine how and when stress exerts its effects on extinction learning and memory to inform potential mechanisms at play.

When stress helps. A systematic review of the enhancing effects of acute stress on extinction learning, relapse phenomena and potential underlying mechanisms

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Contributions:

Andrew, Elpiniki: conceptualization, methodology, formal analysis, data curation, writing-original draft preparation, review & editing, visualization; **Todd, Jemma**: Conceptualization, Methodology, Writing-review & editing. **Dadds, Mark:** Conceptualization, Supervision, Writing-Review & Editing.

Abstract

Exposure-based treatments are the most effective in reducing clinical symptoms of anxiety and distress, but relapse is not uncommon. Studies have shown that stress levels influence the learning underlying these exposure-based treatments, and thus might be manipulated during therapy as a way of improving outcomes. This systematic review focusses on putative mechanisms underlying stress effects and evaluates the evidence that stress-related adjuncts to exposure therapy can attenuate mechanisms related to three types of relapse (spontaneous recovery, renewal and reinstatement). We also focus on the effects of stress on different indices of fear (subjective, physiological and behavioural) across time-dependent stages of treatment (i.e., during extinction learning, immediately after or at follow-up). A framework of measurement to test these mechanisms is provided. Eleven studies were identified for inclusion, including six treatment and five experimental studies. Risk of bias and study results were assessed and reviewed for each study. The findings indicate that heightened stress states generally lead to enhanced extinction learning and better treatment outcomes in the long-term. We propose an Integrated Model of Stress-Augmentation which suggests neural (noradrenaline, cortisol and synaptic plasticity) and cognitive processes (attention and enhanced expectancy of harm) may have a role to play in the therapeutic benefit of stress. Overall, existing evidence indicates that stress augmentation of exposure therapy has immediate and long-term benefits on extinction learning and memory. The proposed cognitive model offers a necessary synthesis of theoretical and empirical work that may facilitate understanding and testing of putative mechanisms underlying stress-augmentation of therapy.

1. Introduction

Anxiety and phobic disorders are among the most debilitating mental health conditions in the world (Australian Bureau of Statistics, 2008). However, treatment for these conditions is far from optimal, as one third of patients experience relapse within the first year following treatment (Scholten, et al., 2013**)**. Current laboratory models used to drive behavioural treatments for anxiety and fear-related disorders are based on contemporary interpretations of the Pavlovian fear extinction paradigm (Vervliet, Craske, & Hermans, 2013). These define extinction as a form of new learning that underlies exposure therapy, where a new safe association with the phobic stimulus is made. Extinction is said to occur when the feared response diminishes as a result of repeated presentations of the phobic stimulus in the absence of an aversive outcome. For example, during exposure therapy, an individual may be repeatedly exposed to a dog in the absence of a dangerous outcome in order to learn that the dog does not signal danger. Thus, exposure therapy can be understood as a learning process in which new non-fearful memory associations (extinction memories) are established (Hermans, Craske, Mineka, & Lovibond, 2006).

However, the return of fear is a significant problem in exposure therapy. This is thought to be because extinction memories compete with, but do not erase the original fear memory associations, leaving extinction memories susceptible to retrieval deficits that enable the recovery of fear (Quirk & Mueller, 2008). This failure to retrieve extinction memories is believed to be a major cause of the return of fear symptoms (i.e. relapse) following exposure-based treatments (Bouton, 2004**;** Vervliet et al., 2013). Animal and human research has demonstrated that failure to retrieve extinction memories can occur as a result of the passage of time (spontaneous recovery), after a change in context (renewal), or after exposure to an aversive

event (reinstatement) (Bouton, 2004). Similarly, exposure to stress or the experience of stressful life events appear to trigger the recovery of fear symptoms and render extinction memories more resistant to retrieval (Shin & Liberzon, 2009; Vervliet et al., 2013). Therefore, new therapeutic approaches are urgently needed to improve the strength and retrieval ability of extinction memories underlying these treatments (Drexler, Merz, Jentsch, & Wolf, 2019).

Evidence from human and animal studies has shown that stress experienced at the time of extinction learning can influence the extent and quality of this learning. Importantly it appears that heightened stress states are associated with better extinction learning. A recent review by Drexler et al., (2019) concluded that the effects of stress are critically dependent on its timing in relation to exposure to the fear stimulus. Stress immediately or shortly prior to extinction learning appears to enhance its effectiveness. Thus, manipulations of stress levels have the potential to improve extinction-based treatments for fear and anxiety disorders. There is evidence from experimental and randomised controlled clinical studies that acute manipulations of stress (i.e., Hydrocortisone tablets or CPT/ SECPT) can reduce fear responding and enhance extincion retention in patients with social anxiety, PTSD, specific phobias or conditioned fear in healthy adults (Soravia et al., 2014; de Quervain et al., 2011; Yehuda et al., 2015; Soravia et al., 2006; Antov et al., 2015**).** However, the mechanisms underlying stress effects on extinction processes need further clarification.

Current reviews on stress and memory postulate that stress exposure *before* extinction facilitates extinction processes by enhancing the consolidation and retention of extinction memories (Maren & Homes, 2015; Stockhurts & Antov, 2016; Drexler et al., 2019). This stress enhancement of extinction learning seems to be most beneficial for clincial use when adminsitered *before* exposure-based psychotherapy because of its ability to render extinction

memories less context-dependent **(**Drexler et al., 2019; Drexler, Merz, & Wolf, 2018). However, there is a complexity to extinction retention and fear responding in humans as fear manifests in different ways. That is, fear can be experienced as negative or anxious thoughts, fearful anticipation, behaviorual avoidance, or a sense of dread or anxiety, and it can also be physiologically observed through changes in heart rate (HR) and Skin Conducatnce response (SCR). Whilst the stress response may look similar to fear, it is considered dinstinct from fear in two ways: Stress involves 1) the perception of an event as unpredictable and uncontrollable; and 2) the activation of the Hypothalamic-Pituatary-Adrenal (HPA)-axis involving the release of stress hormones. Given the cognitive component of stress can be difficult to measure subjectively, biological markers of stress are generally used to uniquely quantify the stress response. Thus, stress hormones (cortisol and noradrenaline [NE]) released during the activation of the HPA-axis are robustly used as markers of stress.

Critically, understanding how stress impacts different manifestations of fear could inform the types of mehcanisms involved. Further, recognising the timing of these changes throughout the extinction process will provide insights into the specific learning processes (i.e., extinction learning, consolidation or retention in the short and long-term) that are modulated by stress. This is of clinical utlilty as it provides practitioners with a model of successful stress-augmented psychotherapy and ideal treatment response trajectories. This will assist clinicans to identify responders and non-responders to treatment. Moroever, direct measures of stress via hair/blood or salivary cortisol, and biomarkers of noradrenaline (including salivary alpha amylase) are important for disentangling the constructs of stress and fear responding.

Thus, here we argue that the mechanisms of stress effects will be better realised if these effects are evaluated with particular reference to how fear manifests following stress exposure

and when these changes occur during the extinction process (i.e., during the extinction learning phase/exposure therapy, immediately after or in the long-term). Thus, the aim of this review is to examine the effects of pre-exposure stress on different indices of fear, and its impact on the temporal topography of extinction and extinction-based treatment**.** These considerations will be used to inform the mechanisms of stress-related changes in extinction learning and determine whether stress-augmentation of therapy has the potential to reduce relapse. We will address questions including: What cognitive, behavioural or physiological changes occur throughout the extinction process following stress exposure? When do these changes occur? How do these changes differ to the topography of standard extinction-based treatment? Does stress reduce the return of fear related to three relapse phenomena? What kinds of mechanisms could be at play (i.e., cognitive, physiological and/or behavioural mechanisms)?

In order to address these questions, we present a systematic review of articles which investigate the effects of pre-exposure/extinction stress on fear responding/ symptoms in humans. In particular, we focus on differences between stress measures of cortisol and noradrenaline (NE), and measures of fear responding/symptoms during extinction/exposure and tests of relapse. Following this examination of the literature, we introduce putative mechanisms underlying these stress effects on extinction. We present a framework for measurement and methods to disentangle these mechanisms, the *Novel Integrated Model of Stress-Augmentation*. The quality of the research and reliability of the findings will also be assessed.

2. Method

2.1. Transparency and Openness

To ensure the clarity and transparency of the data, research materials and results reported, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidelines were adhered to (Moher, et al., 2009). This review project was preregistered and is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=237762.

2.2. Summary of search strategy

A comprehensive literature search was conducted among published articles indexed in the following databases: Medline, PsycInfo, PubMed, and Web of Science. Subject headings were imploded and the key words included: ('*Stress* OR '*Acute Stress* OR '*cortisol' OR 'glucocorticoids' NOT 'chronic stress'*) AND ('exposure therapy' OR '*extinction learning'*) AND *('Anxiety'* OR '*Anxiety Disorder'* OR '*Fear'* OR '*Phobia'*). Articles were limited to English-language papers and confined to studies conducted in humans. There were no limitations regarding publication date and the last date searched was 10th April 2021. Google Scholar and reference lists of included studies were also assessed to identify additional relevant studies.

In addition, we evaluated the quality of the research and the reliability of the findings, through an assessment of risk of bias (based on the domains suggested by the Cochrane Handbook for Systematic Reviews; Higgins & Green, 2011). This included an assessment of the integrity of the interventions/experimental procedures and the generalisability of the findings.

2.3. Study selection and exclusion

Inclusion criteria were identified according to the types of participants, intervention, control condition, outcome measures and study design (PICOS) formula (CRD, 2009). Studies were retained if they a) were conducted in healthy adults or patients with an anxiety or fear-based disorder, b) examined the effect of acute stress on exposure therapy or fear extinction learning, c) employed a control group or comparison group, d) measured pre-extinction stress (cortisol) in an experimental situation, and e) measured fear responding. Studies were excluded if they were a) non-experimental, b) did not examine the effect of acute stress on emotional memories (e.g., a neutral predictive learning task), c) did not assess and manipulate stress (exogenous or endogenous cortisol) before extinction or exposure therapy, d) did not include meaningful primary quantitative statistical analyses (such as case studies or reviews) or e) were not peer-reviewed. Given the limited number of studies, no other methodological limitations were applied, including no restrictions based on sample size.

Based on the criteria, published papers were initially selected by their titles, followed by their abstracts and full-text screening, by two authors. To avoid bias, a random sample of 10% were screened at each step by another author which yielded 98% agreement in the selection of relevant titles and abstracts, and 96% agreement in the selection of full texts articles. All remaining articles were discussed between the raters and agreement reached as to whether they met criteria for inclusion. The overall search yielded 2337 articles, of which 10 articles (with a total of 11 studies) were identified through this search strategy as eligible for inclusion in this review. Of the 11 studies, 5 were experimental designs and 6 were treatment studies. A flow diagram of the study selection is displayed in Figure 1.

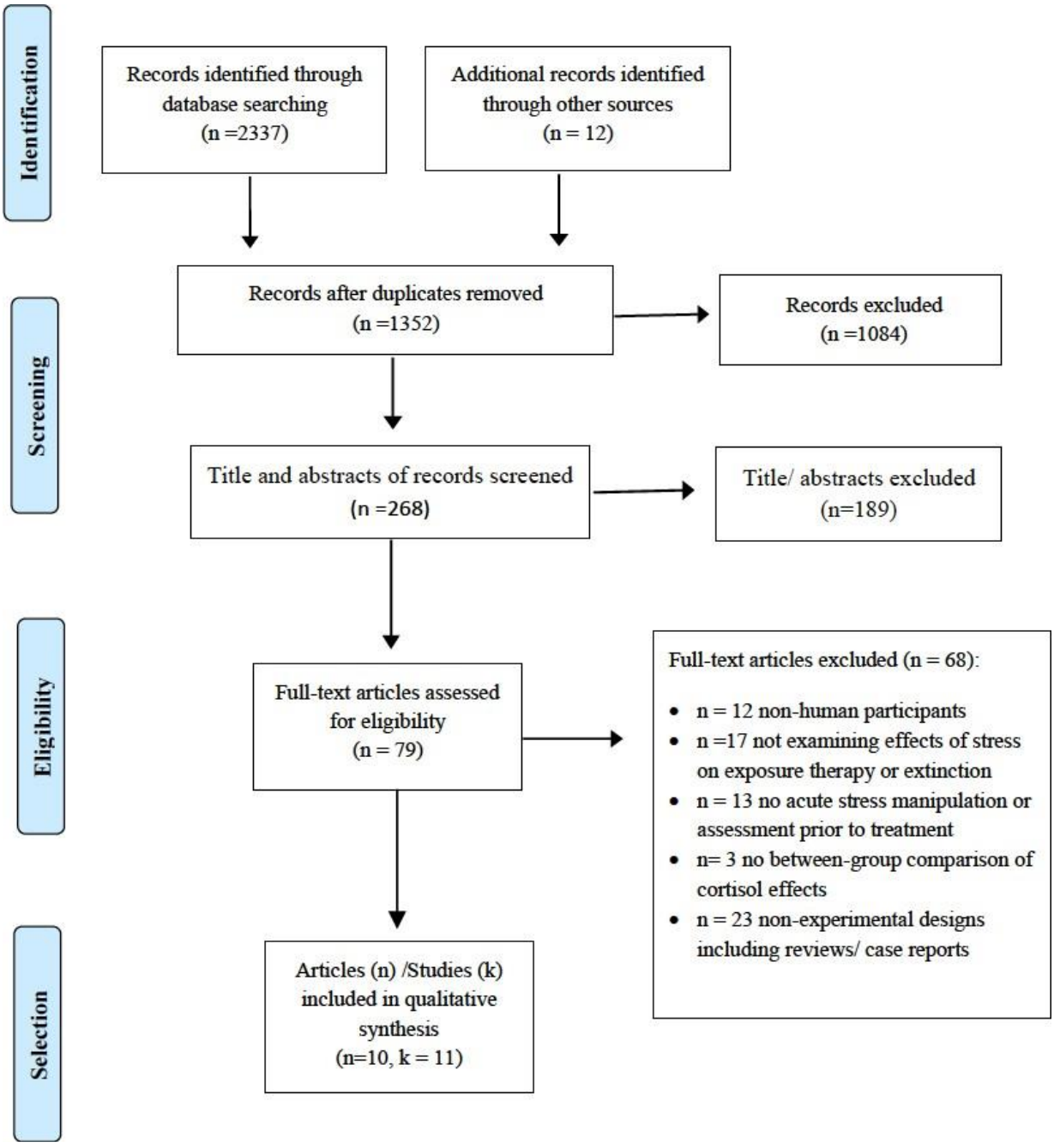

Figure 1. Study flow diagram adapted from Moher, Liberati,Tetzlaff, and Altman (2009).

2.4. Data extraction and quality assessment

For each identified study, the following data was extracted: first author, year of publication, aim, participant characteristics (i.e., sample size, sex, age range or mean age, eligibility criteria), study design, stressor type, dose and timing in relation to extinction/exposure procedures, type of control condition, details of intervention or experimental paradigm, cortisol measure, pre, post and follow-up outcome/fear measures (where applicable), effect sizes, means, and confidence intervals, direction of findings, suggested mechanisms, and limitations. To ascertain the validity of eligible studies, risk of bias was evaluated based on the five items specified by the Cochrane risk of bias tool: adequacy of randomization and concealment of allocation (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), nature and handling of incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias) (Higgins & Green, 2011). Each category was coded as low, high or unclear risk of bias based on the criteria for judging risk of bias provided by the Cochrane risk of bias assessment tool (Higgins & Green, 2011).

A system for scoring methodological quality was also developed to address potential confounders relevant to cortisol studies including cortisol measures, management of confounding variables, and intervention integrity. A study was deemed of good quality if it considered or controlled age, gender, smoking, medication, clear instructions to participants regarding sampling procedure (e.g., no eating or drinking 15min before sampling, or exercise 24 hours prior) and time of day. Studies were classified into high- or low-quality categories depending on their fulfilment of criteria.

3. Results

The results of this review are summarized across two dominant study designs, including: (1) experimental studies and (2) treatment studies. Between-group effects at different stages throughout the extinction process are reported (i.e., during exposure therapy/extinction learning, post-treatment/ extinction retention, and long-term follow up/extinction recall). Findings are summarized according to three indices of fear: 1) self-reported, 2) behavioural 3) physiological measures. The study characteristics are presented in Table 1 and main findings are presented in Table 2.

3.1 Overview of Study Characteristics

Of the eleven studies, five were experimental studies employing a fear conditioning paradigm (Bentz et al., 2013; Merz et al., 2014; Antov et al., 2015; Drexler et al., 2018; Merz et al., 2018) and six were treatment studies (Soravia et al., 2006, S1, S2; de Quervain et al., 2011; Soravia et al., 2014; Yehuda et al., 2015; Lass-Hennemann & Michael, 2014). The earliest study was published in 2006, and the most recent study was published in 2019. All studies were controlled and included random allocation to condition. Treatment was identical across groups for all studies, with the exception of the type of adjunct to extinction learning and/or treatment (placebo/control or stress adjunct). Three studies included a behavioural intervention (Cold Presser Task[3] or Socially Evaluated Cold Presser Task[4]) as the stress condition and hand

[3] Cold Presser Task (CPT): Behavioural task that involves immersing one's hand into ice cold water, usually for three minutes.

[4] Socially Evaluated Cold Presser Task (SECPT): Is an extension of the CPT with a socially evaluative component. That is, it involves immersing one's hand into ice cold water (physical stressor) whilst being recorded by a video camera and observed by an experimenter (social-evaluative stressor).

immersion into warm water as the control condition (Bentz et al., 2013; Antov et al., 2015; Drexler et al., 2018). Seven studies involved oral or intravenous administration of hydrocortisone or placebo to individuals assigned to the stress or control group, respectively (Soravia et al., 2006, S1, S2; de Quervain et al., 2011; Merz et al., 2014; Soravia et al., 2014; Yehuda et al., 2015; Merz et al., 2018). One treatment study allocated individuals to receive either morning therapy (when endogenous cortisol is highest) or evening therapy (when endogenous cortisol is lowest) (Lass-Hennemann & Michael, 2014). Across experimental studies, sample sizes ranged from N= 32-48 (per study), participants were 18-35 years old, and four out of five studies recruited only male participants. Across treatment studies, sample sizes ranged from N= 20-60 (per study) participants were 18-60 years, and two out of six studies recruited only male or only female participants.

3.2 Design/Intervention Characteristics

Experimental Studies: Five studies conditioned healthy adult participants using a standard classical fear conditioning procedure. In three studies, fear was acquired to a neutral geometric shape (CS) by pairing it with a shock (US) (Bentz et al., 2013; Merz et al., 2015) or a loud sound (Antov et al., 2015). The remaining two studies (Drexler et al., 2018; Merz et al., 2018) paired a neutral coloured-lamp (CS) with a shock (US) with fear acquisition and extinction occurring in two distinct contexts. All studies included an equal number of fixed paired and unpaired trials. The number of trials (CS+ and CS-) varied between 5 to 16. All studies included acquisition, extinction and retrieval test procedures (in acquisition context). These procedures occurred on three consecutive days in three studies (Bentz et al., 2013; Drexler et al., 2018; Metz et al., 2018), two consecutive days in one study (i.e., acquisition and extinction on the first day) (Antov et al., 2015) and on one day in the remaining study (Merz et al., 2014).

Treatment Studies: Five studies provided individualized treatments (Soravia et al., 2006, S1, S2; de Quervain et al., 2011; Yehuda et al., 2015; Lass-Hennemann & Michael, 2014) and one involved group therapy (Soravia et al., 2014). Four studies involved in-vivo exposure (Soravia et al., 2006, S1, S2; Soravia et al., 2014; Lass-Hennemann & Michael, 2014), one included virtual reality exposure (de Quervain et al., 2011), and one used imaginal exposure (Yehuda et al., 2015). Treatment duration ranged from 1 to 10 sessions with an average duration of 3.5 weeks. Treatment studies varied in the clinical status of their participants; three studies employed patients with specific phobia of spiders (Soravia et al., 2006, S1; Soravia et al., 2014; Lass-Hennemann & Michael, 2012) or heights (de Quervain et al., 2011), one study included patients with PTSD (Yehuda et al., 2015), and one study used patients with social phobia (Soravia et al., 2006, S1).

Table 1. Summary of study characteristics

	Population	N (% of Males), Age	Stressor Type (Dose), Timing	Control/ Comparison Group	Cortisol Measure	Outcome Measures	Number of sessions or extinction trials	Method
Experimental Studies								
Bentz et al. (2013)	Healthy Individuals	35(37% M), 18-35 age range	CPT, 20min prior to extinction	Warm water	Salivary cortisol	US-expectancy ratings, SCR, HR	10 trials total (5 x Ext 1 and 5x Ext 2)	Cued classical fear conditioning Day 1: Fear acquisition (neutral shape paired with shock), followed by control condition (warm water). Day 2: Stress induction followed by extinction training (Ext 1) and memory retrieval Day 3: Extinction training (Ext 2) and memory retrieval test again
Merz et al. (2014)	Healthy Individuals	32(100% M), 18-35 age range	Hydrocortisone (30mg), 45 min prior to fear extinction	Placebo	Salivary cortisol	diffSCR, BOLD responses (fMRI)	16 trials	Cued classical fear conditioning Fear acquisition (neutral shape paired with a shock) followed by extinction (using a partial reinforcement schedule).
Antov et al. (2015)	Healthy Individuals	40 (100%M), 22.2 average age	CPT, imm. Prior to extinction	Warm water	Salivary cortisol, BP, subjective ratings	diffSCR	12 trials	Auditory fear conditioning Day 1: Fear acquisition (neutral car paired with car wreck sound), immediately followed by stress or control induction, then extinction training Day 2: Extinction retrieval test

Drexler et al. (2018)	Healthy university students	40 (100%M), 18-35 age range	SECPT, 25min prior to extinction	Warm water and no recording	Salivary cortisol, BP, HR, subjective ratings	SCR	16 trials	Contextual fear conditioning Day 1: Fear acquisition (coloured lamp paired with shock in context (A) Day 2: Stress or control induction, followed by fear extinction training in a different context (B) Day 3: Fear recall- test in acquisition Context (A) and extinction context (B)
Merz et al. (2018)	Healthy Individuals	48 (100%M), 18-35 age range	Hydrocortisone (30mg)	Placebo	Salivary cortisol	SCR, BOLD responses (FMRI)	16 trials	Contextual fear conditioning Day 1: Fear acquisition in context (A) Day 2: Stress or control induction, followed by fear extinction in a different context (B) Day 3: Fear recall- test in extinction Context (B) and novel context (C)
Treatment Studies								
Soravia et al. (2006) Study 1	Individuals with Social Phobia	40 (53%M),	Hydrocortisone (25mg), prior to exposure therapy	Placebo	Salivary cortisol	HR, STAI-state, VAS, Mood/activity Questionnaire	One session	One-session social stress exposure Phase 1: Cortisol or placebo administration Phase 2: The Socio-evaluative stress test (TSST) where participants are instructed to prepare (anticipatory face of 10min) and present (exposure phase) a 5min speech to convince someone to hire them, followed by a mental arithmetic task (total duration 30min). Phase 3: Recovery and debriefing (60min)

Soravia et al. (2006) Study 2	Individuals with Spider Phobia	20(20%M),	Hydrocortisone (10mg), 60 min prior to exposure therapy	Placebo	Salivary cortisol	VAS, STAI-state	Six sessions (Distributed over 2 weeks). Cortisol administered only on sessions 2-5.	Individual exposure therapy Spider-related stimuli presented to participants during each session. Session 1 and 6 were used to assess baseline measures. Post-treatment (session 6): 2 days after cortisol-treated session.
de Quervain et al. (2011)	Individuals with Height Phobia	40 18-60 age range	Hydrocortisone (20mg), 60min prior to exposure therapy	Placebo	Salivary Cortisol	AES, ATHQ, AQ, BAT, SCR, SUDs	Three sessions within one week (One day a part)	Individual VR-exposure therapy Standardised exposure hierarchies used. Psychoeducation about exposure therapy and instructions to cope with avoidance strategies provided before treatment. Exposure steps repeated until last SUD < 30 or if SUD >30 had to continue until anxiety (SUD) reduced by 20%. Participants stayed in VR for 20min. Post-treatment: 3-5 days after treatment Follow-up**:** 28-35 days after treatment
Soravia et al. (2014)	Individuals with Spider Phobia	22(23%M) 20-60 age range	Hydrocortisone (20mg), 60min prior to exposure therapy	Placebo	Salivary cortisol	FSQ, STAIT-state, VAS	Two sessions (One week a part)	Group in-vivo exposure therapy Exposure conducted in groups of 5 - 6. All sessions included one hour of psychoeducation and 1.5 of in-vivo exposure to different spiders. Post-treatment: Immediately after treatment Follow-Up: 28-32 days after final treatment
Yehuda et al. (2015)	War Veterans with PTSD	24(100% M), 44.2 average age	Hydrocortisone (30mg), 20 min	Placebo	Blood	CAPs	Ten weekly sessions. Cortisol	Individual prolonged exposure Sessions manualised PE psychotherapy.

			before exposure therapy		(Assess glucocorticoid sensitivity)		administered only on sessions 3-10.	Follow Up: 6 weeks after treatment
Lass-Hennemann & Michael (2014)	Individuals with Spider Phobia	60 23.33 average age	Morning therapy at 8:00am (High cortisol group)	Evening Therapy at 6:00pm (Low cortisol group)	Hair and salivary cortisol	BAT, BDI, FSQ, MEQ, PANAS, STAI-trait,	One session	<u>Individual in-vivo exposure therapy</u> Interview and questionnaires, followed by 3h exposure session. Exposure session included introduction, demonstration of exposure steps. Exposure steps repeated until anxiety (SUDs) was < 50% and with several spiders. Post-treatment: 1 week after treatment Follow-Up: 12-14 weeks after treatment

AES, Anxiety Expectancy Scale; AQ, Acrophobia Questionnaire ATHQ, Attitude Towards Heights Questionnaires; BAT, Behavioural Avoidance Test; BDI, Beck Depression Inventory; BP, Blood Pressure; diffSCR, Difference in skin conductance response; FSQ, Fear of Spider Questionnaire; HR, Heart rate, HRV, Heart rate variability; MEQ, Morningness-eveningness Questionnaire; PANAS, Positive and Negative Affect Schedule; STAI-state, State-Trait Anxiety Inventory; SPQ, Spider Phobia Questionnaire; SCR, Skin conductance response, SUDs, Subjective Units of Distress; VAS, Visual analog scales

Table 2. Summary of stress effects on different indices of fear across extinction/treatment stages.

	Extinction Learning/ Exposure			**Extinction Retention/ Post-treatment**			**Extinction recall/ Long-term Follow-Up**		
	Subj.	Phys.	Beh.	Subj.	Phys.	Beh.	Subj.	Phys.	Beh.
	Experimental Studies								
Bentz et al. (2013)	√ US-exp ratings (men only)	-	-	√ US-exp ratings (men only)	-	-	-	-	-
Merz et al. (2014)	-	√ diffSCR	-	-	-	-	-	-	-
Antov et al. (2015)	-	√ diffSCR	-	-	√ diffSCR	-	-	-	-
Drexler et al. (2018)	-	NS SCR	-	-	√ SCR-renewal	-	-	-	-
Merz et al. (2018)	-	√ CR	-	-	NS SCR	-	-	-	-
	Treatment Studies								
Soravia et al. (2006) Study 1	√ VAS STAI-state	√ HR change	-	√ VAS STAI-state	√ HR change	-	-	-	-
Soravia et al. (2006) Study 2	√ VAS	-	-	√ VAS	-	-	-	-	-
de Quervain et al. (2011)	-	-	-	√ AQ, SUDs	NS SCR	-	√ (AQ) AES, ATHQ	√ SCR	√ (BAT)
Soravia et al. (2014)	NS VAS STAI-state	-	-	NS VAS STAI-state	-	-	√ FSQ, SPQ, VAS (STAI-state)	-	-
Yehuda et al. (2015)	-	-	√ Retention	NS CAPs	-	-	√ CAPs	-	-

Lass-Hennemann & Michael (2014)	-	-	NS no. of steps completed	NS FSQ	-	√ BAT	√ (FSQ)	-	√ BAT

√ = significant group difference favouring stress or high cortisol group (i.e., less fear responding in stress relative to control group observed). Fear index within parenthesis indicate there was a trend towards significance on this measure.

NS = no significant group differences in fear responding

AES, Anxiety Expectancy Scale; AQ, Acrophobia Questionnaire ATHQ, Attitude Towards Heights Questionnaires; BAT, Behavioural Avoidance Test; Beh, Behavioural; diffSCR, Difference in skin conductance response; FSQ, Fear of Spider Questionnaire; HR, Heart rate, HRV, Heart rate variability; Phys, Physiological; STAI-state, State-Trait Anxiety Inventory; SPQ, Spider Phobia Questionnaire; SCR, Skin conductance response, Subj, Subjective; SUDs, Subjective Units of Distress; VAS, Visual analog scales

3.3 Immediate Effects of Stress: Exposure Therapy/Extinction Learning

Experimental studies: All five experimental studies assessed for group differences during extinction training, with mixed effects. One study demonstrated no significant differences between cortisol and control conditions during extinction training, as measured by physiological SCR (Drexler et al., 2018). However, four studies reported significant group differences in opposing directions (measured by SCR). Merz et al. (2014) showed higher differential SCR (diffSCR) (i.e., greater discriminability between CS+/CS-) in the cortisol group relative to placebo group during late extinction trials (in particular), signifying reduced extinction learning in the cortisol group. However, in contrast, Antov et al (2015) found an attenuation of SCR during extinction in the stress group (CPT) but not control group, indicating a failure to extinguish by controls. Bentz et al. (2013) showed male participants in the stress group had reduced US-expectancy ratings relative to men in the control group. Similarly, Merz et al. (2018) found less fear responding in the cortisol group (as measured by SCR) during the first and

second blocks of extinction training, relative to placebo. That is, cortisol group showed more discriminability between CS+/CS-, indicating that the cortisol group had learnt the CS-no US association faster than the placebo group.

Treatment studies: Only some of the treatment studies (four out of six) assessed for group differences in performance (i.e., learning) during exposure treatment (Soravia et al., 2006, S1, S2; Soravia et al., 2014; Lass-Hennemann & Michael, 2014). Two out of six studies measuring subjective fear reported significant group differences in performance during exposure treatment: high cortisol or cortisol groups demonstrated less self-reported fear during exposure relative to controls or low cortisol groups. Specifically, Soravia and colleagues (2006) found that relative to placebo, subjective ratings of fear and avoidance were reduced in the cortisol group during a single phobic exposure session (Study 1) and across multiple phobic exposure sessions (Study 2), However, Soravia and colleagues (2014) found no effect of stress on subjective fear ratings during a single phobic exposure. Only one study analysed physiological fear (Soravia et al., 2006, S1) and found no significant group differences in this measure (change in heart rate) during social stressor exposure. Group differences in behavioural avoidance indicated mixed findings. Lass-Hennemann and Michael (2014) reported no significant group differences in progress (i.e., number of steps completed) throughout exposure treatment. Although, Yehuda and colleagues (2015) did not assess for group differences in learning, they reported significantly lower attrition rates in the cortisol group compared to the placebo group (i.e., cortisol group completed a higher average number of sessions); and this was interpreted as diminished behavioural avoidance in cortisol treated participants.

Taken together, treatment studies generally show group differences in self-reported fear during exposure therapy, suggesting enhanced extinction learning could be a mechanism of effect. However, more studies are required to draw reliable conclusions.

3.4 Short-term Effects of Stress: Post- Treatment / Extinction Retention.

Experimental studies with stress administration: Of the five experimental studies, four assessed extinction retention, approximately 24 hours after extinction. Two studies reported greater extinction retention in the stress group relative to the control group as indexed by subjective US-expectancy ratings (Bentz et al., 2013) and objective SCR (Antov et al., 2015). Two studies measuring SCR did not observe significant group differences in differential SCR responding (Bentz et al., 2013; Merz et al., 2018), however Merz and colleagues (2018) found a trend towards overall reduced SCR in the cortisol-treated participants, relative to controls. One study (Drexler et al., 2018) assessing for differences in renewal of fear (as measured by SCR), reported no renewal effect in the stress group compared to the control group where a renewal effect was observed.

Treatment studies: Five studies examined group differences at post-treatment. Three studies reported significant reductions in self-reported symptomatology measures including fear of heights (Cohens d= 0.6) (de Quervain et al., 2011) spiders (Soravia et al., 2006, S1), and social phobia (Soravia et al., 2006, S1). However, three studies reported no differences in symptomatology of PTSD (Yehuda et al., 2015), and specific phobia (Soravia et al., 2014; Lass-Hennemann & Michael, 2014) at post-treatment. Two studies demonstrated less anxiety in cortisol treated participants relative to placebo after exposure as measured by the STAI-state (Soravia et al., 2006, S1) or SUDs levels (de Quervain et al., 2011). de Quervain and colleagues

(2011) reported this effect size to be large (Cohen's d = 1.00). For studies that assessed subjective avoidance, one study reported significantly less avoidance in the cortisol group compared to the placebo group (Soravia et al., 2006, S1), whilst another study reported nil group differences in avoidance ratings at post-treatment (Soravia et al., 2014). Behavioural avoidance was measured by one study (Lass-Hennemann & Michael, 2014). This study reported a greater reduction in behavioural avoidance in the high cortisol (morning therapy) group relative to the low cortisol group (evening therapy group). In addition, only two studies (Soravia et al., 2006, S1; de Quervain et al., 2011) assessed physiological outcome measures. De Quervain and colleagues (2011) did not find significant group differences in SCR post-treatment. However, Soravia and Colleagues (2006) reported a significant treatment effect of change in heart rate, during the recovery phase of the TSST, where the cortisol group showed deceleration of HR after phobic exposure, while the control group displayed no change in HR (i.e., it remained high).

In summary, studies generally found enhanced stress levels facilitated or had no effect on extinction retention/post-treatment outcomes, relative to control conditions. Group differences were not demonstrated by all indices of fear (i.e., subjective, physiological and behavioural) within each study, therefore no inference could be made regarding the types of mechanisms underlying stress-related changes.

3.5 Long-term Effects of Stress: Relapse

Two experimental studies assessed for renewal of fear by testing participants in both the acquisition and extinction context (Drexler et al., 2018) or the acquisition and a novel context (Merz et al., 2018). Four treatment studies assessed for spontaneous recovery in follow-up assessments conducted approximately one-month (de Quervain et al., 2011; Soravia et al., 2015),

six weeks (Yehuda et al., 2015) or 12-14 weeks after the final treatment session (Lass-Hennemann & Michael, 2014). No study assessed for reinstatement of fear. These results are considered in turn, by fear measure (self-reported fear symptomatology, subjective discomfort/distress, behavioural avoidance, and psychophysiological indicators).

3.5.1. Spontaneous Recovery of Fear

Compared to placebo, all treatment studies showed significantly less spontaneous recovery as measured by self-reported fear symptomatology at follow-up assessment (de Quervain et al., 2011; Soravia et al., 2015; Yehuda et al., 2015). That is, cortisol treatment was more effective than placebo at reducing PTSD severity scores (Cohen's d = 0.4; Yehuda et al., 2015), spider phobia (Cohen's d = 1.04; Soravia et al., 2014) and height phobia symptoms (Cohen's d = 0.6; de Quervain et al., 2011) in the long-term. These effect sizes were reportedly moderate to large. One study reported less subjective fear and physical discomfort in the cortisol group in the long term, and this was considered a large effect size (Cohen's d = -1.6; Soravia et al., 2014). However, no significant group differences in avoidance as measured by self-reports were observed in this study. Another study (Lass-Hennemann & Michael, 2014), using objective measures, reported a significant improvement in behavioural avoidance (BAT scores) in the high cortisol group (morning therapy) as compared to the low cortisol group (evening therapy). Only one study investigated psychophysiological data. This study found significantly less SCR at follow-up in the stress group as compared to placebo group (de Quervain et al., 2011).

Therefore, taken together acute stress generally reduces spontaneous recovery of fear (including disorder-related fear symptoms, subjective ratings, physiological arousal and behavioural avoidance) after a period of one to three months.

3.5.2 Renewal of Fear

Of the two experimental studies assessing renewal of fear, findings were mixed. One study reported significant group differences in renewal of fear (Drexler et al., 2018), whereas another study did not (Merz et al., 2018). Specifically, Drexler et al., (2018) reported SCR was greater in the extinction context than in the acquisition context for control participants (demonstrating fear renewal in the control group), but no difference in SCR between these contexts was observed in stressed participants (demonstrating no renewal effect in stress group). In contrast, Merz et al., (2018) found no group differences in fear responding (as measured by SCR) as both stress and control groups demonstrated a renewal of fear in a novel context. Thus, from two studies, there is insufficient evidence to determine the effect of stress on renewal.

3.6 Changes in Cortisol and Noradrenaline as a Manipulation Check

Experimental studies: Experimental studies included a single administration of CPT (Bentz et al., 2013; Antov et al., 2015), SECPT (Drexler et al., 2018) or 30mg of Hydrocortisone (Merz et al., 2014; Merz et al., 2018). All studies measured salivary cortisol to verify their stress manipulation, however no study directly measured noradrenergic activity. Only three (Drexler et. al., 2018; Merz et al., 2018; Merz et al., 2014) out of five studies demonstrated heightened cortisol levels in the stress group as compared to the control group following stress manipulation. One study failed to show cortisol increases after administration of CPT (Antov et al., 2015;) and another study found a cortisol response in males but not female participants following exposure to the CPT (Bentz et al., 2013). Studies showing cortisol increases in the stress group reported enhanced extinction retention at test as compared to control (Drexler et al., 2018; Merz et al., 2014, Merz et al., 2018).

Treatment studies: Cortisol levels were assessed in all treatment studies using saliva (Soravia et al., 2006, S1, S2; de Quervain et al., 2011; Soravia et al., 2014; Lass-Hennemann & Michael, 2014) or blood (assessing for glucocorticoid sensitivity) samples (Yehuda et al., 2015). All treatment studies measuring cortisol demonstrated greater salivary cortisol levels in the stress group relative to the control group during exposure therapy. One study reported a correlation between change in cortisol levels and change in fear ratings in the placebo group (Soravia et al., 2006, S2). This suggests, changes in cortisol levels (i.e., increases in cortisol) during exposure therapy could be responsible for the observed improvements in fear responding. A change in glucocorticoid sensitivity was also associated with a change in PTSD symptom severity (i.e., CAPS scores) in one study (Yehuda et al., 2015). This implies that individuals with greater glucocorticoid sensitivity respond more positively to cortisol treatment and hence show more pronounced improvements in fear symptoms.

Taken together, the association between heightened cortisol levels and the reduction in fear responding in the stress groups suggests that changes in cortisol could explain these effects. However, due to the absence of direct noradrenergic measures in these studies, no conclusions about the role of NE in the stress-enhancing effects on extinction processes could be made.

3.7 Risk of bias

Risk of bias for individual studies is reported in Table 3. An adapted version of the domains and formatting suggested by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011) was used. Other sources of bias were assessed including integrity of the interventions, cortisol assessment and manipulation, and control of confounders. Unclear risk of bias indicates that insufficient information was available to permit judgment of

"low risk" or "high risk" (Higgins & Green, 2011). Included articles were coded by two raters for all risk of bias domains, with final ratings representing agreement between the two raters.

All treatment studies and all but one experimental study demonstrated blinding of participants, indicating low *performance bias*. All except one study reported random allocation to condition and three studies reported allocation concealment, indicating overall moderate risk of *selection bias.* Only three out of ten studies reportedly assessed for blinding of outcome assessment which increased the risk of *detection bias. Attrition* bias in the short term (< 4 weeks) was generally low, as most studies reported low attrition or controlled for attrition rates through statistical analysis. However, *attrition bias* in the long term (> 4 weeks) was generally high or unclear as attrition rates were higher at follow-up or not accounted for through statistical analysis. All, but one treatment study controlled for time of day, but only two controlled for additional confounding variables of stress including BMI, hormonal contraceptive use, smoking and exercise. In contrast, all experimental studies controlled for confounds of stress, reflecting low risk of bias from *other sources* in experimental studies. *Reporting bias* was varied across studies as all, but one treatment study reported results for pre-specified primary outcome measures, while experimental studies did not provide enough information for coding. Moreover, the integrity of the interventions varied across treatment and experimental studies as four out of the ten studies reported extinction failure in the control group, increasing the risk of bias relevant to *reporting* for those studies. *Other sources* of bias associated with successful stress manipulation or proof of manipulation was high for experimental studies as half these studies failed to show group differences in cortisol levels or did not include a cortisol measure. In contrast, all but one treatment study demonstrated increased cortisol levels in the stress group,

indicating a low bias due to problems of stress induction. Sources of bias ratings for individual studies can be made available upon request.

Table 3. Percentage of studies within risk of bias levels according to an adapted version of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011)

	Treatment Studies			**Experimental Studies**		
Type of Bias	*High Risk*	*Low Risk*	*Unclear Risk*	*High Risk*	*Low Risk*	*Unclear Risk*
Selection		75%	25%		40%	60%
Performance	17%	83%			60%	40%
Detection		66%	33%		40%	60%
Attrition	18%	55%	27%		100%	
Reporting	16.5%	67%	16.5%		40%	60%
Other Sources	39%	61%		40%	60%	

4. Discussion

Given the recent interest in the therapeutic benefits of stress for extinction learning, this review had two aims: 1) to determine whether stress-augmentation interventions for anxiety and fear-based disorders can attenuate three different forms of relapse, and 2) to investigate and synthesize the evidence for possible mechanisms of these effects of stress. Research in this area is relatively recent (first study published in 2006), thus only 5 experimental studies and 6 treatment studies of exposure therapy were identified.

Results of experimental and treatment studies indicate that stress before fear extinction or exposure therapy generally provides significant benefits for reducing fear symptoms in the long-term. These benefits are over and above the benefits achieved with standard exposure therapy. All stress conditions in the reviewed treatment studies led to greater long-term improvements at follow-up (4-6 weeks) compared to standard exposure treatment (placebo/control conditions). However, the impact of stress on the generalizability of extinction memory was mixed. That is, experimental studies showed stress administration yielded either no renewal effect following test in the acquisition context, or a renewal effect following testing in a novel context. This may suggest cortisol treatment promotes resistance to renewal of fear in the fear learning context (acquisition context) but may not generalize extinction learning to an unfamiliar context (novel context). No study investigated stress effects on the reinstatement of fear. Such findings indicate stress-augmentation has the potential to reduce spontaneous recovery but further research is needed to delineate the effects of stress on other forms of relapse (renewal and reinstatement).

In addition, treatment studies generally observed an immediate effect of stress on extinction learning. During exposure therapy, fear ratings and/or symptomatology tended to significantly improve in the high cortisol group relative to the placebo or low cortisol conditions. However, experimental studies revealed mixed findings. This could be explained by methodological differences in the paradigms used. Both studies which did not observe significant group differences during extinction learning used behavioural interventions (CPT and SECPT) to enhance endogenous levels of stress. Type of stress induction may therefore influence the facilitatory effects of stress on extinction learning in healthy controls. In fact, several studies have stipulated that arousal (in the form of NE activation) is a key modulator of the stress effects on extinction learning (see review by Stockhurst & Antov, 2016). Behavioural interventions may

not have increased NE levels enough in non-phobic participants (i.e., healthy controls) to produce immediate effects. In addition, one study did not provide evidence of successful extinction training in both groups (i.e., no reduction in subjective-ratings, SCR or HR was observed) and this was speculated to be due to the low number of extinction trials. Thus, methodological differences in the number of extinction trials and type of stress administration may account for the discrepancies amongst experimental studies in the immediate effects of stress on extinction learning.

Importantly, all studies measuring cortisol showed stress-treated participants had significantly elevated cortisol levels and greater treatment outcomes, relative to control-treated participants. This suggests cortisol could explain the benefits of the stress effects on extinction learning. Consistent with this, two reviewed studies (Soravia et al., 2006, S1; Yehuda et al., 2015) reported that an increase in cortisol levels and glucocorticoid sensitivity was related to a decline in fear symptoms**.** Hence, benefits to therapy observed following stress administration could be mediated by cortisol levels and an individual's glucocorticoid responsiveness. Indeed, there is evidence to support this as a study by Meuret and colleagues (2015) found that cortisol mediated the benefits of morning psychotherapy, where higher absolute cortisol levels during exposure and non-exposure days predicted greater treatment outcomes. Similarly, another study demonstrated that higher average cortisol levels predicted greater improvements in PTSD symptoms, where most of the variance in symptom change was accounted for by cortisol (Van Gelderen, et al., 2020). No study measured NE arousal directly and therefore no conclusions could be drawn regarding the role of NE in the therapeutic benefit of stress. Future studies should measure noradrenergic activity in order to ascertain its involvement in the enhancing effects stress. This could inform the underlying mechanisms of these affects, especially since

both NE and cortisol are required for the facilitatory effects of stress (Cahill & Alkire, 2003; Mueller & Cahill, 2010; Buchanan & Lovallo, 2001; Quirarte et al., 1997, Roozendaal et al., 2002).

4.1 Stress as a potential enhancer of cognitive processes underlying exposure therapy

Stress-induced improvements in fear were largely demonstrated by subjective and physiological measures of fear specific to contingency learning (i.e., diffSCR), whereas general physiological (i.e., SCR) and objective behavioural measures of fear were mixed. This is in line with reviewed studies demonstrating stress enhances cognitive processes of extinction learning, consolidation and retrieval (see reviews: de Quervain, Schwabe, & Roozendaal, 2017; Maren & Holmes, 2016; Stockhorst & Antov, 2016; Wolf, Atsak, de Quervain, Roozendaal, & Wingenfeld, 2016). In fact, the enhanicng effects of stress were observed throughout the extinction/treatment phases of the studies reviewed and were most robust (affected all indices of fear) at long term follow up. This suggests stress has both immediate and delayed effects on extinction learning and memory, which are strengthened with time. Thus, the general finding that stress facilitates *learning* during exposure therapy and enhances *memory* of this learning in the long term may imply that cognitive processes have a role to play in the therapeutic benefit of stress. Given these findings, we now turn to the potential mechanisms that may explain the impact of stress on these cognitive processes (learning and memory) and the discrepancies of these effects. Below we examine reviewed studies and the broader literature in order to develop a novel, hypotheses-generating model of the mechanisms underlying the stress-enhancing effects on extinction-based treatment.

4.1.1 Immediate effects of stress: Mechanisms of stress-induced extinction learning

Models of cortisol-induced enhancement of extinction (de Quervain, Wolf & Roozendaal, 2019) postulate that cortisol inhibits the retrieval of aversive memories, and there is compelling evidence from human and animal studies to support this (see reviews, Bentz et al. 2010; de Quervain et al., 2017). In fact, two reviewed studies (Bentz et al., 2013; Merz et al., 2018) found stress attenuated fear responding at the beginning of extinction learning, and this was interpreted as impaired fear memory retrieval. Whilst this implies cortisol impacts fear retrieval and/or fear expression but not necessarily extinction learning (Merz et al., 2014; Bentz et al. 2013), researchers have hypothesized that reduced fear recall may facilitate extinction learning through the association of the phobic object with a less aversive experience, resulting in reduced fear responding (Soravia et al., 2014).

Whilst these mechanisms are convincing, there have been discrepancies in the effects of stress on extinction learning (Drexler et al. 2018; Stockhorst & Antov, 2016). Two reviewed studies showed an intact fear memory retrieval (Drexler et al. 2018; Lass-Hennemann & Michael, 2014) and one study found an opposing effect (Merz et al., 2014). That is, Merz and colleagues (2014) found a cortisol-induced enhancement of SCR during the early stages of extinction learning relative to the late stages and this was observed at the neural level. This suggests cortisol may have enhanced fear memory retrieval, or perhaps other mechanisms could be at play.

There is evidence that emotional arousal specifically involving the activation of NE *enhances* fear responding towards the phobic object (Kausche et al., 2021), implying emotional arousal may underly the immediate effects of stress on extinction learning. Evidence for this hypothesis is provided by studies demonstrating that NE-arousal during the stress

response is necessary for the enhancement of encoding (learning) (Cahill and Alkire, 2003). Moreover, animal, and human studies reveal that it is the combination of NE and cortisol that is required for the influence of cortisol on memory processes. This is because antagonists of adrenergic receptors (block NE release) or a delay between cortisol and NE activations block the enhancing effects of stress (Quirarte et al., 1007; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006). Moreover, when these hormones are manipulated separately, NE appears to override the effects of cortisol as there is no difference between NE manipulation and NE + Cortisol manipulations (Kausche et al., 2021). Therefore, it is possible that arousal-induced nordarenergc activity may drive the learning and memory-enhancing effects of stress.

In fact, emotional arousal associated with stress may facilitate extinction learning by increasing the change in expectancy of harm, which is proposed to explain the strength and rate of contingency learning during extinction. According to the Rescorla-Wagner model (1972), learning can be maximised when there is a greater discrepancy between what is expected (an aversive outcome), and what actually occurs (no aversive outcome). According to Rescorla (2000), one way to maximize this discrepancy is to increase the expectation of harm with the addition of an excitatory stimulus during extinction. This has been shown to enhance fear responding during extinction but reduce spontaneous recovery of fear (i.e., attenuate fear responding at follow-up). Indeed, there is evidence that stress can amplify fear to increase the violation of harm expectancy during extinction/exposure (Zillmann, Katcher, & Milavsky, 1972). Interestingly, Kalbe and colleagues (2020), demonstrated that when stress-induced expectancy of harm violation was reduced, memory enhancing effects were impaired. Their findings suggest that stress may enhance exposure-based therapy by maximizing expectancy violation to produce greater learning and longer-lasting benefits.

Another feature of the expectancy violation model which might explain the stress-induced facilitation of extinction learning is the role of attention to the phobic stimulus. Rescorla and Wagner (1972) posit that enhanced attention to the CS can strengthen the association of the CS with the non-occurrence of the US (i.e., increase extinction learning). Studies have shown that manipulating attention towards the phobic stimulus results in enhanced fear extinction learning and less return of fear (Barry et al., 2017; O'Malley & Waters, 2018). In line with this, studies have demonstrated that greater engagement with the phobic stimulus during exposure therapy is related to better treatment outcomes (see review Barry et al., 2015). In fact, stress has been shown to enhance attention to threat, facilitating the processing and storage of relevant information into long-term memory (Weymar et al., 2012). If we consider a unified account of the Mackintosh (1975) and Pearce and Hall (1980) models of selective attention, it is argued that there is an initial 'automatic' selection of attention towards stimuli which have a predictive value or arousing qualities. There is also a 'controlled' selection of attention which involves maintenance of sensory focus on stimuli that have unpredictable outcomes (see Hogarth et al., 2008). Stress has been shown to modulate both of these processes in a time-dependent manner by initially increasing vigilance towards threat and subsequently enhancing sustained attention when cortisol is heightened (Henckens, van Wingen, Joëls, & Fernández, 2012). In addition, manipulating attention towards threat has been shown to increase cortisol levels (Pilgrim et al., 2014), suggesting heightened cortisol is associated with enhanced attention to the phobic stimulus during exposure therapy. Thus, in line with these findings and the Pearce-Hall model of selective attention, it is proposed that stress may first enhance 'automatic' selective attention to the stimulus predicting threat, facilitating the detection of a prediction error (i.e., no-US), and subsequently enhance 'controlled' attention towards the stimulus as the uncertainty of the

stimulus-outcome contingency requires further learning. Therefore, cortisol-induced changes in 'automatic' and 'controlled' attention may account for the benefits of stress on extinction learning.

4.1.2 Delayed effects of Stress: Mechanism of stress-enhanced long-term memory

There is extensive evidence from empirical studies that stress enhances the consolidation of extinction memories (Bentz, Michael, de Quervain, & Wilhelm, 2010) and may explain the pronounced faciliatory effects of stress in the long term. This is because cortisol-induced activation of NE is shown to enhance synaptic plasticity, which is critical for long term memory (Krugers, Karst &Marian, 2012). Specifically, stress activates the amygdala during encoding which is known to directly strengthen connections (i.e., synapses) over time to form long lasting memories (Cahill, 2000). Converging findings demonstrate that the degree of arousal-induced amygdala activation around the time of encoding is highly associated with subseuqent recall (McGaugh, 2004). Stress may in fact enhance consolidation of memories by increasing the emotional arousal of the extinction memory, and in turn the retrieval ability of these memories. Studies have shown that NE enhances the excitabilty of neruons (i.e., arousal) in order to facilitate synaptic plasticity (see review Tully & Bolshakov, 2010) and stabilize memories. This means that extinction memory traces are more frequently activated (i.e retrieved) over time, strengthening synaptic connections to produce stable memories. Importantly, consolidation and stabilisation of new extinction memories takes time (McGaugh, 2000) i.e., weeks, months and years. Therefore, the involvement of stress in extinction-related plasictity may explain why reviewed studies generally reported greater benefits of stress on all indices of fear in the long-term (4-6 week follow up) and were less robust in the short-term (post-treatment).

4.1.3 Proposed Model Here, we propose a tentative hypothesis-generating model that considers both the immediate and long-term effects of stress on learning and memory and builds upon existing literature and models of cortisol-augmentation of extinction-based therapy. The aim of this model is to suggest potential underlying mechanisms of stress-induced effects on extinction learning and memory and provide a framework for assessing these.

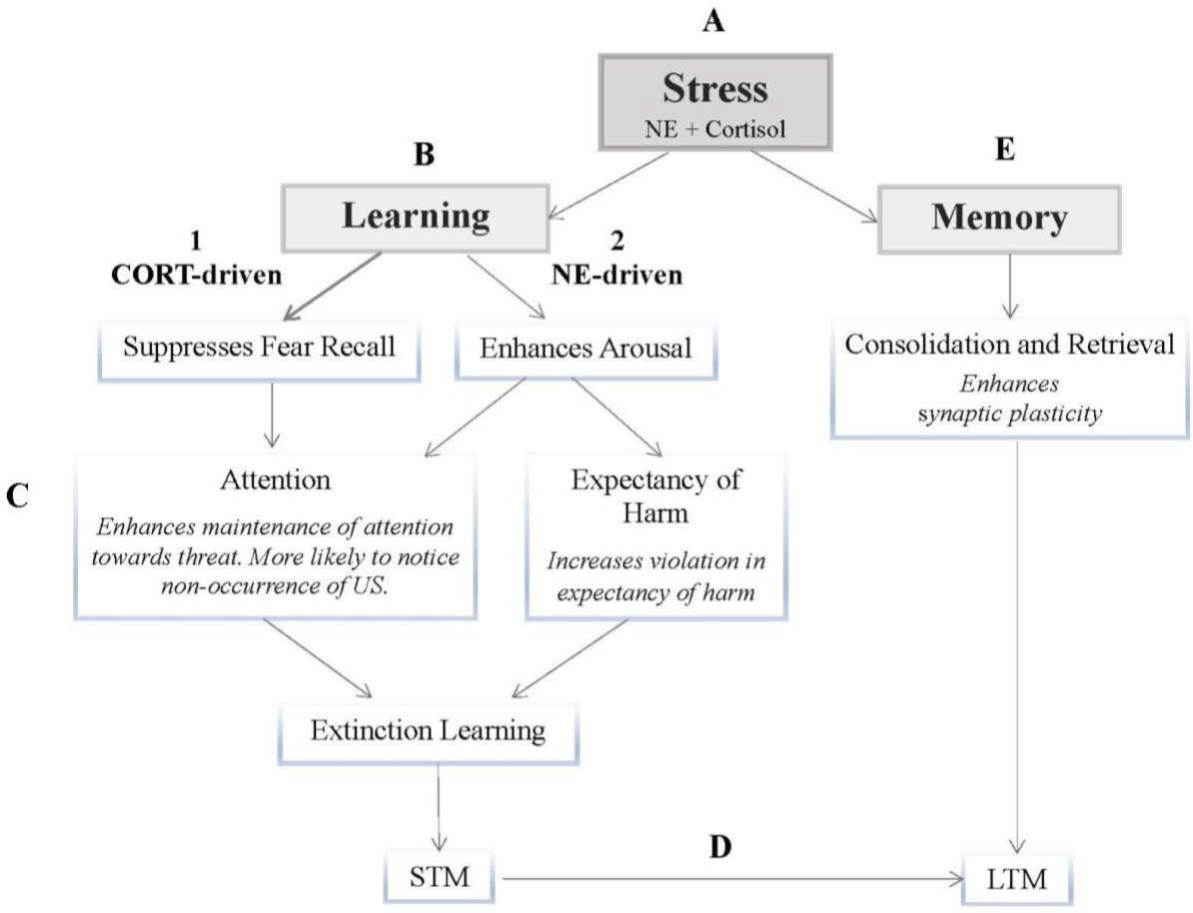

Figure 2. An integrated model of stress-augmentation.

The *Integrated Model of Stress-augmentation* (presented in Fig. 2) represents the potential pathways in which cortisol and noradrenaline associated with the stress response (A) can have direct and indirect effects on learning and memory. It is hypothesized that during extinction learning (B), stress may promote learning via two pathways: 1) suppression of the fear memory (primarily driven by cortisol) which may reduce avoidance and enhance maintenance of attention towards threat (C1), and 2) by enhancing emotional arousal (primarily driven by NE) which may influence cognitive factors such as an individual's expectancy of harm and their attention to threat (C2). These cognitive processes (C2), make it more likely that the absence of harm is noticed, and learning is maximised as there is a greater discrepancy between expectancy (aversive reaction-US) and outcome (no aversive reaction-no US). These processes are suggested to enhance extinction learning and in turn result in a stronger extinction memory which is more easily retrieved in the long-term (D). In addition, stress can directly increase consolidation of long-term memory (a process that involves weeks, months, years) by enhancing synaptic plasticity (connections between neurons) that is required to form lasting memories (E).

Notably, other researchers have also indicated the possible memory consolidation effects of stress and its role in weakening the fear memory trace (de Quervain& Margraf, 2008; de Quervain et al. 2017). However, to date, The *Integrated Model of Stress-Augmentation*, is the first to explicitly differentiate the effects of NE and cortisol on extinction learning processes and is the first to propose two distinct pathways (driven by NE and cortisol) in which stress can augment extinction learning. The proposed attentional mechanism is in part consistent with models postulating stress promotes an enhanced attention to contextual cues to form a less context-dependent memory (Drexler, Merz & Wolf, 2019). However, this is the first model to propose the role of attention in mediating stress-related effects on extinction learning. Moreover,

the tentative role of expectancy of harm contrasts with strict attenuated fear retrieval accounts of stress. Therefore, these unique mechanisms (attention and expectancy of harm) are invited by the model to be tested.

4.2. Methods for Testing Hypotheses arising from the Proposed Model

Future avenues of research should focus on disentangling the unique effects of stress-induced NE and cortisol on extinction learning. The model hypothesizes that NE and cortisol release associated with the stress response have distinct impacts on learning processes and could explain discrepancies in the findings. Specifically, the model predicts heightened emotional arousal (measured by NE) during extinction learning will be associated with greater expectancy of harm and attention to threat (Pathway 2). In contrast, heightened cortisol levels during extinction learning are hypothesized to be associated with less fear responding and enhanced attention to threat during extinction learning (Pathway 1). Future studies should directly measure stress-induced noradrenergic arousal during extinction learning and conduct mediation analyses to quantify the role of NE in stress-enhancing effects. Studies should also try to determine whether fear responding and attention during extinction learning moderate and/or predict treatment outcomes. If there is a relationship between these variables, the direction of these effects will provide insight into the mechanisms proposed by each *pathway* of the model. That is, for studies demonstrating clinical improvements, individuals are predicted to show less fear responding and enhance attention throughout extinction learning, which would support Pathway 1. Studies demonstrating that initial heightened fear responding and enhanced attention during extinction learning predict treatment outcomes, would provide support for Pathway 2**.** Moreover, studies could provide support for the expectancy of harm account of stress by demonstrating that stress leads to *enhanced* fear responding (US-expectancy ratings and SCR) during the early

stages of extinction and *reduced* fear responding at the late stages. Direct measures of attention (such as eye gaze) during extinction-based learning could be used to more precisely investigate the role of attention (Armstrong & Olatunji, 2012). Moreover, pharmacological and behavioural manipulations of stress should be compared with respect to their impact on different indices of fear **(**physiological, subjective, behavioural) and neuronal functions. Our model hypothesizes that behavioural manipulations of stress may increase emotional arousal (measured by NE) more than pharmacological manipulations of cortisol.

4.3. Limitations and Future Directions

The clinical data reviewed regarding stress-related enhancement of extinction/exposure procedures is limited in scope and has methodological inadequacies. Sample sizes across the studies ranged from 22 to 60 with only two studies reporting sufficient power from a power analysis, suggesting that power was a source of bias. The generalizability of the findings within each study was low as study samples tended to be young, and the proportion of males to females in each group were generally unmatched. Moreover, some studies employed very stringent criteria (such as BMI and oral contraception) to reduce cortisol-related confounders however this also reduced the generalizability of the results. To overcome some of these limitations, we recommend that researchers conduct adequately powered studies with matched samples across treatment arms, and that some studies use strict control of confounders to quantify mechanisms, whilst others investigate the ecological validity of these mechanisms by using broader samples.

Other limitations in the study design and method included: limited measurements of fear, problems with cortisol administration and extinction paradigms. Specifically, the majority of experimental studies used only one measure of fear which was physiological (SCR), and in

contrast only half the treatment studies used objective (i.e., behavioural and physiological) measures of fear such as the BAT or physiological reactivity (HR and SCR). Studies using a single measurement of fear and those not including objectively measured indicators of fear are problematic as they can be misleading and may not capture the various systems (i.e., physiological, behavioural and cognitive) influenced by stress. In addition, a handful of studies had potential sources of bias related to their study design. That is, some studies did not demonstrate the significant differences in cortisol level required to validate the stress manipulation. Alarmingly, four studies reported stress-related improvements in fear responding as compared to control, despite extinction failure in control participants. This makes it difficult to assess the added benefit of stress to standard exposure or extinction procedures, as the differences in responding could have been a consequence of ineffective learning in the control group rather than the faciliatory effects of stress on extinction learning. It is important that studies a) establish exposure-related extinction, before assessing the additional benefits of stress, b) ensure that stress has been adequately induced by assessing changes in cortisol and NE, and c) use robust, objective measurements of fear outcomes that are less susceptible to bias.

Moreover, future studies should aim to improve the translational value of this research by examining the effects of stress on different relapse phenomena and treatment stages in clinical populations. Specifically, longitudinal studies with large clinical samples should be conducted to increase the power and generalizability of findings. Studies should also investigate the impact of stress during extinction procedures/exposure therapy in order to determine the immediate effects of stress on extinction learning. Moreover, future research is warranted to investigate whether stress enhancers are more or less appropriate for specific individuals, conditions and treatment durations (Singewald, Schmuckermair, Whittle, Holmes & Ressler, 2014). Finally, behavioural

interventions of stress such as the SECPT should be investigated more in clinical populations as a safe option of extinction augmentation.

5. Conclusions

The clinical utility of stress to enhance exposure-based treatments is promising, with emerging evidence for the use of stress-related adjuncts to facilitate exposure therapy and attenuate relapse. The findings of this systematic review and general research in this area have direct clinical relevance for practitioners as they 1) have the potential to inform how exposure therapy can be conducted in the clinical setting to optimize treatment outcomes, and 2) can provide clinicians with a map of evaluating the success of their interventions, both during and after treatment.

Experimental and treatment studies indicate that pre-exposure stress yields clinically significant benefits for reducing fear responding and symptomatology in healthy adults with acquired fear, or clinical patients with PTSD and phobias, during treatment and in the long-term. These are predominantly medium to large effect sizes at four-to-six-week follow-up. However, results at post-treatment are less consistent. The long-term benefits of stress on exposure therapy suggest that pre-exposure stress increases the durability of extinction/exposure memories, although its effects on relapse phenomena such as renewal have not been directly assessed in clinical patients. Based on the existing evidence, we conclude that acute stress has immediate and long-term positive effects on extinction-based processes, suggesting stress plays both a learning and memory-enhancing role in extinction-based treatment. The *Integrated model of Stress-Augmentation* is a tentative and novel model that can be used as a framework for

assessment of putative mechanisms (such as fear memory retrieval, attention, and expectancy of harm).

In summary, stress administration before exposure therapy offers a relatively safe and easy approach to the augmentation of treatment for anxiety and fear-based disorders. It has the potential to enhance symptom remission, reduce relapse rates, as well as the duration, intensity, and cost of psychotherapy. However, it is critical that future avenues of research involve large randomized-controlled trials and testing of proposed mechanisms presented in our model.

Chapter 3:

Study 2: The effects of stress on relapse phenomena (spontaneous recovery and renewal) and the role of NE and cortisol in the stress-augmentation of exposure therapy

This chapter has been submitted for publication to *Journal of Anxiety Disorders*. Based on the literature and systematic reviews presented in Chapters 2 and 3, this chapter presents a pilot study designed to provide a first examination of the potential for acute stress to reduce two relapse phenomena within clinical patients and determine the relationship between NE, cortisol and stress-enhancing effects.

Acute stress prior to virtual reality exposure therapy reduces spontaneous recovery of fear in a clinical sample

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Abstract

Experimental and clinical studies have indicated that acute stress can be used to enhance extinction learning and memory consolidation, with evidence suggesting it has the potential to reduce or prevent relapse. This pilot study investigated whether stress administration prior to in vivo exposure-based therapy could enhance the durability and generalisability of extinction memory, thereby reducing relapse related to spontaneous recovery and renewal of fear. The role of noradrenaline and cortisol in producing these effects were examined to further understand the mechanisms at play. In a double-blind randomised controlled pilot study, 18 individuals with a specific phobia of spiders were treated with two virtual reality exposure therapy sessions. In addition, patients received either the Socially Evaluated Cold Presser Task (SECPT) or a control procedure, 25 minutes prior to each session. Renewal in a novel context was assessed at post-treatment and 7 months after treatment, and spontaneous recovery in the original treatment context was assessed 3 and 7-months after treatment, along with spider phobic questionnaires. Individuals in the stress group reported significantly greater reductions in phobic symptoms across follow-up periods with the fear of spider questionnaire (FSQ) and at 7-months follow-up with the spider phobia questionnaire (SPQ), relative to the control group, who showed a recovery of fear. No renewal effect was established in either group. However, the enhancing effects of stress generalised to a novel context at 7-months follow up. Cortisol and noradrenaline were associated with long-term benefits of stress. These findings demonstrate that stress augmentation of therapy is a promising approach to prevent spontaneous recovery of fear, but further research is needed to determine its effects on renewal.

1. Introduction

Research has shown that Cognitive-Behavioural Therapy (CBT) is the most effective non-pharmacological treatment for anxiety and fear-based disorders (Ströhle, Gensichen, & Domschke, 2018). However, despite successful extinction-based treatment, patients may fail to retrieve extinction memories, resulting in the return of fear. This failure to retrieve extinction memories is known to occur in three ways: 1) as a result of the passage of time (spontaneous recovery); 2) following a physical change in context (renewal); or 3) following exposure to an aversive event (reinstatement) (Bouton, 2004). One explanation for this is that extinction memories are highly sensitive to changes in temporal (i.e. time) and physical context (Bouton, 1993). In turn, extinction memories are considered specific to the context where they were formed (context-dependent), making them more labile and susceptible to relapse phenomena (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). In contrast, fear memories are mostly context-independent and easily generalise across contexts. Consistent with this, relapse is known to occur within 33-50% of successfully treated patients with exposure procedures (Boschen, Neumann, & Waters, 2009). Improving our knowledge of how and when extinction learning fails has the potential to optimise outcomes for exposure-based treatments.

Stress hormones such as cortisol and noradrenaline have been shown to influence the learning underlying exposure therapy (i.e., extinction) and new therapeutic approaches have emerged to optimise stress levels that may strengthen extinction learning and memory. Stress promotes the consolidation of emotional memories and impairs the retrieval of competing emotional memories (Buchanan et al., 2006, Roozendaal, 2002, Merz, Hamacher-Dang & Wolf, 2014). In turn, approaches that acutely elevate stress levels around the time of exposure therapy, have been used to facilitate extinction learning and the retrieval ability of these memories.

Successful manipulation of stress levels via pharmacological (i.e., hydrocortisone tablets) and behavioural interventions [Cold Presser Task (CPT), Socially Evaluated Cold Presser Task (SECPT)] administered prior to extinction-based learning (e.g., exposure therapy) enhance treatment outcomes, in a variety of clinical patients, including patients with spider phobia, panic disorder, height phobia, social anxiety and PTSD (Sovaria et al., 2014; de Quervain et al., 2011; Yehuda et al., 2015; Soravia et al., 2006; Antov et al., 2015). These benefits are observed over and above standard exposure therapy and appear most pronounced in the long-term (i.e., 4- 6-weeks). Critically, these effects have been found to be modulated by the interaction of noradrenaline and glucocorticoids following a stressful event (Quirarte et al., 1007; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006), and these are the same properties causing 'over-consolidated' and 'over-generalised' fear memories (Drexler, Merz & Wolf, 2019). Hence, if these memory-enhancing properties can be used to strengthen extinction memories and enhance their generalisability, perhaps they may be more resist to relapse, following stress-augmentation of therapy (Drexler, Merz & Wolf, 2019).

A recent model by Drexler and colleagues (2019) posits that stress prior to extinction learning renders these memories less context-dependent, whilst stress after extinction enhances the context-dependency of memory. This suggests, pre-exposure stress may prevent the renewal of fear, and post-exposure stress may enhance the return of fear following a change in context. These hypotheses are supported by laboratory studies (Drexler, Merz & Wolf, 2018; Hamacher-Fang, Merz & Wolf, 2015) and of particular interest is the study by Drexler and colleagues (2018) who found that pre-extinction stress prevented the renewal of fear in forty conditioned healthy adults. That is, stressed participants did not show a return of fear [measured by skin conductance response (SCR)] following testing in a novel context, as compared to control

participants, suggesting stress prior to extinction learning strengthens the generalisability of extinction memory. However, it remains unclear whether this stress-related attenuation of renewal is observed in clinical populations and whether these benefits extend to other forms of relapse (such as spontaneous recovery).

Moreover, the mechanisms by which stress aids extinction learning and memory are not entirely clear (Otto, McHugh, & Kantak, 2010). Studies in the last decade have focused on the role of cortisol in mediating the long-term success of stress on exposure therapy (Meuret et al., 2016). However, there is increasing evidence from human and animal research indicating emotional arousal (from noradrenergic activation) is required to support the enhancing effects of cortisol on extinction (Otto et al., 2010). In fact, it is the arousal component of stress that may disrupt contextualisation of memories as emotional arousal is shown to narrow the focus of attention to cues (i.e., phobic object) rather than to the broader context (i.e., the treatment environment) (Drexler et al. 2018). Therefore, it is reasonable to speculate that emotional arousal could be associated with the cortisol effects on extinction and relapse. Also, behavioural stress induction such as the SECPT, is often seen comparable to pharmacological manipulations of stress in its learning and memory-enhancing effects, however, it may have different effects on physiological and emotional arousal. Understanding the role of noradrenergic arousal in the therapeutic benefit of stress is a necessary avenue of research to further inform the types of stress adjuncts and conditions required for clinical use.

The current investigation is a study designed to provide a first examination of the potential for acute stress to reduce relapse associated with spontaneous recovery and renewal of fear within clinical patients. We also examined the role of emotional arousal indexed by noradrenaline (NE) in producing these effects of stress on extinction and relapse processes.

Participants with a specific phobia of spiders completed two weekly virtual-reality (VR) exposure sessions and were randomised to receive a behavioural stressor (SECPT) or control procedure, 25 minutes prior to treatment on both days. Saliva samples were collected at certain time points to measure NE and cortisol concentrations. Phobic symptoms were assessed with objective and subjective measures prior to the start of treatment (pre-treatment), one week (post-treatment), three months (3mfu) and seven months (7mfu) after the final treatment session. Renewal of fear was assessed at post-treatment and 7mfu with the presentation of the spider in a novel context, and spontaneous recovery assessed at 3- and 7-mfu via the presentation of the spider in the original treatment context. It was hypothesised that stressed participants would show less fear towards the spider following test in a novel context (less renewal at post-treatment), and in the long-term (less spontaneous recovery tested at 3- and 7-mfu), relative to control participants. It was also hypothesised that NE arousal would be associated with the cortisol effects on extinction and relapse.

2. Method

The study protocol was approved by the Human Research Ethics Committee at the University of Sydney (2019/502) and registered under the Australian New Zealand Clinical Trials Registry (ACTRN12619001661167).

2.1 Participants

Male and Female participants aged between 18 and 60 years with spider phobia were recruited via advertisements on posters, community websites and social media. A total of 77 were assessed for eligibility, and following a telephone screening, were invited for a structured diagnostic assessment using the diagnostic interview for mental disorders (mini-DIPs) (Margrad

& Cwik. 2017). Of these participants, forty participants fulfilled DSM-5 criteria for a specific phobia of spiders and satisfied eligibility criteria. However, due to COVID-19 lockdowns only twenty participants (5 male and 16 female) were able to complete the study. This is because, following university lockdowns, participants had moved away, were unable to be contacted or no longer eligible to participate. The study period commenced in January 2020 and ended October 2020, with a lockdown period of 4-5 months from March to August 2020. Exclusion criteria included: current engagement in other active psychological or pharmacological treatment, comorbid disorder that is more primary or distressing, presence of serious or chronic medical illness, substance abuse problems, psychosis, and pregnant or lactating women. Participants enrolled were randomly allocated to either a stress or control condition. One participant withdrew from the study prior to commencing and another was excluded following their first treatment session due to the discovery of a more primary condition. All remaining 18 participants in this study were included in the analysis (n=8 stress, n=10 control).

2.2 Measures

2.2.1. Self-reported measures

Spider-related questionnaires. Fear of Spider Questionnaire (FSQ; Szymanski & O' Donohue, 1995) and Spider Phobia Questionnaire (Klorman, Weerts, Hastings, Melamed, & Lang, 1974) are self-report measures which assess the severity of spider phobic symptoms. Both were used to evaluate treatment outcomes due to their unique strengths; FSQ is more sensitive to therapeutic change across phobic and non-phobic subjects, and SPQ measures different qualities of subjective fear (i.e. fear of harm) (Muris & Merckelbach, 1996). They have been found to

correlate in a meaningful way with the Behavioural Avoidance Test (BAT, objective measures of phobias) and possess good reliability and convergent validity (Szymanski & O'Donohue, 1995).

Depression anxiety and stress scales-21 item version. Baseline depression, anxiety and stress symptoms were assessed using the Depression Anxiety and Stress Scales (DASS; Lovibond & Lovibond, 1995) to account for any group differences in mental health symptoms at assessment.

Spielberger state-trait anxiety inventory. Acute subjective anxiety prior to each visit (assessment and treatment sessions) was measured using the Spielberger State-Trait Anxiety Inventory (STAI-state; Spielberger, 1983) to ensure group differences in treatment outcomes were not accounted for by changes in subjective anxiety at the time of assessment.

Subjective units of distress. A subjective measure of the intensity of distress experienced by participants was rated on a scale from 0 (not at all) to 10 (extremely) during behavioural tests and exposure therapy tasks.

Subjective US-expectancy ratings. A subjective measure of the extent to which participants expect an aversive outcome to occur in the presence of a spider. This was used to index the strength of the CS (spider)- US (danger) contingency throughout exposure therapy. Fear outcomes were determined at the start of behavioural assessments as well as exposure tasks and could include responses such as “the spider will jump on me” or “bite me”. Participants provided expectancy ratings using a ten-point Likert scale in response to two questions: “How much fear/distress/disgust will you experience when you see the spider?” (0= no fear at all, 10= extreme fear) and “How likely do you think [*feared outcome*] will occur? (0= certainly not, 10= certainly).

Subjective ratings of stress, pain and unpleasantness. Subjective ratings were collected immediately following the stress/control condition. Adopted from the Schwabe, Haddad, and Schachinger (2008) rating method, participants specified how stressful, painful, and unpleasant the previous situation was on a scale from 0 (not at all) to 10 (very much).

2.2.2 Behavioural and objective measures

Behavioural avoidance test (BAT). An objective measure to assess actual avoidance of spiders. Participants were asked to approach the virtual reality spider placed in a clear container 3 metres away, without encouragement from the therapist. Once they indicated they could not go any further, they were asked to rate their level of anxiety using the subjective units of distress scale (Wolpe, 1969). A scale adapted from Garcia-Palacios, Hoffman, Carlin, Furness Iii, and Botella (2002), was used to convert the minimum distance between the participant and the spider into a performance score ranging from 1 to 5; where 1= within 3m from the spider, 2= within 2m from the spider, 3= within 1m from the spider, 4= within 0.5m from the spider, and 5 =lifts lid of the container. However, as all participants were able to lift the lid of the container at post-treatment (producing a ceiling effect) the minimum distance between the participant and the spider was used for analysis.

Physiological measurement. An E4 Empatica (Empatica, Milano, Italy) wristband was used to record participants heart rate. This physiological data was wirelessly transmitted and uploaded onto a server during participant performance. Heart Rate was sampled at a rate of 1 Hz (1 sample/per 1 second), with an average rate computed every 10 seconds.

2.2.3 Saliva measurement and analysis.

Levels of endogenous stress hormones (noradrenaline and cortisol) were indexed via saliva sampling. Saliva samples were acquired via the passive drool method, which required participants to use a saliva collection aid to fill a vial with 0.5ml of saliva. After each exposure sessions, saliva samples were frozen at -20o C until assay and analysed by the UNSW Salivary Bioscience Research Centre. Cortisol concentration was assessed to index HPA axis activation and salivary alpha amylase (sAA) to index noradrenergic activity and arousal. This is because the sAA protein is co-secreted with noradrenaline and found to be a reliable and non-invasive marker of noradrenergic activity (Nater & Rohleder,2009). Participants were requested to refrain from drinking alcohol or caffeine 3 hours prior to the session, eating 1 hour prior to the session, or exercising the day before (24-hour) the session. Saliva was taken 15min after participants arrival and before the beginning of the stress/control procedure to determine baseline cortisol levels. Saliva was subsequently collected 1, and 25-30 min after stress/control procedure, as well as immediately after the exposure session. Peak levels of cortisol were assessed approximately 25min after the onset of the stress procedure. See supplementary file (Appendix B) for sample time of each hormone.

2.3 Procedure

This study was a randomized, double-blind controlled trial conducted in person at the University of Sydney Psychology Clinic at the Brain and Mind Centre. Participation involved five appointments: an initial 10-15 min screening session to clarify eligibility and assess symptoms, a pre-treatment assessment, two treatment sessions one week apart, as well as a post-treatment assessment and two follow-up assessments (one week, 3 months and 7-months after the final treatment session). See supplementary file (Appendix B) for the procedures and

treatment implementation measures at each visit. During the first visit participants completed a diagnostic interview (using MINI-DIPs), obtained informed consent if eligibility criteria was satisfied, followed by baseline measures including subjective questionnaires (DASS-21, STAI, SPQ, FSQ, stress and saliva-related questions) (see Appendix A) and objective measures (psychophysiological, salivary cortisol/alpha amylase and a behavioural avoidance test). Enrolled participants received a study number to de-identify their participation within the research project and were randomised to either the stress or control condition by a research assistant using a random sequence generator. Twenty-five minutes prior to each treatment session, participants either received a behavioural stress intervention (SCEPT) or control procedure (warm water condition). Treatment sessions involved virtually-reality exposure to spiders with a discussion of coping strategies and psychoeducation material provided prior to the session

2.3.1 Stress or control procedure

Participants in the stress group completed the socially evaluated cold-pressor test (SECPT) which involved placing their dominant hand into an esky filled with ice cold water (0-2°C) for 3 minutes whilst being recorded by a video camera and observed by a researcher. Researchers were unknown to participants and remained neutral in their interactions. The same researcher was generally used for each participant, and they had no other contact with participants. In line with previous research and guidelines for administration of the SECPT (Schwabe et al., 2008; Schwabe & Schachinger, 2018), participants were given written instructions to keep their hand open to avoid making a fist in the water until they were instructed to stop. They were informed they would be videotaped for analysis of their facial expressions and performance on the task and were told this procedure would improve their treatment

outcomes. The camera screen was on a computer turned towards the participant so that they could see their face on the screen and was placed approximately 1 metre away from their face. Stress participants signed a consent form to be videotaped and time indicators including clocks and watches were removed from the room. In contrast, control participants immersed their hand into warm water (35-37 °C) for 3 minutes with no videorecording or researcher present. To avoid performance bias, written instructions were comparable in length to the stress procedure and both conditions were informed their procedure would maximise their treatment outcomes. Notably, control participants were told about the duration of the task with time indicators present.

2.3.2 VR treatment sessions

All participants were scheduled to receive two sessions of guided VR exposure therapy adapted from Garcia-Palacios et al. (2002). Participants received therapy in the afternoons between 12pm and 6pm, to avoid the peak cortisol levels in the morning. On the first session, participants were prepared with psychoeducation material about exposure therapy and instructions on how to reframe from using cognitive avoidance strategies. They were shown how to use the VR machine and provided time to habituate to the software. Twenty-five minutes prior to each exposure session, participants were administered either the stress or control procedure. They were then systematically guided through a set of exposure tasks for a maximum of 50 minutes on each treatment day and completed a minimum of 2 and maximum of 5 exposure tasks across two treatment days (one week a part). They were asked for SUDs (subjective units of distress) and US expectancy ratings every 2 minutes and were required to engage in a particular task until their SUDS < 3 or reduced to half their peak rating; whichever was higher. This criterion was used to determine the end of the exposure task, which meant that participants were required to repeat a task (i.e., another trial) until they reached the aforementioned criteria before

approaching the next task. Treatment ended after the completion of the final task of the day or once 50 minutes had elapsed. Incomplete tasks on the first treatment day were approached on the second. See supplementary (Appendix B) for task details.

At the end of each treatment session, participants were presented with their subjective ratings to highlight their expectancy violations and reinforce extinction learning. This is in line with cognitive behavioural approaches used in the therapy room to treat anxiety and fear-based disorders and incorporated to enhance ecological validity.

2.3.3 Post- and Follow-Up Assessments:

Renewal Test: Approximately one week after the final treatment session, participants were tested for renewal of fear using the BAT in a novel context (virtual outdoor garden). We further assessed renewal of fear at 7-month follow-up by comparing the BAT findings in the novel (virtual garden) vs original treatment context (virtual kitchen). Self-reported questionnaires including SPQ, FSQ, DASS-21, STAI and stress-related questionnaires were obtained prior to the renewal test.

Spontaneous Recovery: Twelve and thirty weeks after the final treatment session, participants completed the same procedure as their post-treatment, except they completed the BAT in the original treatment context (virtual kitchen) to assess for spontaneous recovery of fear.

2.4 Statistical analysis

All data were entered into the SPSS statistics package for Macintosh (v.26). To assess for any group differences in demographic and clinical characteristics, independent sample t-tests were conducted for continuous variables and chi-squared analyses for categorical variables.

Repeated measures ANOVAs were used to analyze effects of VR exposure-based therapy on treatment outcomes, with treatment scores (FSQ, SPQ, BAT) at certain time points (pre, post and follow-up), as within-subject variables. To assess stress-induced changes in treatment outcomes ANCOVAs were used with group as the independent variable, follow-up treatment scores (FSQ, SPQ, BAT) as the dependent variable, and corresponding pre-treatment scores as a covariate. Group comparisons in cortisol, noradrenaline and subjective ratings following the stress/control procedure were analysed with independent sample t-tests. Significant ANCOVAs were followed by Bonferroni-adjusted *post-hoc* tests. All t-tests were two-tailed. Bivariate Pearson Correlation analysis was used to measure the relationship between noradrenaline, cortisol and treatment outcomes (improvement scores on FSQ, SPQ and BAT). All reported results were corrected by using the Greenhouse-Geisser procedure, where appropriate. Based on a power analysis using G*power version 3.1 with a significance criterion of a=.05, and power of .08, a minimum sample size of N = 16 would be sufficient to detect a large effect size for an ANCOVA analysis, which would be comparable to effect sizes found in previous literature (Soravia et al., 2014). The magnitude of the effect size was categorised as small (0.01), medium (0.06) or large (0.14) based on criteria (Cohen, 2013; Olejnik & Algina, 2000).

3. Results

3.1 Participant characteristics

Table 1. presents participant characteristics. The stress and control groups did not significantly differ in demographic or clinical characteristics including age, gender, DASS21 STAI, SPQ, and FSQ, pre-treatment scores, as well as baseline cortisol levels (all p>.05).

Table 1. Demographic and clinical characteristics, and pre-treatment baseline measures

	Stress Group	*Control Group*	*Significance*
Age	32(3.39)	28(2.94)	.389
Gender	75% Female	80% Female	.800
Contraception	25%	20%	.800
DASS21: Stress	0.75 (1.17)	2.40(4.25)	.304
DASS21: Anxiety,	2.13(3.14)	2.80(3.12)	.655
DASS21: Depression	2.75(2.32)	5.40(4.12)	.124
STAI Total	42.63(5.55)	44.89(6.10)	.436
FSQ Total	93.88(18.41)	96.90(15.67)	.711
SPQ Total	10.50(2.39)	11.80(2.25)	.253
BAT Expectancy	6.88(1.81)	7.40(1.43)	.501
BAT SUDs	6.38(2.07)	7.05(1.34)	.414
BAT Min. Distance	1.80(.57)	1.88(.65)	.810
Baseline cortisol Day 1	.08(.09)	.09(.06)	.867
Baseline sAA Day 1	115.10(103.99)	91.79(82.82)	.637

Note: Data presented as mean (SD), BAT, Behavioural Avoidance Test; DASS21, Depression, Anxiety, Stress Scale-21; FSQ, Fear Spider Questionnaire; SPQ, Spider Phobia Questionnaire; STAIT, State- trait anxiety inventory; SUDs, Subjective Units of Discomfort

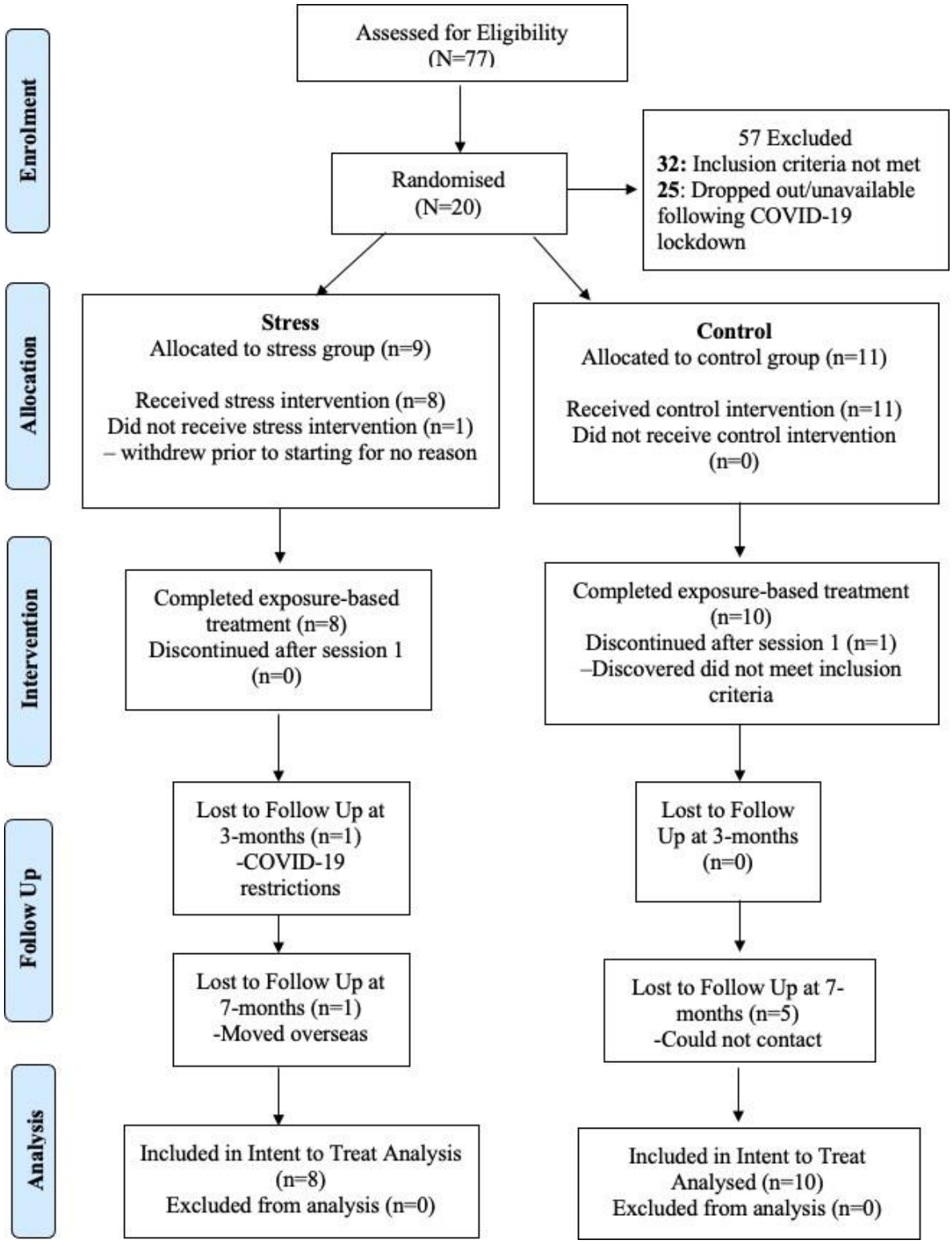

Figure 1. *CONSORT randomisation flow diagram* of participants progress throughout the recruitment phases of the pilot study.

3.2. Cortisol and noradrenergic response to stress

There were no significant group differences in baseline cortisol concentrations or cortisol levels 30 min after the stress/control condition (T3) at Session 1 or o 2 ($p > .05$). Similarly, no group differences were seen in baseline sAA concentrations prior to Sessions 1 or 2 ($p > .05$). However, significantly higher sAA concentrations were observed in participants in the stress group relative to those in the control group, 1min after the SECPT/control manipulation (T2) at Session 1 (S1) ($t_{15} = 2.19$, $p < .05$) and Session 2 (S2) ($t_{16} = 2.88$, $p < .05$) (see Figure 2. T2)**.** Group differences immediately after exposure therapy (T3) were just below statistical significance at Session 1 ($p = .096$) and Session 2 ($p = .05$), with higher levels of sAA appearing in the stress relative to the control group. Moreover, participants in the stress group experienced the behavioural procedure to be more stressful (S1: $t_{16} = 2.41$, $p < .05$; S2: $t_{16} = 5.78$, $p < .001$), painful (S1: $t_{16} = 10.46$, $p < .001$; S2: $t_{16} = 5.06$, $p < .001$), and unpleasant (S1: $t_{16} = 15.95$, $p < .001$; S2: $t_{16} = 6.35$, $p < .001$),), than the control group at Session 1 and 2 (see Table 2. for means, standard deviations and p-values of ratings, cortisol and sAA levels).

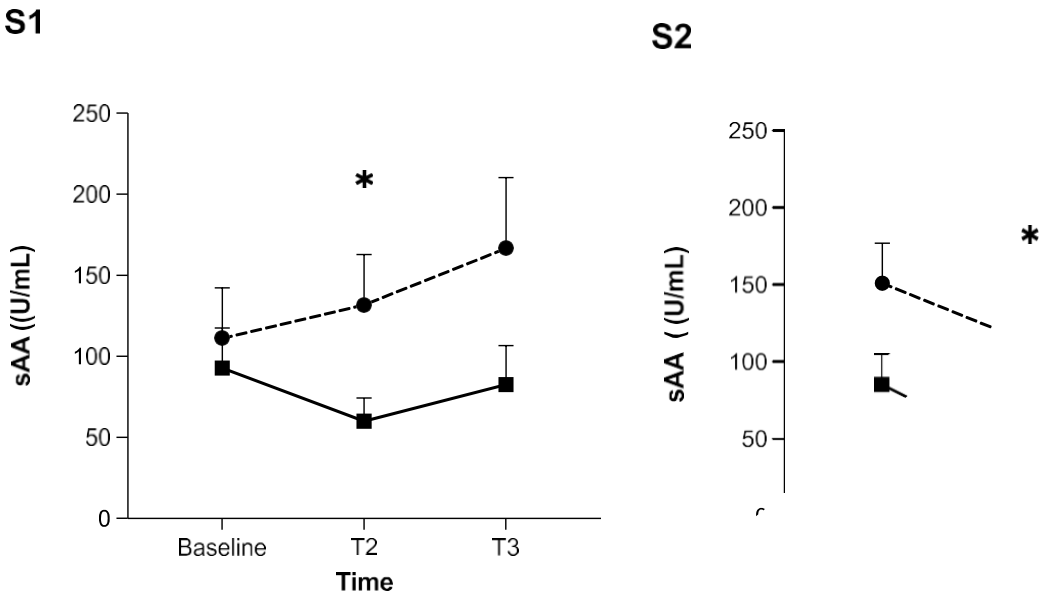

Figure 2. Noradrenergic response at session 1 (S1) and session 2(S2), across time points. Baseline,1 min. after stress or control procedure (T2), and immediately after exposure therapy (T3). Note: Error bars represent standard error of means and * p-value <.05 indicates significant difference between stress and control group at a certain time. Cortisol concentrations are not displayed in a figure as they were not significant (see Appendix B for tables and figures).

Table 2. Stress hormone levels and subjective ratings. Means (SD) are presented below. ***P<.001 or *P<.05 indicates a significant difference between stress and control groups (independent t-test). Stressfulness, painfulness and unpleasantness were rated on a scale from 0 (not at all) to 10 (very much).

Session 1	*Stress (n=8)*	*Control (n=10)*
Cortisol baseline	0.090 (0.07)	0.094 (0.06)
Cortisol T3	0.115 (0.13)	0.095 (0.08)
sAA baseline	111.160 (88.19)	92.873 (78.16)
sAA T2	**131.849 (87.45)***	**60.042 (42.887)**
sAA T3	166.675 (123.44)	82.777(76.78)
Unpleasant	**8.875 (0.83)*****	**0.900 (1.20)**
Painful	**7.875 (1.36)*****	**0.500(1.58)**
Stressful	**3.875 (2.03)***	**1.500 (2.12)**
Session 2		
Cortisol baseline	0.162(0.31)	0.107(.07)
Cortisol T3	0.104(0.1)	0.083(0.05)
sAA baseline	151.413 (73.31)	86.461 (61.95)
sAA T2	**112.791 (74.43)***	**38.51 (30.69)**
sAA T3	118.080 (61.74)	61.48 (51.85)
Unpleasant	**7.125 (2.85) *****	**0.857 (1.17)**
Painful	**6.625 (3.70) *****	**0.437 (1.08)**
Stressful	**3.875 (2.03)***	**1.500 (2.12)**

3.3 Effects of VR exposure therapy

A one-way repeated measures ANOVA on the whole sample revealed spider phobic symptoms significantly varied across time points (pre, post, 3-month and 7-month follow-up assessment) as measured with the FSQ ($F_{3,51}$ = 73.51, p<.001) and SPQ ($F_{3,51}$ = 14.97, p<.001). A significant reduction in FSQ scores was found from pre (95.56 ± 16.49, mean ± SD) to post-treatment (52.30 ± 12.82, p<.001), and post-treatment to 3-month follow-up (43.51 ± 10.57 p=.003). However, no significant fear symptom change from 3-month to 7-month follow up (50.02 ± 12.87, p=.053) was found.

Spider phobic symptoms measured with SPQ similarly showed a significant symptom decrease from pre- (11.22 ± 2.3) to post-treatment (8.12 ± 3.48, p<.001). No significant symptom change was observed from post- to 3-month (6.87 ± 2.46, p=.063) and 3-month to 7-month follow up (7.67 ± 3.27, p=.256).

BAT data was not available at post-treatment (due to testing in a different context) or at 3-month follow-up[5]. From pre-treatment to 7-month follow up, participants demonstrated a significant reduction in the minimum distance ($F_{1,17}$ = 56.99, p<.001), their expectancy ($F_{1,17}$ = 26.53, p<.001) and SUDs ratings ($F_{1,17}$ = 48.8, p<.001) during the BAT.

3.4 Effects of stress manipulation on exposure-therapy

Stress and Control participants did not significantly differ in the total duration, number of trials and tasks completed across exposure therapy sessions.

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[5] due to COVID-19 restrictions

3.5 Effects of stress manipulation on spontaneous recovery of fear

To assess stress-induced changes in treatment outcomes (FSQ, SPQ and BAT) multivariate ANCOVAs were used with pre-treatment scores as a covariate. Participants in the stress condition showed significantly less phobic symptoms as measured with the FSQ across the follow-up periods**,** relative to the control condition, and this was of a large effect (main effect of group, $F_{1,15,} = 12.81$, p= .003, $\eta^2 = .461$), (Figure 3.). No significant interaction effect was observed, indicating differences between groups were sustained over time.

Analysis of fear symptoms measured with the SPQ scores, revealed no main effect of group. However, a significant large interaction effect was observed, indicating differences in fear symptoms measured with the SPQ varied across the follow up periods (group x time interaction effect, $F_{1,15,} =15.52$, p= .046, $\eta^2 = .241$, pre-treatment scores as a covariate). That is stressed participants showed greater improvements (of a large effect size) in their fear towards spiders (measured with the SPQ) at 7-month follow up (Stress, 5.78 ± 2.9, Control, 9.12 ± 2.85; $F_{1,16,} = 5.77$, p= .029, $\eta^2 = .273$, pre-treatment scores as a covariate) but not 3-month follow up (Stress, 6.35 ± 2.6, Control 7.28 ± 2.4; $F_{1,16,} = 6.29$, p= .446), relative to control participants**.**

Due to unforeseen circumstances, as stated above, only 7-month follow-up behavioural data was obtained. During the 7-month follow up BAT assessment (in Context A), groups did not differ, in their expectancy ratings (p=. 104) or avoidance behaviour (p=.109). However, participants in the stress condition reported significantly less anxiety as measured by SUDs ratings (Stress, 2.3 ± 1.2, Control, 3.35 ± 1.19; $F_{1,15,} = 4.89$, p= .043, $\eta^2 = .246$, pre-treatment ratings as a covariate) and less physiological distress measured by heart rate (Stress, 75.8 ± 5, Control, 84.1 ± 6.3; $F_{1,14,} = 9.62$, p= .008, $\eta^2 = .407$), relative to control participants. Both results

found large effect sizes (Figure 4.). Thus, these findings generally demonstrate less spontaneous recovery of fear is observed in participants in the stress condition, as compared to participants in the control condition at 7-month follow up.

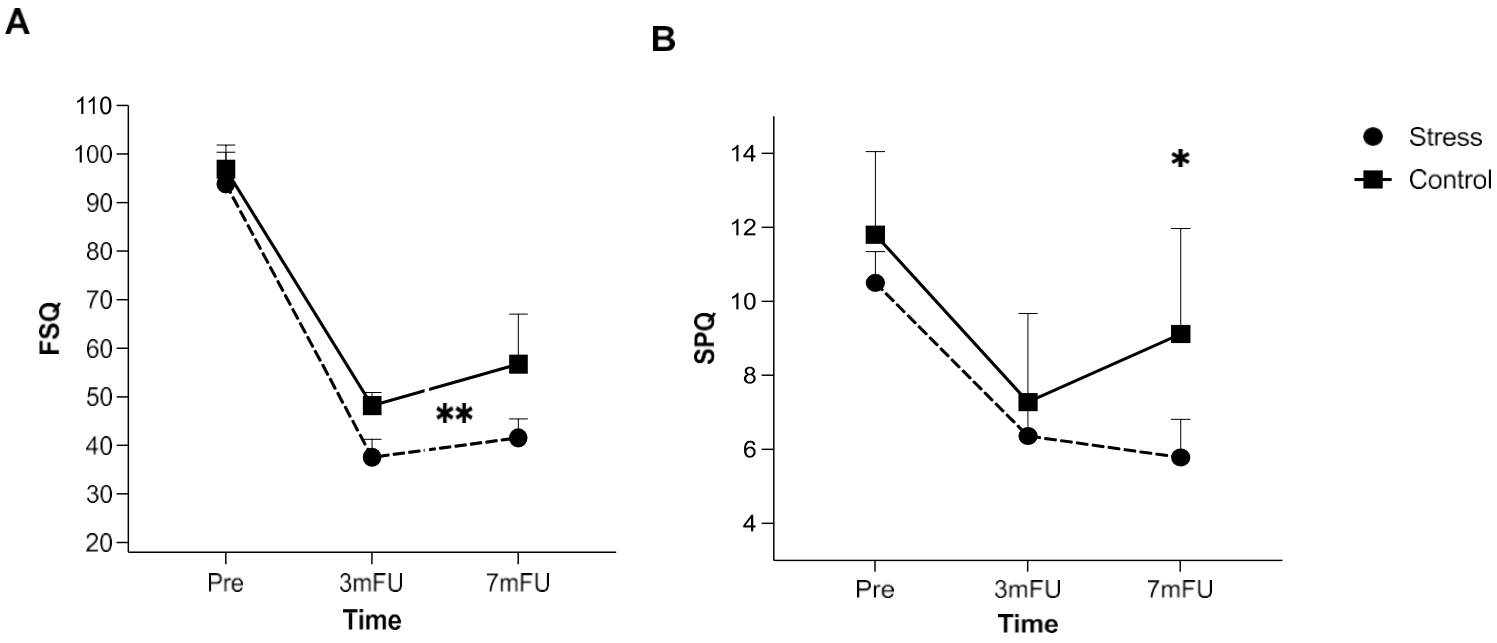

Figure 3. Self-reported fear over time. This includes fear measured at pre-treatment, 3-month and 7-month follow-up, by (A) the fear of spider questionnaire (FSQ), and (B) the spider phobia questionnaire (SPQ). Error bars represent standard error of the means and * P-value <.05, or ** P-value <.01 indicate significant difference between stress and control group at a certain time point.

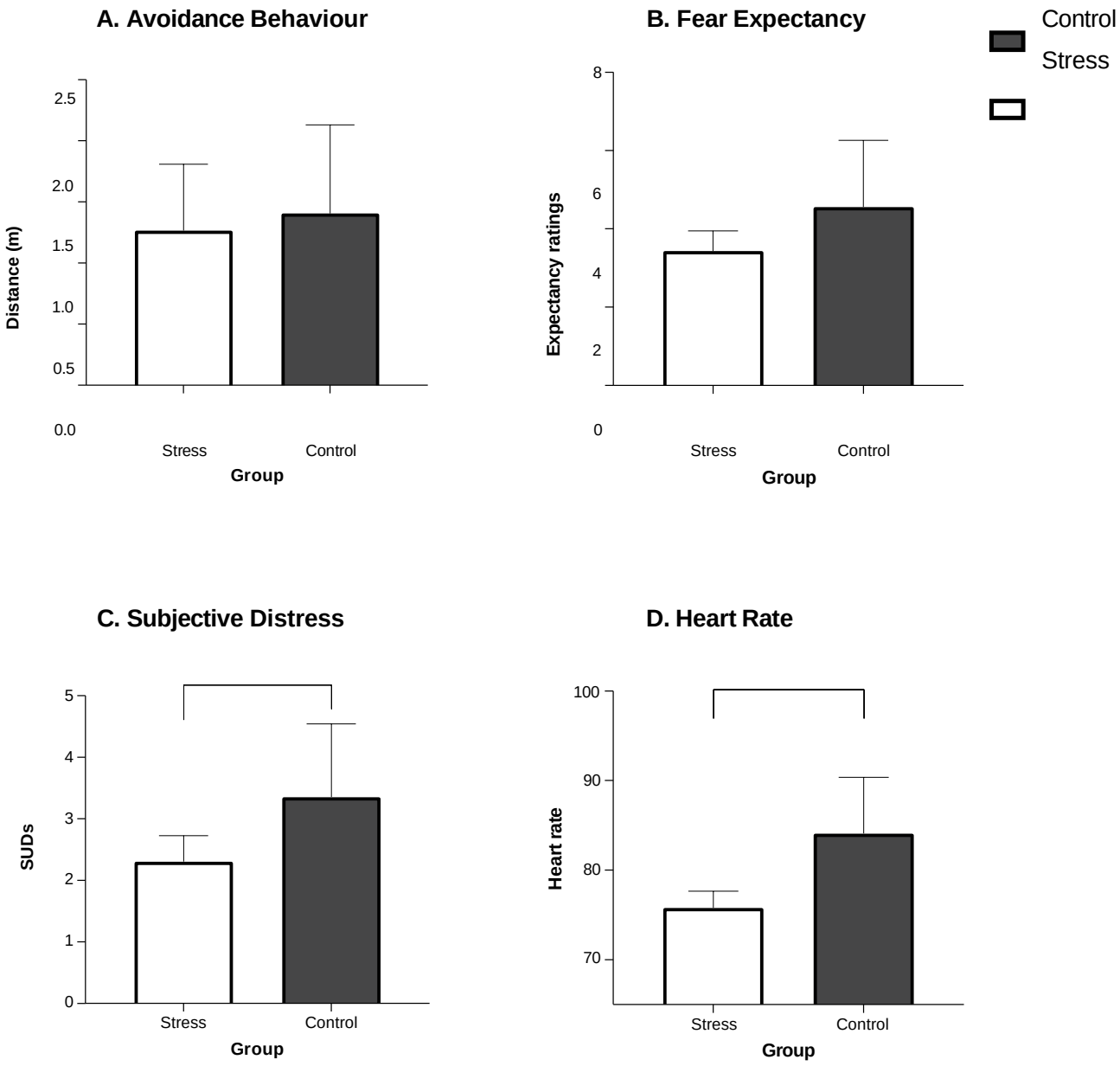

Figure 4. Participants performance on the BAT at 7-months follow-up. Includes avoidance behaviour (A), fear expectancy (B) subjective units of distress (SUDs)(C) and mean heart rate (D) during the behavioural avoidance test (BAT). BAT data was not available at 3-month follow up. Values refer to the testing that occurred in the original treatment context, assessing spontaneous recovery of fear. Note: Error bars represent standard error of the mean and * P-value <.05 or ** P-value <.01 indicates significant difference between stress and control group on that measure.

3.6 Effects of Stress on Renewal of fear

For the assessment of renewal of fear, participants were tested in the novel Context B during BAT at post-treatment, and a univariate analysis, controlling for pre-treatment scores was used to analyse group differences on each BAT-related measure. The findings revealed groups did not differ in their avoidance behaviour (p=.919), expectancy ratings (p=.613), SUDs (p=.515) or average heart rate (p=.257) during the BAT renewal test at post-treatment (see figure in supplementary file, Appendix B).

To further assess the effects of stress on renewal, we also tested participants in the novel Context B at the 7-month follow up assessment. A two-way repeated measures ANVOA analysis was used to compare group differences in fear responding between Context A and B at the 7-month follow up period. Findings (see Figure 5.) revealed no group difference in behavioural avoidance at 7-month-follow-up in the novel context (Context B), relative to the original treatment context (Context A) (group x context interaction effect, $F_{1,16,} = .746$, p=.400) or across contexts (Context main effect, $F_{1,16,} = .746$, p=.244). This demonstrates no renewal effect occurred in either group at post-treatment or 7-month-follow-up. However, relative to control participants, participants in the stress condition had a significantly lower average heart rate (main effect of group,; $F_{1,15,} = 15.87$, $p < .001$, $\eta^2 = .514$) and reported less anxiety (measured by SUDs ratings) (main effect of group, $F_{1,16,} = 4.910$, p= .042, $\eta^2 = .235$), both of a large effect, at 7-month-follow up across contexts. This suggests pre-exposure stress led to a deeper extinction memory which generalised across to a novel context, relative to the control condition.

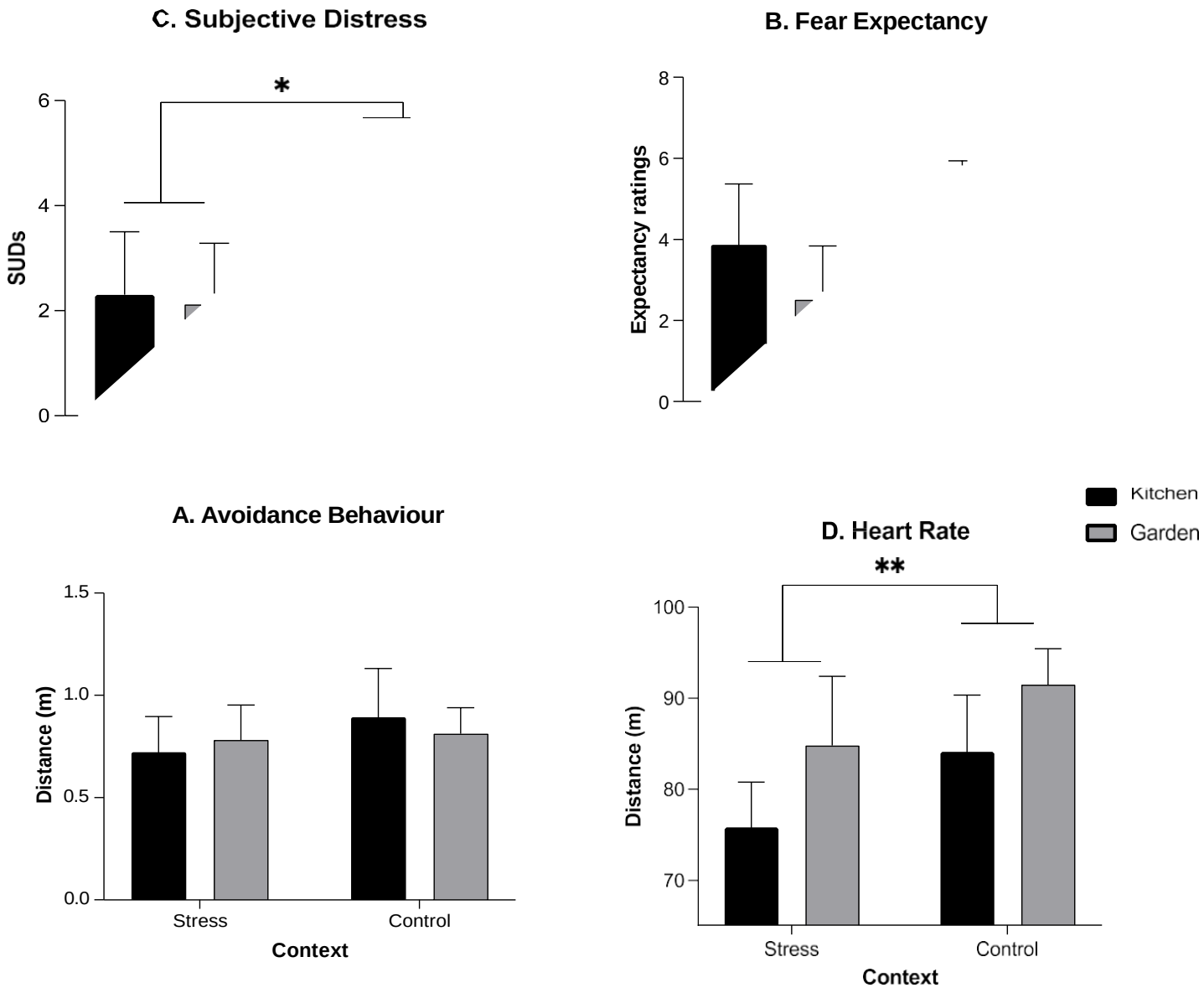

Figure 5. Participants performance on the BAT during the renewal test at 7-months follow-up. This includes participants avoidance behaviour (A), fear expectancy (2) and SUDs ratings (3) in both contexts (Kitchen and Garden) during the BAT test. No renewal effect was observed in either group at 7mfu (i.e., no difference in avoidance behaviour between Kitchen or Garden context, across or between groups). However, the stress group reported experiencing less subjective distress across both contexts relative to the control group, as measured by SUDs. Error bars represent standard error of the mean and * P-value <.05, ** P-value <.01 indicates significant difference between stress and control group across contexts.

3.7 Relationship between cortisol, noradrenaline and treatment outcomes

Bivariate correlations were used to assess the relationship between stress (NE and cortisol concentrations) and clinical improvements (difference scores from pre- to post-treatment, pre to 3-month follow-up and pre to 7-month follow up) measured by the BAT, SPQ and FSQ.

Across all participants, cortisol and NE levels at session 2, but not session 1 were associated with long-term clinical improvements. Cortisol levels prior to exposure therapy at session 2, significantly correlated with clinical improvements in phobic symptoms (measured by SPQ and FSQ) but not behavioural avoidance (measured by the BAT) at the 7-month follow up. That is, higher baseline cortisol levels at Session 2, were related to greater improvements from pre-7-month follow up on the SPQ ($r = .60$, $p = .009$) and FSQ ($r = .52$, $p = .029$), but not the BAT (distance, expectancy and SUDs ratings, $p > .05$). Higher cortisol levels after the stress/control procedure at session 2 were also associated with greater improvements from pre to 7-month follow up on the SPQ ($r = .52$, $p = .029$), but not the FSQ and BAT. Moreover, higher levels of NE after the stress/control procedure at session 2 significantly correlated with greater improvements on the SPQ from pre-treatment to 7-month follow up ($r = .51$, $p = .036$). No significant correlations between stress hormone levels (NE and cortisol) and treatment outcomes at other time points (post-treatment and 3-month follow up were found ($p > .05$). This demonstrates, higher cortisol and NE levels prior to/during exposure therapy after the first session, are associated with enhanced long-term, but not short-term treatment outcomes (i.e., less spontaneous recovery of fear). See supplementary file (Appendix B) for correlations table.

4. Discussion

The use of acute stress prior to exposure therapy has been shown to improve treatment retention and reduce symptoms (de Quervain et al., 2011; Soravia et al., 2006; Soravia et al., 2014), with evidence suggesting that it may enhance the durability and generalisability of these memories (Drexler, Merz, & Wolf, 2018). This study had two aims: 1) to determine whether stress could attenuate relapse associated with a change in context (renewal) or with the passage of time (spontaneous recovery); and 2) examine the role of the stress hormone noradrenaline (NE) in producing these effects. Spontaneous recovery was assessed at 3-month and 7-month follow-up, and renewal assessed at post-treatment and 7-month follow up in a novel context. The findings of the current study indicated that stress administration prior to exposure therapy enhanced the durability (i.e., prevented spontaneous recovery of fear) but not necessarily the generalizability (i.e., no impact on renewal of fear) of extinction memories.

The results of this study provide first evidence for specific long-term (i.e., 7-month follow up) benefits of stress on relapse associated with the passing of time (spontaneous recovery) or a shift in context (renewal). It is also the first study to investigate the effect of stress on renewal of fear within a clinical population.

The current findings are generally consistent with previous studies that report greater clinical improvements following stress exposure in the long-term (4-6weeks follow-up) (de Quervain et al., 2011; Soravia et al., 2015; Yehuda et al., 2015; Lass-Hennemann & Michael, 2014), but not in the short-term (post-treatment) (Soravia et al., 2015; Yehuda et al., 2015; Lass-Hennemann & Michael, 2014), supporting the memory enhancing hypothesis of stress (Roozendaal, 2002)**.** The renewal test findings are in line with Merz et al., 2018 who found no effect of stress on renewal. That is, healthy adults who completed fear conditioning in a context

A, followed by extinction in context B, and recall in context B and context C, one week later, did not differ in their fear responding in a novel context C. This contrasts to Drexler et al. 2018 study which found stress prevented renewal of fear, following testing in the fear learning (acquisition) context A. This indicates, stress may enhance generalization to the acquisition (or a familiar) context, but not an unfamiliar one. Alternatively, the absence of an establishment renewal effect (i.e., no return of fear in the novel context in either group) in the present and the Merz et al. 2018 study may account for the discrepancies.

The finding that fear responding generalized across contexts at 7-month follow-up, but not at post-treatment, suggests stress may exert its effects on memory generalization in the long-term but not the short-term. This might be because stress affects consolidation processes, including consolidation of extinction memories, which may require longer than a week to take effect. Another explanation is that the presentation of the extinction context, prior to the novel one at 7-month follow-up acted as a retrieval cue to promote generalization (Bouton, 1993). In fact, an experimental study by Merz and colleagues (2018) found a similar pattern of results where stress exerted no effect on the generalization of learning to a novel context during the early stages of recall but found stress led to a general reduction of fear across contexts (extinction and novel) during the late stages of recall. The order of testing in each context was the same in the aforementioned and the current one (i.e., participants tested in the extinction and then novel context), suggesting testing in the original extinction context may enhance the retrieval of extinction memory in the stress group to promote generalization. Importantly, participants were not tested in the extinction context at post-treatment in the current study, and the order of testing in each context was not counterbalanced at 7-month follow-up. Hence, we cannot disentangle the effect of retrieval cues and the long-lasting effects of stress on the

generalization of extinction memory. Future studies should elucidate whether the same results occur in the short-term (i.e., post-treatment) following testing in the extinction context and/or counterbalance the order of testing at follow-up periods.

4.1 Cortisol and noradrenaline as a mechanism

The present study did not observe a significant cortisol increase in the stress group compared to the control group, however studies have observed stress effects without significant cortisol increases (Antov, Melicherová, & Stockhorst, 2015). Factors such as sex, oral contraceptive (OC) use and time of day which are known to affect the stress response and its influence on extinction (Lovallo et al., 2019; Nielsen, et al., 2013; Verma, Balhara, & Gupta, 2011), may be hypothesized to explain the findings. However, they are unlikely to have accounted for this study's findings as the proportion of women on OC's, and ratio of males to females did not vary between groups.

As expected, NE concentrations were significantly elevated from baseline to post stress induction on both treatment days, suggesting the observed effects may be driven by NE arousal. If NE does facilitate extinction processes, it may do so by producing a similar effect to D-cycloserine (DCS); an effective adjunct to therapy known to enhance consolidation of emotional memories but have no effect on renewal (Smits et al., 2013). Whilst stress is linked to rises in both NE and cortisol, they are known to have opposing effects on memory accuracy and generalization (Bahtiyar, Karaca, Henckens, & Roozendaal, 2020)**.** In turn, there may well be differences in their effects on relapse (renewal and spontaneous recovery) depending on factors such as the timing of their peak hormone levels during treatment and the type of stress

administered (hydrocortisone or a behavioural intervention). Additional research is needed to disentangle the role of cortisol and noradrenaline on relapse phenomena.

The finding that cortisol and NE levels shortly prior to exposure correlate with long-term treatment outcomes, suggests NE and cortisol could modulate the effects of stress on relapse. This is supported by previous findings, that reveal heightened cortisol levels during exposure and non-exposure days moderate clinical improvements, implying higher levels of cortisol (both stress-induced and basal levels) optimise treatment outcomes (Meuret et al., 2015). Cortisol levels have also been shown to mediate the benefits of early morning therapy (when endogenous cortisol levels are highest) on treatment outcomes (Meuret et al., 2016). Future studies should assess whether NE may also underly the enhancing effects of stress on treatment outcomes, and to what extent cortisol and NE account for these benefits.

4.2 Limitations and recommendations

This was a proof-of-concept study, and the small sample size potentially limits the generalizability of the findings. Due to attrition, some BAT data was imputed at 7-month follow up. However, the pattern of results remained the same with a per protocol analysis, suggesting that this imputation did not unduly influence the results.

Several critical methodological considerations should be taken into account for future research. Firstly, a reliable cortisol increase was not established which may reflect limitations in the type of stressor. Future studies could utilize other behavioural stressors such as the Maastricht Acute Stress Test (MAST) or the Trier Social Stress Test (TSST), which are shown to reach higher levels of cortisol (Smeets et al., 2012). Secondly, the VR treatment was very effective in leading to behavioural change as all participants were able to remove the lid of the

contained spider during the BAT. Future studies could avoid ceiling effects by increasing the difficulty of the BAT task. Finally, the novel context may have been too similar to the treatment context to produce a renewal effect. Selecting a more distinct and fear-provoking context to assess renewal such as a spider in the bedroom may overcome this challenge. Future studies could also take into account sex differences by measuring sex hormones (i.e., estradiol) known to interfere with cortisol administration.

We also note the current study has three main strengths. Firstly, this is the first clinical study to use multiple indices to measure renewal of fear (e.g., expectancy of harm, physiological arousal and behavioural avoidance). Secondly, the present study employed less stringent exclusion criteria (i.e., included women and those on OC's) relative to other studies to enhance the ecological validity and generalizability of the findings. Furthermore, stress administration was not limited to just one session, and thus we could examine the real-world application of repeated stress administration to treatment.

4.3 Implications

Our findings suggest stress adjuncts to therapy have the potential to improve symptom remission and reduce relapse in the long-term. Understanding the components of stress that improve treatment outcomes will inform the optimal conditions for exposure-based treatment and the precise methods for optimizing stress in the therapy room. The significant relationships between NE, cortisol and enhanced long-term treatment outcomes confirm previous research highlighting the role of these hormones in facilitating long-term memory consolidation (Roozendaal, Carmi, & McGaugh, 1996) and holds promise for improving treatment by targeting these potential mechanisms. However, additional research is needed to further elucidate the role

of these hormones in the enhancing long-term effects of stress, particularly because stress effects are observed without significant cortisol increases. This would provide insight into safe, convenient, and effective methods of stress induction. Whilst this study ties together clinical and experimental research, discrepancies in renewal of fear between these studies invite further research into the clinical characteristics which may affect the impact of stress on extinction generalization.

5. Conclusions

Together the findings suggest that stress can prevent the spontaneous recovery of fear and these effects generalize to a novel context in the long-term. However, the potential for pre-exposure stress to attenuate renewal of fear remains unclear, as no renewal effect was established in this study. The long-term beneficial effects of stress are associated with higher NE and cortisol concentrations shortly prior to exposure therapy. Follow-up studies with larger sample sizes, designed to clarify mechanisms and assess the generalizability of these memories, have the potential to have a significant impact on the long-term success of treatment.

Chapter 4:

Study 3: Randomized control trial (RCT) investigating the effects of pre-exposure stress on relapse phenomena and potential underlying mechanisms (cortisol, noradrenaline, expectancy of harm and attention)

Based on the findings reported above and methodological considerations emerging from the pilot study, several changes were made to the stress procedure and relapse tests for the next trial. The final study reported below thus aimed to replicate the previous pilot study using a larger sample size to assess the generalizability of the findings and test additional (cognitive) mechanisms underlying the stress effects.

1. Introduction

Although it is well-established that exposure therapy is the gold standard treatment for anxiety and phobic disorders (McNally, 2007), we still have a long way to go to the address the problem of relapse. In fact, 19-62% of patients experience a return of symptoms following successful treatment (Craske & Mystkowski, 2006) and 40- 50% fail to achieve significant symptom improvement (Loerinc et al., 2015). This has prompted research into aiming to improve our understanding of the mechanisms underlying fear learning and unlearning in order to optimize exposure therapies.

One of the targeted mechanisms of exposure therapy is extinction learning, which involves learning a new safe (i.e., extinction) memory that competes with the original fear memory, and the relative strength and retrieval ability of these memories influence the intensity of the fear response (Bouton, 2004; Vervliet, Craske & Hermans, 2013). However, unlike fear memories, extinction memories are context-specific, making them less generalizable and more susceptible to relapse. In turn changes in temporal (shift in time) and physical context (shift in setting) can influence the retrievable ability of extinction memories resulting in a return of fear. Bouton and colleagues describe these relapse phenomena as 'spontaneous recovery' (i.e., when fear returns as time passes) or 'renewal' (when fear returns following a shift in physical context) (Bouton, 2002). Hence these relapse phenomena pose a major challenge for the longevity of treatment success (Drexler et al., 2018; Vervliet, Baeyens et al., 2013) and urgent attention is needed to ensure sustained treatment gains.

In response to this problem, studies have found that pharmacological and behavioural adjuncts designed to elevate stress hormones (noradrenaline and cortisol) can augment extinction processes. Clinical studies have shown that administering acute stress shortly prior to exposure

therapy can enhance clinical improvements at short follow-up periods (4 -6 weeks). Two naturalistic exposure studies have demonstrated that higher cortisol levels during exposure therapy are associated with enhanced clinical outcomes (Meuret et al., 2016; Siegmund et al., 2011) and consistent with this, therapy conducted in the mornings when endogenous cortisol levels are highest has been found to lead to greater symptom improvement, relative to the evening when cortisol levels are lowest (Lass-Hennemann & Michael, 2014). These promising findings highlight the potential for heightened stress at the time of exposure to facilitate treatment outcomes and prevent the return of fear. Whilst studies have found stress promotes symptom improvement at shorter follow-up periods, it unclear whether stress induction can prevent the spontaneous recovery of fear in the long-term.

The recent STAR model (Drexler et al. 2019), suggests that stress administered prior to learning leads to a more durable and less context-dependent memory. This is believed to occur because stress disrupts contextual processing and enhances the consolidation of emotional memories (Drexler, Merz, & Wolf, 2018). Previous studies have demonstrated that stress abolishes contextual fear learning (Simon-Kutscher, Wanke, Hiller, & Schwabe, 2019) and in fact, pre-exposure stress has been shown to prevent the renewal of fear in conditioned healthy adults (Drexler et al., 2018). However, these studies have tended to be in non-clinical samples and are yet to be tested within a clinical sample.

Besides the memory-enhancing role of stress, stress has been shown to enhance approach behaviour and reduce fear responding during treatment (Lass-Hennemann & Michael, 2014) inferring there is an immediate effect of stress on extinction learning which could account for the success of treatment. One explanation for this is that cortisol reduces the retrieval of fear memories to promote approach behaviour and the formation of a new safe memory (Bentz, de

Quervain, et al., 2013). However, it is reasonable to suspect that other factors during therapy which drive symptom improvement including *attention* towards the phobic object and *expectancy of harm* may also account for the findings. In particular, studies have shown that increased engagement with the phobic object during exposure therapy leads to greater improvement in clinical symptoms (see review Barry et al., 2015), and that manipulation of attention towards the phobic object enhances extinction learning and reduces the return of fear (Barry, Vervliet, & Hermans, 2017; O'Malley & Waters, 2018). According to the Pearce and Mackintosh (2010) model of extinction learning, this is thought to occur because narrowly focused attention upon a phobic object, increases its salience to maximize extinction learning and the rate of learning. This narrowed attention also leads to restricted encoding of the phobic object rather than the surrounding context, decreasing the context-dependent extinction learning (Zbozinek & Craske, 2017). Similarly, expectancy violation, which is the magnitude of the difference between what is expected (negative outcome) and what actually happens (no negative outcome) during exposure therapy is believed to lead to better treatment outcomes (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Hofmann & Smits, 2008)

Interestingly, both these factors (attention and expectancy of harm) are influenced by noradrenergic arousal and cortisol associated with the stress response. Specifically, heightened cortisol has been shown to enhance initial hypervigilance towards threat and later increase sustained attention (Henckens, van Wingen, Joëls, & Fernández, 2012). In addition, manipulation of attention towards threat increases cortisol levels (Pilgrim et al., 2014), suggesting heightened cortisol is associated with enhanced attention to the phobic object during exposure therapy.

Other findings suggest emotional arousal associated with stress can amplify fear to increase the violation of harm expectancy during extinction/exposure. A cognitive model by Trapp, O'Doherty, and Schwabe (2018) posits that the unpredictability associated with stress may elicit a greater prediction error (expectancy violation) to facilitate and deepen extinction learning. In support of this, the memory-enhancing effects of stress have been shown to be impaired when stress-induced expectancy of harm changes are reduced, suggesting expectancy violation could mediate the faciliatory effects of stress on memory (Kalbe, Bange, Lutz, & Schwabe, 2020). Together, this research points towards the possibility that attention and expectancy of harm may have a causal role to play in the stress-related reduction of clinical symptoms and effects on relapse. However, no study to date has investigated attention and expectancy of harm as potential mediators of the effects of stress on exposure-based treatment.

Prior research has focused on the role of cortisol, in producing these learning and memory-enhancing effects (Van Stegeren et al., 2007), with only one naturalistic study confirming cortisol is a mediator (Meuret et al., 2016). However, given that both NE and cortisol are required for the therapeutic benefit of stress (Cahill and Alkire, 2003; Quirarte et al., 1007; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006), it is surprising that no study has directly tested noradrenaline as a mediator of these effects. Investigating the contribution of both these hormones, will offer further insights into the mechanisms underlying stress effects and allow for more optimal designs of exposure therapy.

This study had two aims: 1) to extend previous research by investigating the potential for stress to prevent relapse associated with the passage of time (spontaneous recovery) and a change in context (renewal) within a clinical population undergoing exposure therapy; and 2) examine putative mechanisms of these effects including cortisol, noradrenaline, attention and expectancy

of harm. In this double-blind experimental design, 52 participants with a clinically significant fear of spiders were randomly allocated to receive a stress intervention (socially evaluated cold presser task) or a control procedure shortly prior to two virtual-reality exposure sessions to spiders. Spontaneous recovery of fear was assessed one week and 3-months after the final treatment session using self-report questionnaires and behavioural testing in the treatment context (Context A). Renewal of fear was assessed one week after treatment by comparing fear responding towards a spider in a novel virtual context and the original treatment context. It was hypothesized that participants receiving the stress intervention, would demonstrate less phobic symptoms, physiological arousal and behavioural avoidance in the original treatment context, one-week and 3-months after treatment, and show less of a return of fear in the novel context relative to those receiving the control procedure. Noradrenaline and cortisol were predicted to mediate the relationship between stress and improvement scores on each measure. Heightened attention towards the spider throughout treatment and greater expectancy violation at the start of treatment were hypothesized to separately mediate the stress effects on treatment outcomes.

2. Method

2.1 Participants

Fifty-two people with heightened fear of spiders aged between 18 and 60 participated in this study. A total of 105 were assessed for eligibility and 53 participants were excluded as they did not meet eligibility criteria or were unavailable to participate. Eligibility criteria included individuals who fulfilled DSM-5 criteria for a specific phobia of spiders. Exclusion criteria included: the presence of chronic medical illness, substance abuse problems, psychosis, pregnant or lactating women and current engagement in psychological or pharmacological treatment. Of

the 52 participants who were enrolled in the study, 15 were excluded for analysis: 14 because they consumed medication that interfered with cortisol secretion (Subramaniam, LoPilato, & Walker, 2019), and one because they were a significant outlier on all primary outcome measures (SPQ, FSQ, BAT, refer to measures below). The final sample consisted of 37 participants, of whom 17 were in the stress condition (6 males, 11 females) and 20 in the control condition (5 males, 15 females). Based on effect sizes reported in previous studies (Soravia et al., 2014), a prior power analysis was conducted using G*power version 3.1 for sample size estimation. With a significance criterion of a=.05 and power = 0.8, a minimum sample size of N= 34 was required to detect a large effect size, for an ANCOVA analysis.

2.2 Measures

2.2.1 Self-report measures

Fear of Spider Questionnaire (FSQ) and Spider Phobia Questionnaire (SPQ). (See Study 2 for details)

Depression Anxiety and Stress Scales-21 item version. (See Study 2 for details).

Spielberger State-Trait Anxiety Inventory. (See Study 2 for details).

Subjective Units of Distress. (See Study 2 for details).

Subjective Ratings of Stress, Pain and Unpleasantness. (See Study 2 for details).

Subjective US-expectancy Ratings. A subjective measure of the extent to which participants expect an aversive outcome to occur in the presence of a spider. This was used to index the strength of the CS (spider)- US (danger) contingency throughout exposure therapy. Fear outcomes were determined at the start of behavioural assessments as well as exposure tasks

and could include responses such as “the spider will jump on me” or “bite me”. Participants provided expectancy ratings using a ten-point Likert scale in response to two questions: “How much fear/distress/disgust will you experience when you see the spider?” (0= no fear at all, 10= extreme fear) and “How likely do you think [*feared outcome*] will occur? (0= certainly not, 10= certainly).

2.2.2 Behavioural and objective measures

Behavioural Avoidance Test (BAT). (See Study 2 for details).

Heart rate measurement. (See Study 2 for details).

Saliva Measurement. (See Study 2 for details).

Attention Measurement. Attentional data was collected with the Tobii eye-tracker headset (HTC VIVE Pro Eye). A unique program was written for this study which included 5-point calibration measures and a specified region of interest (ROI) to quantify attentional maintenance towards the spider. Data obtained was sampled at a rate of 120 Hz, which included a ‘true’ or ‘false’ value reported every 120 seconds to indicate gaze within or outside the ROI, respectively. A proportion of eye gaze within the ROI was calculated for each trial (as a measure of total attention), as well as for a segment within each trial (to capture critical moments). Critical moments for each trial (e.g., touching the spider, lifting the lid of the container) was defined as an average arm length away from the spider (i.e., 0.75m).

2.3 Design and Procedure

The study procedure largely replicated the pilot study (see Study 2). However, small modifications to the stress procedure and renewal test were incorporated to improve the method

based on the pilot findings. Also, a number of changes had to be made due to unforeseen COVID-19 restrictions; these included use of masks for all experimenters and exclusion of 6-month follow-up assessment as majority of study participants were unable to be contacted and were not permitted to attend face-to-face assessments.

In this randomized, double-blind control trial enrolled participants were invited to complete baseline assessments of the severity of their symptoms, followed by two virtual reality exposure therapy sessions to spiders (one week a part). They were then asked to complete two follow-up assessments; the first, one week after treatment (post-treatment) and the second, 3-months after the final treatment session (3-month follow-up). See Study 2 for details of the procedure at each study visit.

Similar to Study 2, baseline measures included subjective questionnaires (DASS-21, STAIT-, SPQ, FSQ, stress and saliva-related questions) and objective measures (psychophysiological, salivary cortisol/alpha amylase and a behavioural avoidance test). Following pre-treatment assessment, participants were randomly assigned to receive a stress or control procedure 25 minutes prior to each exposure sessions, when cortisol levels are at their peak (Schwabe, Haddad, & Schachinger, 2008; Schwabe & Schachinger, 2018). Exposure therapy occurred between 12pm and 6pm to control for the circadian rhythm of cortisol (specifically elevated cortisol levels in the morning). During exposure sessions, participants completed graded tasks involving interaction with a virtual reality spider and were asked to provide US-expectancy and SUDs ratings before the beginning of every task and approximately every 1-2 minutes thereafter. One-week later participants completed subjective questionnaires and a renewal test (assessed in both the original treatment context and a novel one) using the

BAT. Approximately 3-months later, participants completed the subjective questionnaires and the BAT to assess spontaneous recovery of fear. See Study 2 for more detail.

2.3.1 Stress or Control Procedure

Participants in the stress group completed the socially evaluated cold-pressor test (SECPT) which involved placing their dominant hand into an esky filled with ice cold water (0-2°C) for 3 minutes whilst being recorded by a video camera and observed by a researcher. Relative to Study 2, the positioning of the camera was modified to be in closer proximity (within 30cm) to the participants at eye level to ensure self-monitoring and optimal cortisol response. In addition, confederates were instructed to avoid forms of reinforcement such as smiling during the task to amplify the socio-evaluative based on previous guidelines for use of behavioural stress interventions (Schwabe & Schachinger, 2018). In contrast, participants in the control group immersed their hand into warm water (35-37 °C) for 3 minutes with no videorecording or researcher present. See Study 2 for further details of each procedure.

2.3.2 Post- and follow-up assessments:

Renewal Test: Relative to Study 2, participants were tested for renewal of fear using the BAT in two virtual reality contexts: the original treatment context (virtual kitchen), and an unfamiliar context (virtual outdoor garden) at post-treatment. All participants completed the BAT in the original context first, followed by the unfamiliar context. This order was selected to test for successful extinction retention to ensure a renewal effect was not accounted for by a failure to retain the extinction memory.

Spontaneous Recovery: Twelve weeks after the final treatment session, participants completed self-reported questionnaires (SPQ, FSQ, DASS-21, STAI) and the BAT in the original treatment context (virtual Kitchen).

2.3.3 Stress hormone analysis

Saliva analyses were performed by Stratech Scientfic APAC and were stored at -20 until biochemical analysis. See Appendix A for details.

2.4 Statistical analysis

Data were entered into the SPSS statistics package for Macintosh (v.26). To assess for any group differences in demographic and clinical characteristics, independent sample t-tests were conducted for continuous variables and chi-squared analyses for categorical variables. Repeated measures ANOVAs were used to analyze effects of VR exposure-based therapy on treatment outcomes, with treatment scores (FSQ, SPQ, BAT) at certain time points (pre, post and follow-up), as within-subject variables. To assess stress-induced changes in treatment outcomes two-way repeated measures ANCOVAs were used with group as the independent variable, follow-up treatment scores (FSQ, SPQ, BAT) at 3-month follow up as the dependent variables, and corresponding pre-treatment scores, age and gender as a covariate. Group comparisons in cortisol, noradrenaline and subjective ratings following the stress/control procedure were analysed with independent sample t-tests. Significant ANCOVAs were followed by Bonferroni-adjusted *post-hoc* tests and all t-tests were two-tailed. To examine proposed mechanisms (cortisol, noradrenaline, expectancy of harm and attention) of the effects of group (stress or control) on treatment outcomes (FSQ, SPQ and BAT), the PROCESS procedure for SPSS (Hayes, 2012) was used. PROCESS produced direct and indirect effects for mediation and

models were tested controlling for age and gender. A measure of effect size using partial eta-squared (η^2) was reported for all primary outcome variables. The magnitude of the effect size was categorized as small (0.01), medium (0.06) or large (0.14) based on established criteria (Cohen, 2013; Olejnik & Algina, 2000). Cohen's d effect sizes were calculated for independent samples t-tests and categorized as small (0.2), medium (0.5) and large (0.8).

3. Results

3.1 Participant Characteristics

Table 1. on the next page presents participant characteristics. The stress and control groups did not significantly differ in demographic or clinical characteristics including age, gender, pre-treatment scores as well as baseline salivary cortisol and alpha amylase level (all $p>.05$;**)**.

Table 1. Demographic and Clinical characteristics, and Pre-treatment Baseline Measures.

	Stress Group	*Control Group*	*Significance*
Age	28(8.97)	29(9.35)	.567
Gender	65% Female	75% Female	.719
DASS21: Stress	6.76 (4.82)	7.35(4.52)	.706
DASS21: Anxiety,	3.47(3.06)	3.20(2.55)	.771
DASS21: Depression	2.88(2.55)	5.15(5.16)	.094
STAI Total	43.00(5.32)	44.30(5.39)	.467
FSQ Total	96.633(17.36)	94.75(20.39)	.766
SPQ Total	11.78(1.93)	11.57(2.81)	.796
BAT Expectancy	7.41(1.54)	6.50(1.79)	.109
BAT SUDs	6.47(2.07)	6.10(1.34)	.478
BAT Behavioural Score	2.35(.86)	2.3(.80)	.908
Baseline cortisol Day 1	.162(.06)	.13(.04)	.060
Baseline sAA Day 1	89.95(45.05)	77.88(53.89)	.470

Note: Data presented as mean (SD), BAT, Behavioural Avoidance Test; DASS21,

Depression, Anxiety, Stress Scale-21; FSQ, Fear Spider Questionnaire; SPQ, Spider Phobia Questionnaire; STAIT, State- trait anxiety inventory; SUDs, Subjective Units of Discomfort

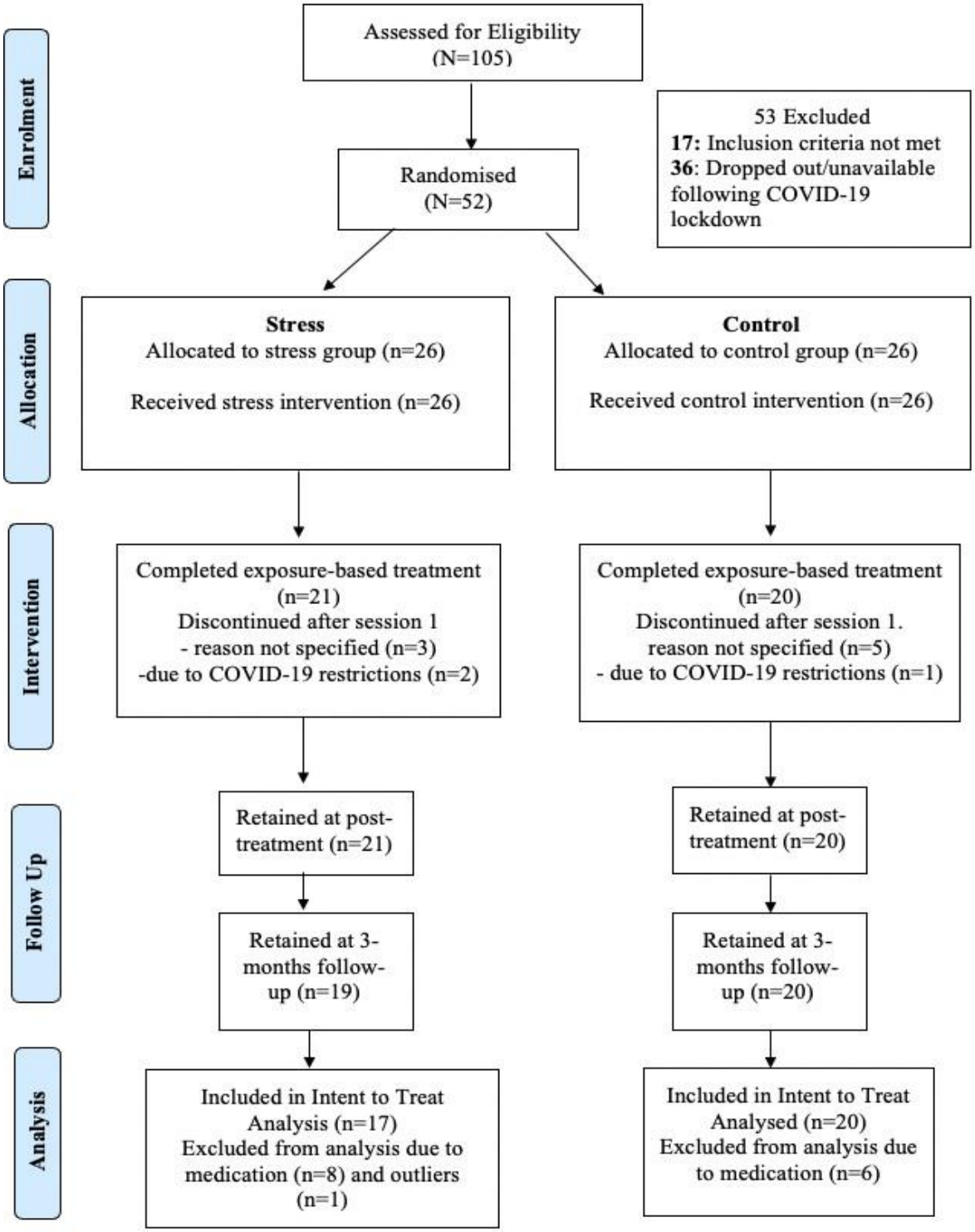

Figure 1. CONSORT randomisation flow diagram of participants progress throughout the recruitment phases of the RCT.

3.2 Stress manipulation check

Two significant outliers were excluded from the cortisol analysis (see Appendix D for details), however the exclusion of this data did not change the pattern of results on the primary outcomes (SPQ, FSQ and BAT). Therefore, they were included in the remaining analyses. The cortisol and sAA analysis revealed there were no significant group differences in baseline cortisol or sAA levels at Session 1 or 2 ($p>.05$). Significantly higher cortisol levels at Session 1 were seen in the stress group relative to the control group 25-30min after the stress/control procedure (T2) ($t_{35} = 3.92$, $p<.001$) (see Figure 2. S1), and this was of a large effect size (Cohen's d=1.3, CI [.05-.15]). In contrast, no significant group differences were observed in cortisol concentrations after the stress/control procedure at Session 2 ($p>0.5$), although a medium effect size (d=0.58, CI [-.01-.10]) was found. The direction of the findings in Session 2, however, is consistent with the type of stress or control procedure administered; the stress group increased, and control group decreased in their cortisol levels from baseline to after the stress/control procedure (see Figure 2. S2). Analysis of sAA did not reveal any group differences 1 min after the stress/control procedure ($p>.05$, d= 1.9, CI [-63.5-35.53]) or immediately after exposure therapy ($p> .05$) at Session 1. Whilst no group differences were observed 1 min after the stress/control procedure at Session 2 ($p >.05$), a medium to large effect size was found (d=.06, CI [-8.8-43.497]). Similarly, no group differences immediately after exposure therapy were observed ($p>.05$, d=0.29, CI [-16.4-41.5]).

Moreover, participants in the stress group experienced the behavioural procedure to be more stressful (S1: $t_{35} = 8.54$, $p<.001$, d=2.8; S2: $t_{35} = 6.56$, $p<.001$, d=1.9), painful (S1: $t_{35} = 16.20$, $p<.001$, d= 5.1; S2: $t_{35} = 8.42$, $p<.001$, d= 2.7), and unpleasant (S1: $t_{35} = 8.69$, $p<.001$, d=2.8 ; S2: $t_{35} = 8.04$, $p<.001$, d=2.6), than the control group at Session 1 and 2, which were all

found to be of a very large effect size. See Table 2. for means, standard deviations and p-values of ratings, cortisol and sAA levels). Stress and control participants did not significantly differ in the total number of tasks and trials completed across exposure sessions (p>.05).

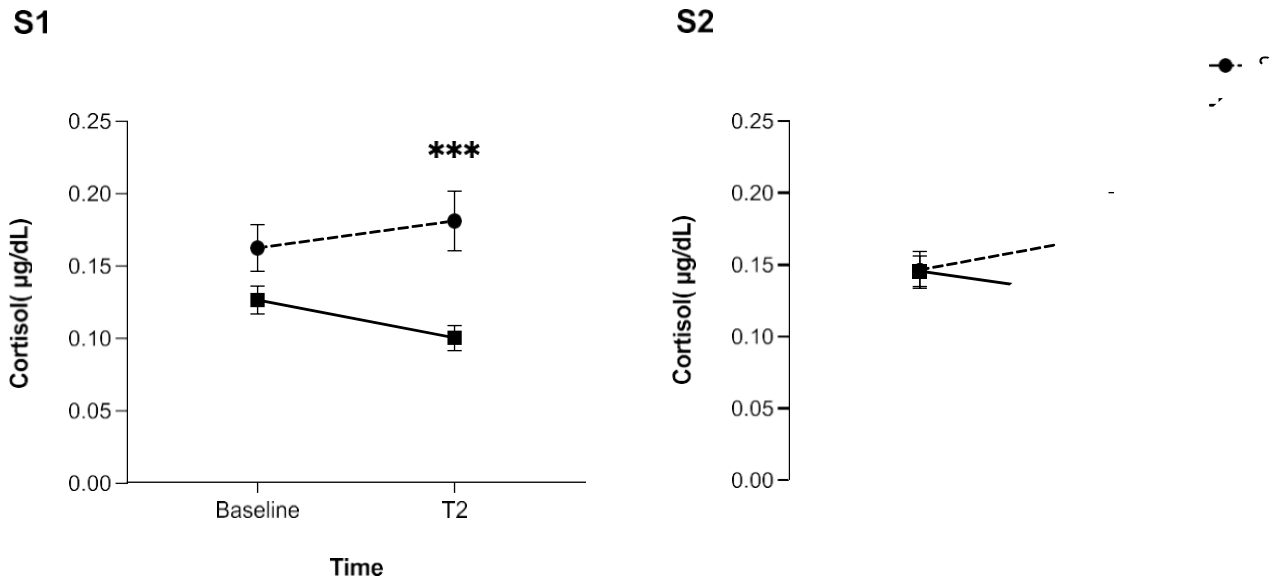

Figure 2. Cortisol Response at Session 1 (S1) and Session 2 (S2), across time points; Baseline and 25-30min after stress or control procedure (T2). Note: Error bars represent standard error of means and *** P-value <.001 indicates significant difference between stress and control group at a certain time.

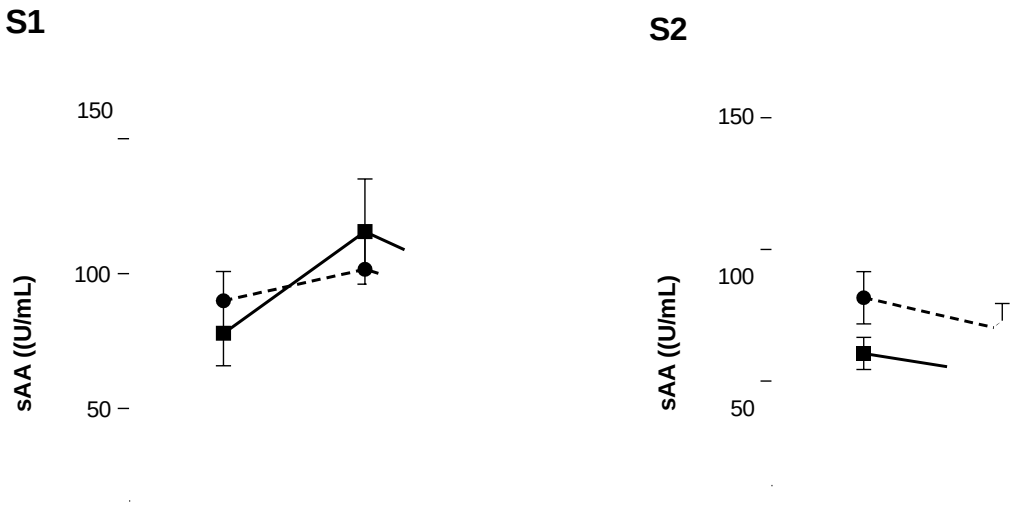

Figure 3. Noradrenergic Response at Session 1 (S1) and Session 2 (S2), across time points; Baseline,1 min. after stress or control procedure (T2), and immediately after exposure therapy (T3). Note: Error bars represent standard error of means.

Table 2. Stress hormone levels and subject ratings.

	Stress (n=17)	*Control (n=20)*
Session 1		
Cortisol baseline	0.162 (0.07)	0.126 (0.04)
Cortisol T2	**0.181(0.08)*** **	**0.100 (0.04)**
sAA baseline	89.946 (45.10)	77.88 (53.87)
sAA T2	101.614 (54.26)	115.608 (42.89)
sAA T3	86.070 (54.37)	91.607 (54.03)
Unpleasant	**8.059 (2.70)*** **	**1.148 (2.13)**
Painful	**8.059 (2.05)*** **	**0.250 (0.64)**
Stressful	**7.000 (2.45)*** **	**9.00(1.89)**
Session 2		
Cortisol baseline	0.147 (0.05)	0.146 (0.05)
Cortisol T2	0.172 (0.11)	0.126 (0.04)
sAA baseline	91.88 (40.96)	70.687 (27.52)
sAA T2	79.760 (40.69)	62.432 (37.66)
sAA T3	92.375 (37.38)	79.805 (47.54)
Unpleasant	**6.804 (2.43) *** **	**1.109 (1.88)**
Painful	**6.395 (2.40) *** **	**0.859 (1.57)**
Stressful	**5.487 (2.43)***	**1.059 (1.66)**

Note. Means (SD). ***p<.001 or *p<.05 indicates a significant difference between stress and control groups (independent t-test). Stressfulness, painfulness and unpleasantness were rated on a scale from 0 (not at all) to 10 (very much).

3.3 Effects of virtual reality exposure therapy

To examine the success of virtual reality therapy on treatment outcomes, three one-way repeated measure ANOVAs were conducted to examine effects on the whole sample across time (pre, post and 3-month follow up) for each of the outcome measures (FSQ, SPQ, BAT). The analysis revealed spider phobic symptoms significantly varied across time as measured with the FSQ ($F_{1.5, 36}$= 111.60, p<.001, η^2 = .756), SPQ ($F_{2, 72}$ = 75.92, p<.001, η^2 = .678), and BAT ($F_{1, 36}$ = 305.567, p<.001, η^2 = .895), and these were all found to be of a very large effect size. Post-hoc tests showed significant reductions from pre- to post-treatment in FSQ (p<.001, d=2.4, CI [34.3-49.59]), SPQ (p<.001, d=1.9, CI [3.8-5.7]) and BAT scores (p<.001, d=4.1, CI [2.5-3.1]), and from pre-treatment to 3-month follow up in those measures (FSQ, p<.001, d=2.3, CI[35.6-50.8]; SPQ, p<.001, d=1.9, CI [3.8-5.7]; BAT, p<.001, d= 4.2 CI [2.5-3.1]). No significant fear symptom change was found from post-treatment to 3-month follow up in any measure (FSQ, p>.05, d=0.07, CI [-5.4- 2.9]; SPQ, p>.05, d= 0.02, CI [-0.8- 0.7]; BAT, p>.05, d=0.35, CI [-.005 -.329]). These effects suggest that the virtual reality exposure therapy was effective in improving spider fear outcomes, and that these outcomes were sustained 3 months later. See supplementary file in Appendix C for means and standard deviations.

3.4 Stress effects on relapse

3.4.1 Effects of Stress Manipulation on Spontaneous Recovery of fear

Stress-induced changes in treatment outcomes (FSQ, SPQ, BAT) across groups were examined using a series of 2 x (2) measures ANCOVAs, with pre-treatment scores, age and gender as covariates, and post-treatment and 3-month follow-up as within-subjects comparators. There were main effects of group for spider fear. That is, participants in the stress group reported

significantly less phobic symptoms of a large effect size across post-treatment and 3-month follow-up assessments, as measured with the FSQ ($F_{1,32,}$ = 4.40, p= .044, η^2 =.121), and SPQ ($F_{1,32,}$ = 5.55, p= .025, η^2 =.148) (Figure 4.), compared to the control group. No significant interaction effects were observed, indicating differences between groups were maintained over time. Note, removing age and gender covariates did not change the findings.

Three BAT outcomes were tested: BAT avoidance score, heart rate during BAT, and BAT speed. There was no main effect of group on behavioural avoidance (measured with a BAT score) (p=.383, η^2 =.024) or BAT heart rate (p = .830, η^2 =.001). However, there was a main effect of group on BAT speed, which was of a medium effect size. That is, those in the stress group approached the spider with greater speed during the BAT across follow-up assessments (post-treatment and 3-months follow-up), relative to the control condition ($F_{1,32}$ = 4.31, p= .046, η^2 = .119) (Figure. 5). No significant interaction effect was observed, indicating differences between groups on BAT speed were sustained over time. These findings demonstrate pre-exposure stress promotes greater improvements in phobic symptoms in the short- (i.e., one week-post-treatment) and long-term (i.e., 3-months follow up), relative to standard exposure therapy, but its effects on behavioural indices of fear are mixed.

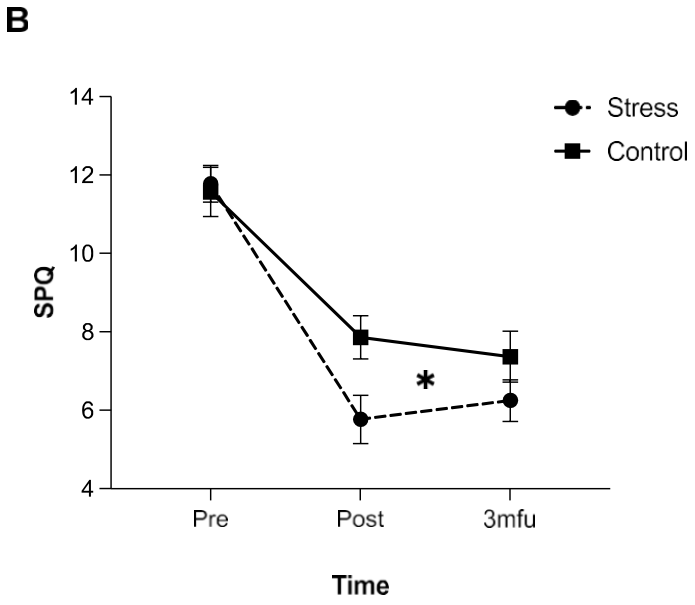

Figure 4. Self-reported fear overtime. This includes fear measured at pre-treatment, post-treatment and 3-month follow-up, by (A) the fear of spider questionnaire (FSQ), and (B) the spider phobia questionnaire (SPQ). Error bars represent standard error of the means and * P-value <.05 indicates significant difference between stress and control group across time points.

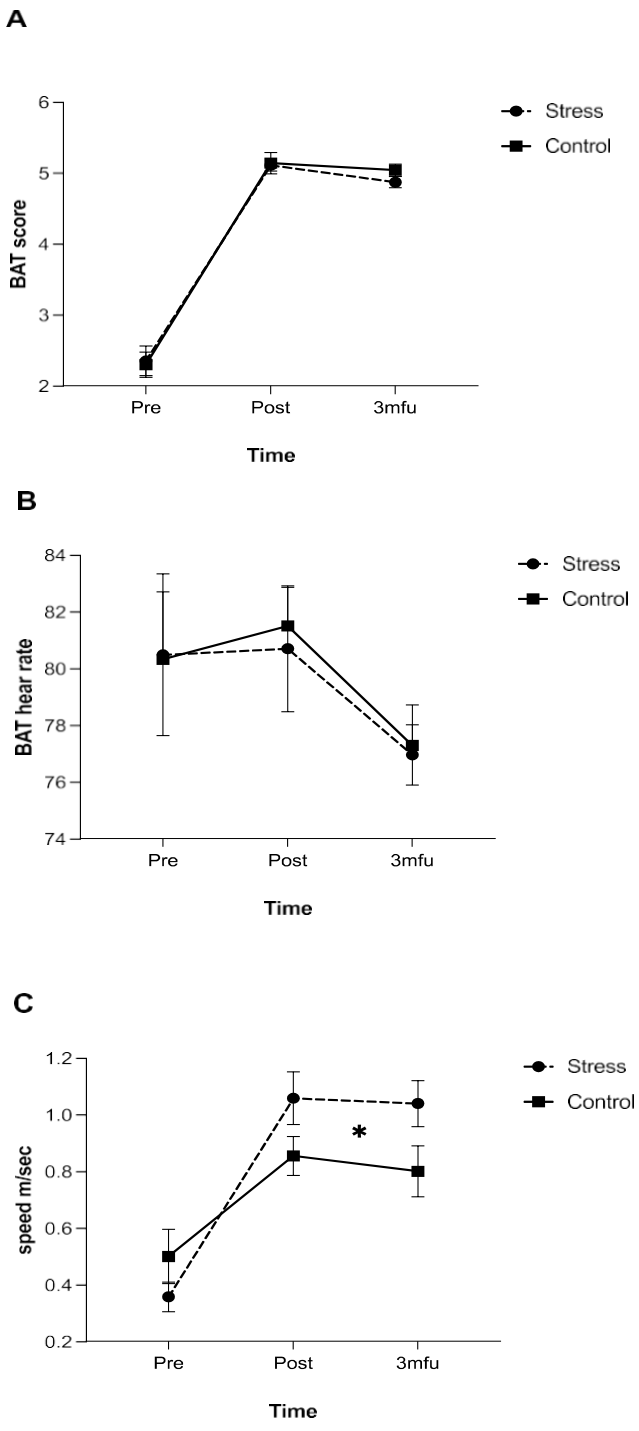

Figure 5. Participants performance on the BAT during the renewal test at 7-months follow-up. This includes performance during the Behavioural avoidance test (BAT) at pre-treatment, post-treatment and 3-month follow-up, measured by (A) behavioural score (B) heart rate, and (C) speed approaching the spider. Error bars represent standard error of the means and * P-value <.05 indicates significant difference between stress and control group across time points.

3.4.2 Effects of Stress on Renewal of fear

To assess renewal of fear participants were tested in the original treatment context A, followed by the novel context B. A series of 2 x (2) ANCOVAs, controlling for age and gender, were used to compare group differences in BAT scores, BAT speed and BAT heart rate, between Context A and B. The findings revealed no significant group x context interaction effect as measured with behavioural avoidance (BAT score) ($F_{1,33,}$ = 2.372, p=.133, η^2 =.067), BAT heart rate ($F_{1,33,}$ = .025, p=.877, η^2 =.001), and BAT speed ($F_{1,33,}$ = 3.802, p=.060, η^2 =.103). There was also no main effect of group for BAT score (p=.351, η^2 =.026), heart rate (p=.750, η^2 =.003) or speed (p=.534, η^2 =.012). However, a significant main effect of context was observed in BAT scores, ($F_{1,33,}$ = 7.717, p=.009, η^2 =.190) and heart rate, ($F_{1,33,}$ = 6.750, p=.014, η^2 =.170); but not speed ($F_{1,33,}$ = .021, p=.887, η^2 =.001). That is, participants' BAT score decreased, and heart rate increased during testing in a novel context B (both of a large effect size), relative to the treatment context A across groups. This suggests a renewal effect occurred in both groups (see supplementary file, Appendix C, for figures), but that stress did not prevent renewal of fear in a novel context.

3.5 Stress effects during exposure therapy

3.5.1 Effect of Stress Manipulation on US-expectancy ratings, SUDs and heart rate

To assess expectancy of harm violation at the start of treatment, a 2 x (2) ANCOVA was conducted to compare group differences in start and end expectancy ratings during the first task, controlling for age and gender. Whilst the main effect of group ($F_{1,33,}$ = 3.91 p= .056, η^2 = .106) and group x time interaction ($F_{1,33,}$ = 3.82 p= .059, η^2 = .104) were not significant, they were both of a large effect size and approaching significance. Therefore, post-hoc tests were

performed, revealing that controlling for age and gender, the stress group had significantly higher expectations of harm which was of a large effect size, relative to the control group, at the start ($F_{1,33,}$ = 4.53 p= .041, η^2 = .121) but not the end ($F_{1,33,}$ = 1.05 p= .313), of the first task.

Similar ANCOVAs were conducted for self-reported anxiety (as measured by SUDs) and heart rate, but there was no main effects of group or group x time interaction effects p<.05.

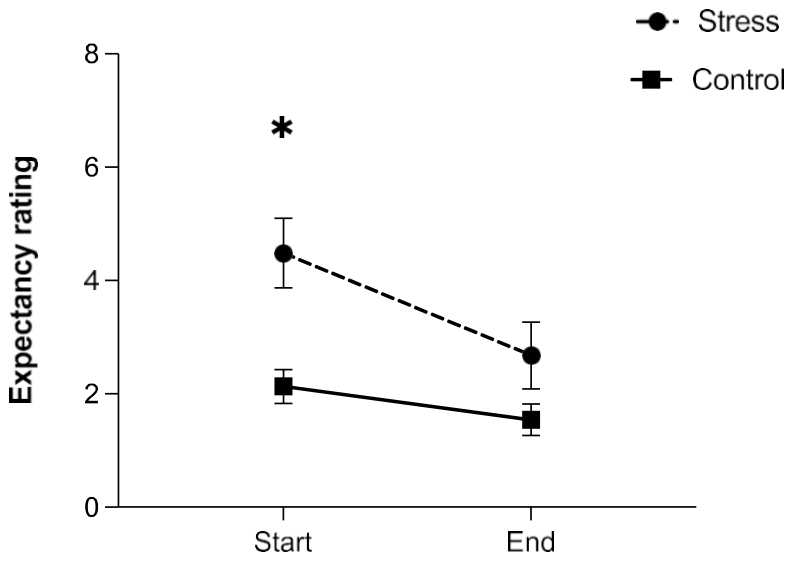

Figure 6. Expectancy of harm ratings, during Task 1; Group differences in start and end expectancy ratings were analysed during the first task. Note: Error bars represent standard error of means.

3.5.2 Effect of Stress Manipulation on Attention

A 2 x (3) way ANCOVA (with age, gender, and number of trials as covariates) was used to assess group differences in the proportion of eye gaze towards the spider across the first three tasks (as these tasks were completed by most participants). No main effect of group (p= .289, η^2 =.035) or task (p= .205, η^2 =.097), or significant group x task interaction (p= .232, η^2 =.090) was found, indicating stress did not influence attention towards the spider across or between tasks.

However, the group x interaction effect was found to be of a medium to large effect size, suggesting a larger sample size may be able to detect possible group differences that vary across tasks. See supplementary file in Appendix C for figure.

3.6 Testing of Mechanisms

3.6.1 Mediators of stress manipulation on clinical outcomes

PROCESS macros were used to investigate the hypotheses that: 1) both stress hormones cortisol and noradrenaline, and 2) expectancy of harm and attention mediate the effect of stress induction on symptom improvement (i.e., difference scores from pre to post, pre to 3-month follow-up, and renewal contexts, measured by SPQ, FSQ and BAT). Figure 7. and 8. present mediation models for the effect of stress on SPQ outcomes with remaining models displayed in the supplementary file (Appendix C). All models were tested with age and gender as covariates. To reduce the number of variables in the analysis, measures of noradrenaline, cortisol, proportion of eye gaze, and expectancy of harm violation were averaged across session 1 and 2. All averaged variables significantly correlated with their corresponding individual measure at each session ($p<.01$). Cortisol and noradrenaline (measured by sAA) were taken after the stress/control procedure for this analysis.

A) Testing stress hormones as mediators

Short-term spontaneous recovery: Results indicated that group significantly predicted clinical improvements on the SPQ from pre- to post-treatment, $b=-17.947$, $t= -2.492$, $p<.05$, however cortisol and NE did not mediate this relationship. Whilst cortisol was not a mediator, group significantly impacted cortisol, $b=-.077$, $t= -3.927$, $p<.001$, and there was a trend towards cortisol predicting pre-to post treatment outcomes on the SPQ relationship, $b=-12.472$, $t= 1.557$,

p=.05 (see Figure 7.). There was no relationship between group and NE, *b*=-.609, t= -0.037, p>.05, or NE and post-treatment outcomes, *b*= -.004, t= -0.472, p>.05. However, the pattern observed for the FSQ and BAT differed somewhat (see supplementary file, Appendix C). That is, group predicted pre-post-treatment outcomes on the FSQ, *b*=-17.947, t=- 2.492, p=.018, but NE and cortisol did not account for this effect. In contrast, group, cortisol, and NE did not predict pre-post outcomes on the BAT.

Long-term spontaneous recovery: Group predicted long-term treatment outcomes (pre-treatment to 3-month follow up), measured with the SPQ, *b*=-3.201, t= -3.662, p<.001. Cortisol was shown to partially mediate this effect, as the effects of group on cortisol, *b*=-.077, t= -3.927, p<.001, and cortisol on long-term treatment outcomes, *b*=-22.9467, t= -3.508, p<.01 were significant (Figure 7.). Group similarly predicted long-term treatment outcomes measured with the FSQ, *b*=-18.6329, t= -2.467, p<.05. However, cortisol was not a significant predictor of long-term improvements in FSQ scores, *b*=-78.864, t= -1.395, p>.05. BAT scores were not associated with group or stress hormones (see supplementary, Appendix C). These results indicate that group allocation predicted both short and long-term symptom improvements (but not behavioural avoidance), and cortisol partially accounted for the effect of group on long (3-month follow-up), but not short-term (post) symptom improvement.

Renewal: Group did not predict renewal of fear measured by the BAT at post-treatment, *b*=.363, t= 1.184, p=.245. Cortisol was also not related to renewal, however NE predicted renewal of fear. Specifically, higher NE levels were found to predict lower BAT scores (greater behavioural avoidance) in the garden compared to the kitchen context, *b*=.007, t= 2.487, p=<.05. However, given NE was not related to group, it did not mediate the relationship between group and renewal.

B) Testing expectancy of harm and attention as mediators

Short-term spontaneous recovery: There was a trend towards group predicting pre- to post-treatment symptom improvement measured with the SPQ, *b*=-1.718, t= -1.974, p=.057 and also a trend towards group predicting expectancy violation of harm, *b*=-1.387, t= -1.956, p=.059 (Figure 8.). However, there was no relationship between pre-to post treatment outcomes on the SPQ and expectancy violation of harm, *b*=-.172, t= -.862, p>.05, indicating expectancy of harm did not mediate the possible effect of group on post-treatment outcomes.

Group was not associated with attention, *b*=-4.261, t= -1.03, p>.05 and no relationship between pre-to post treatment outcomes on the SPQ and attention, *b*=-.046, t= -1.336, p>.05, was found. This indicated attention was also not a mediator of the effect of group on post-treatment outcomes. These results were generally consistent with post-treatment improvement scores measured by the FSQ and BAT (see supplementary, Appendix C).

Long-term spontaneous recovery: Group did not predict pre-treatment to 3-month follow-up (i.e., long-term) improvement scores measured with the SPQ, *b*=-1.491, t= -1.674, p>.05. Attention and expectancy violation also did not mediate the effects of stress on long-term outcomes measured with the SPQ. That is, long-term treatment outcomes on the SPQ were not related to expectancy of harm, *b*=-079, t= .388, p>.05 or attention, *b*=-.038, t= -1.081, p>.05. There was a trend towards group predicting long-term treatment outcomes measured with the FSQ but not with the SPQ and BAT. However, there was a similar pattern of results to the SPQ in the relationships between long-term treatment outcomes (measured with FSQ and BAT) and attention, and expectancy violation of harm (see supplementary, Appendix C).

Renewal: A trend towards group predicting renewal was found, *b*=.543, t= -1.909, p=.068. However, expectancy violation and attention did not account for the effects of group on renewal.

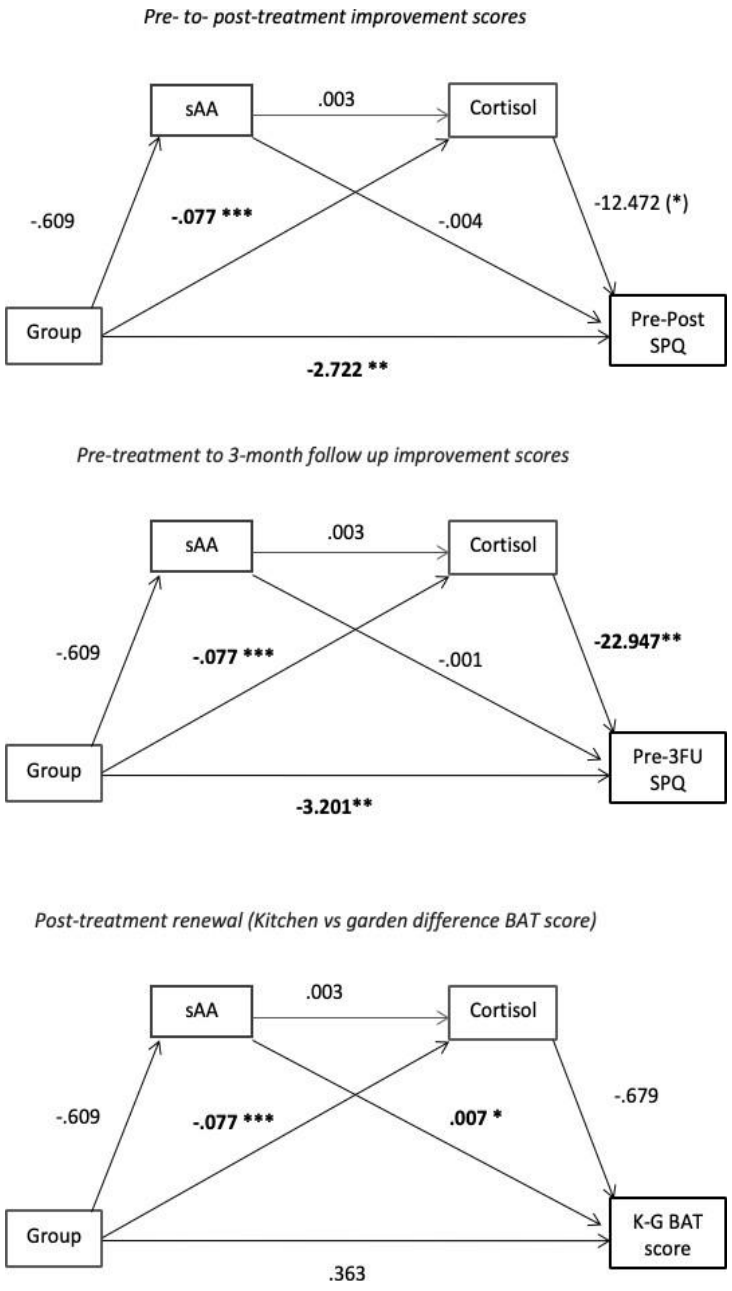

Figure 7. Mediation Model 1 for NE and cortisol mediating the effect of group on symptom improvement from pre- to post-treatment (Pre-Post), pre-treatment to 3-month follow-up (Pre-3FU) measured by the Spider Phobia Questionnaire (SPQ), and difference in behavioural avoidance between the kitchen and the garden context (K-G), measured by the Behavioural Avoidance Test (BAT). Note control variables were age and gender. *** P<.001** P<.01, *P<.05, (*) indicates p-value is approaching significance.

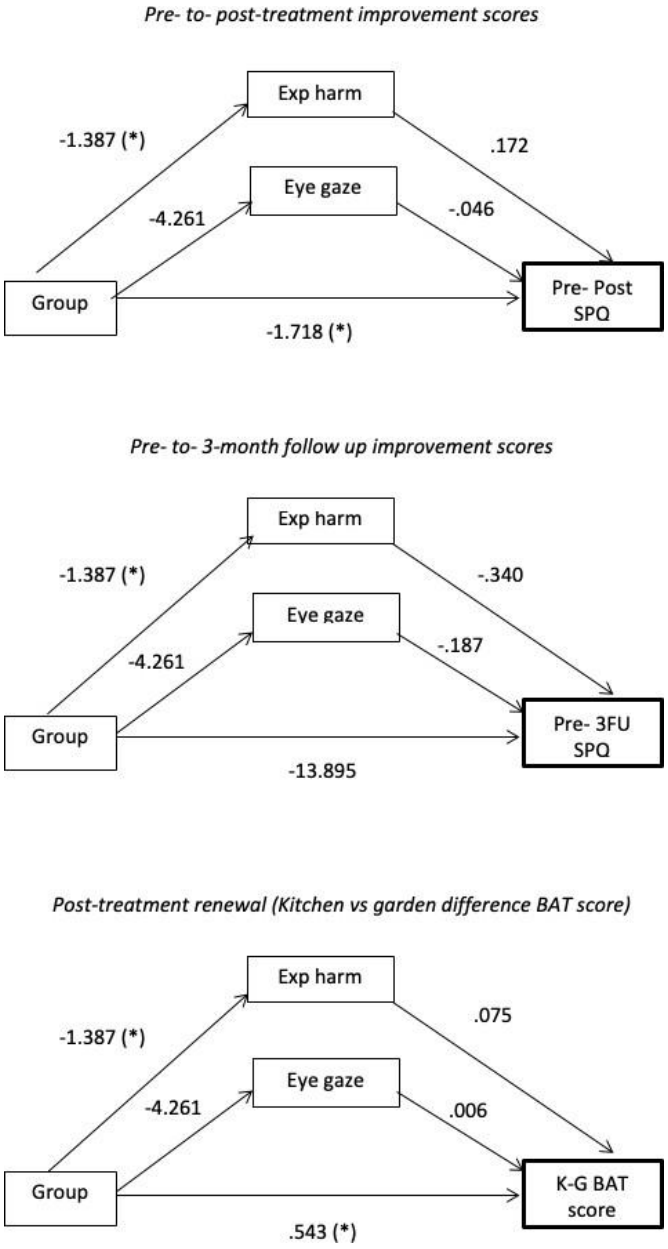

Figure 8. Mediation Model 2 for expectancy of harm violation and eyegaze separately mediating the effect of group on symptom improvement from pre- to post-treatment (Pre-Post), pre-treatment to 3-month follow-up (Pre-3FU) measured by the Spider Phobia Questionnaire (SPQ), and difference in behavioural avoidance between the kitchen and the garden context (K-G), measured by the Behavioural Avoidance Test (BAT). Note control variables were age and gender. (*) indicates p-value is approaching significance.

4. Discussion

This study examined the effects of acute stress on two relapse phenomena, spontaneous recovery and renewal of fear, and tested potential neural (cortisol, noradrenaline) and cognitive (attention and expectancy violation of harm) mechanisms of these effects. Findings revealed acute stress administered via the SECPT prior to exposure, enhanced symptom improvements across post-treatment and 3-month follow-up assessments, as measured with two spider phobic questionnaires (SPQ and FSQ), relative to standard exposure. Stress induction did not influence behavioural avoidance measured with the behavioural avoidance test (BAT), however patients receiving the stress intervention approached the spider with greater speed across follow-up periods, relative to those receiving the control procedure. This demonstrated stress led to a more pronounce treatment outcome which was sustained after 3-months. However, there was no evidence of spontaneous recovery of fear (return of fear from post-treatment to 3-month follow-up) in either group, therefore no conclusions could be made regarding the impact of stress on spontaneous recovery. In contrast, a renewal effect occurred in both groups. That is, both stress and control procedures led to a return of fear in a novel context (B) at post-treatment, relative to the treatment context (A), but there were no group differences in these effects.

Type of condition (stress or control**)** predicted post and 3-month follow-up symptom improvement, in that the stress group showed greater improvement. Cortisol partially accounted for the long but not short-term treatment effects, suggesting other factors could mediate the short-term benefits of stress. Contrary to what was hypothesized, NE, attention and expectancy of harm violation did not mediate the relationship between stress manipulation and treatment outcomes. However, there was a trend towards group predicting expectancy of harm violation at

the start but not the end of treatment, suggesting expectancy of harm may have a role to play in the effects of stress.

Taken together, these findings indicate that acute stress can benefit long-term exposure outcomes, with some indication of cortisol as the mechanism. However, effects do not seem to specifically benefit spontaneous recovery or renewal which are two common concerns with current exposure-based treatments.

The present findings extend previous studies using stress adjuncts to exposure therapy, demonstrating that within a clinical sample, stress effects are maintained at longer follow-up periods but are not resistant to renewal in new contexts, at least in the short-term. This corroborates previous studies demonstrating stress-adjuncts to exposure therapy enhance treatment gains after 1 to 4 weeks (de Quervain et al., 2011; Soravia et al., 2006; Soravia et al., 2014) and are partially consistent with a study that found pre-exposure stress did not generalize its effects on treated stimuli (spiders) towards untreated stimuli (cockroaches) (Zlomuzica et al., 2021). However, present findings did not replicate, experimental studies which found stress prevented context-dependent renewal (Drexler, Hamacher-Dang, & Wolf, 2017; Drexler et al., 2018) and another study which did not establish a renewal effect in either stress or control groups (Merz, Hamacher-Dang, Stark, Wolf, & Hermann, 2018).

Discrepancies between the present findings and above experimental studies may be explained by methodological differences. This includes the testing context (novel vs fear learning context), type of stressor (pharmacological or behavioural intervention), characteristics of the sample (clinical vs healthy adults), conditions around testing that influence cortisol (stress, prior exercise, food and alcohol consumption), or timing of recall and relapse testing (short vs

long-term recall). Interestingly, higher NE levels were associated with a greater renewal effect in the present study, suggesting higher NE levels may be responsible for the observed renewal effects. This is in line with research indicating NE promotes memory accuracy by strengthening amygdala-hippocampal connections increasing the specificity of contextual memories, which is in contrast to the enhanced memory generalization effects of cortisol (Bahtiyar, Gulmez Karaca, Henckens, & Roozendaal, 2020). Alternatively, studies have shown that the context-dependency of emotional memories lead to accelerated weakening of their context-dependency with time (Cox, Meeter, Kindt, & van Ast, 2022). Therefore, another possible explanation is that stress enhances the generalization of extinction memory in the long-term and the present study was not able to capture this effect after one week when renewal was assessed. Future studies should assess the effects of stress on renewal of fear at longer follow-up periods.

We examined whether stress hormones of cortisol and NE mediated treatment effects. Indeed, cortisol mediated the effect of stress on long-term treatment gains, reinforcing the critical role of cortisol in the consolidation of emotional memories. However, cortisol did not mediate short-term treatment outcomes, suggesting short-term benefits of stress could be underpinned by different mechanisms. In contrast to prior research concluding NE is critical for the memory-enhancing effects of stress, no relationship between NE and treatment gains was found. It may be that we were not able to detect NE effects in the present study, even if they were present. This would explain the absence of group differences in NE. Since NE arousal during extinction learning is associated with less fear at retest and facilitates the consolidation of emotional memories (Cain, Blouin, & Barad, 2004), the timing of NE sampling may have been too early to detect increases that predict treatment outcomes. Another consideration is that NE may uniquely exert more immediate effects on extinction learning (Wade, Blackley, & Felmingham, 2013)

than in the long-term. Future studies could measure NE throughout extinction learning and focus on disentangling the role of NE in the stress-augmentation of fear extinction, particularly within clinical populations.

The study findings revealed attention and expectancy of harm were not mechanisms of the effects of stress. The absence of stress effects on attention is in opposition to studies that show stress enhances attentional and cognitive control functioning (Beste, Yildiz, Meissner, & Wolf, 2013; Chajut & Algom, 2003; Kofman, Meiran, Greenberg, Balas, & Cohen, 2006). One possible explanation for this may be associated with the lack of observed group differences in the release of NE. It has been shown that when NE and cortisol are released simultaneously, cortisol can predict measures of attention, suggesting an increase in NE release is required to facilitate the effects of cortisol on attention (Skosnik, Chatterton, Swisher, & Park, 2000). Moreover, the time-dependent physiological effects of the behavioural stress task could also be a consideration. That is, the stress response may have subsided during the time of exposure and potential effects of stress may not have been captured across all the tasks. Future studies could compare eye gaze at the beginning of exposure between groups, use a shorter exposure duration or compare changes in attention across time.

Moreover, whilst expectancy of harm violation did not predict treatment outcomes, there was a trend towards stress enhancing the expectancy of harm at the start of treatment. This is in accordance with the effects of NE on prediction error (Janak & Corbit, 2011; Wade et al., 2013), but contradicts studies which show cortisol attenuates expectancy of harm during extinction learning (Bentz, Michael, et al., 2013). Discrepancies between the current study and previous literature may be explained by different designs, samples, or type of stress administration. For example, Bentz et al. (2013) study found cortisol reduced expectancy of harm in a male-only

sample, which contrasts to the predominately female sample in the present study. Human and animal research indicate sex differences exist in hippocampal learning and amygdala activity (Cahill, 2006), with menstrual cycle and oral contraceptive use modulating the increased activation of these brain regions (Day & Stevenson, 2020). Future studies should assess sex differences including the extent to which sex hormones moderate the relationship between stress and expectancy violation during extinction learning.

4.1 Limitations and Future Directions

Several limitations of the present study should be noted. First the sample was restricted to men and free-cycling woman, with the exclusion of a proportion of participants consuming cortisol-interfering medication, which could limit the generalizability of results. However, these variables which are known to moderate cortisol reactivity, were selected for exclusion to ensure group differences were accounted for by the stress/control manipulation and not confounding factors. Second, given there was no significant group differences in NE levels after the stress/control procedure, future studies could use pharmacological manipulations or other behavioural stressors that lead to a more pronounced arousal to assess its effects (such as exercise) (Bouchet et al., 2017). Alternatively, pharmacological blockers of NE could be considered to isolate the effects of noradrenergic arousal on stress-augmentation of therapy. A better understanding of NE's role in the faciliatory effects of stress on extinction learning is critical from a clinical perspective to identify strategies that optimize arousal symptoms for extinction learning. Future studies should consider the unique and interactive roles of NE and cortisol to delineate the relapse findings. Moreover, studies could assess the effects of pharmacological manipulations of cortisol on relapse as these stressors have been shown to lead to more pronounced cortisol effect, than behavioural stressors. Given the small sample size and

relatively brief follow-up, future studies should include larger sample sizes and longitudinal data with 6-month, 1-year and even 2-year follow-up periods to assess the long-term robust effects of stress-adjuncts to therapy. Investigating the time-dependent effects of stress on renewal and spontaneous recovery of fear will pave the way for relapse prevention strategies.

5. Conclusions

Overall, the current study provides evidence for the enhancing effects of pre-exposure stress on treatment outcomes within a clinical sample of males and females and offers further insights into the potential mechanisms and effects on relapse. Specifically, the findings corroborate cortisol as a mediator of the long but not necessarily the short-term benefits of stress. However, the findings do not support the hypothesis that pre-exposure stress prevents relapse as no reduction in contextual renewal was observed in the stress group, and no spontaneous recovery effect was established in either group to draw conclusions about the impact of stress on spontaneous recovery. Moreover, the hypothesis that NE arousal, attention and expectancy of harm mediate the effects of stress induction on treatment outcomes is not supported by the findings, however there is trend evidence that stress influences expectancy of harm violation during exposure, indicating a potential cognitive role of stress in extinction-based therapy.

Together the findings are promising and point towards potential opportunities for enhancing the long-term success of exposure-based therapy for anxiety disorders. However, they highlight the need for more mechanistic and relapse research to expand the understanding of conditions that govern effective use of stress-adjuncts to exposure therapy.

Chapter 5: General Discussion

This thesis had two primary aims: 1) to investigate the potential for pre-exposure stress to strengthen the durability and generalizability of extinction memories; and 2) to identify and test potential mechanisms that may underlie the therapeutic benefits of stress. In doing so this thesis addressed research questions including: Can pre-exposure stress reduce relapse associated with spontaneous recovery and renewal of fear? When and how does stress impact extinction learning and memory throughout the treatment process? What is the role of stress hormones, noradrenaline and cortisol, in the effects of stress? Does emotional arousal, indexed by levels of noradrenaline, mediate the benefits of stress? Can cognitive processes such as attention and expectancy of harm account for the benefits of stress? To address these questions, a systematic review of stress-augmentation studies was conducted, as well as a pilot study and randomized controlled trial which involved stress exposure prior to virtual-reality exposure therapy for spider phobia. This chapter begins with a summary of the main findings which are discussed within the context of the boarder literature and the theoretical model proposed in chapter 2. Methodological limitations, future directions and clinical implications of the findings are subsequently considered.

1. Summary of findings

The systematic review presented in Chapter 2, generally found that pre-exposure stress facilitated extinction learning and led to less return of fear at follow-up, when compared to control treatments that did not include a stress induction. This was demonstrated primarily by self-reported and physiological indices of fear including expectancy of harm and differential skin conductance response (diffSCR) during learning, and all indices of fear in the long-term. Similarly, the present empirical studies found that pre-exposure stress enhanced clinical

improvements at follow-up periods of up to 7-months in the pilot study, and 3-months in the RCT, relative to standard exposure therapy. There was evidence from the pilot study, that stress administration prevented the return of fear (i.e., spontaneous recovery) at 7-months follow up and that this generalized to a novel context. These long-term benefits of stress were associated with heightened noradrenaline and cortisol shortly prior to and during exposure therapy in the pilot study. There was no evidence that stress induction affected renewal of fear tested in the short-term (i.e., one week after treatment). Cortisol (but not noradrenaline) was shown to mediate the effects of stress in the long-term but not the short-term in the RCT. Regarding potential cognitive mechanisms, there was trend evidence stress enhanced expectancy of harm at the start of exposure therapy but did not affect attention towards the phobic object (i.e., the spider) during exposure therapy. These cognitive processes did not mediate the effects of stress on treatment outcomes.

Taken together, the benefits of stress appear more pronounced in the long-term (several months after treatment) than in the short-term (during exposure therapy and one week after). These novel findings support the hypothesis that pre-exposure stress can enhance the durability and/or retrievability of extinction memories, thereby reducing spontaneous recovery of fear. However, we cannot completely support or reject the hypothesis that stress enhances the generalizability of extinction memories to mitigate context renewal. This is because a context renewal effect was established in one study but not the other. Additionally, there is some evidence that stress may positively affect the generalization of extinction memories in the long-term, based on group differences in fear reduction (in the extinction context) being sustained in a novel context. However, this invites further investigation. The present results suggest that the effects of stress appear largely driven by neural mechanisms affecting memory consolidation

(specifically cortisol), rather than cognitive processes (expectancy of harm and attention) during extinction learning. Whilst noradrenaline, expectancy of harm and attention were not found to be mediators of the effects of stress, it cannot be ruled out that noradrenaline and expectancy of harm have a role to play in the positive effects of stress on extinction. This is because stress induction was found to produce significant changes in both mechanisms and noradrenaline was associated with long-term treatment outcomes in the pilot study.

These studies are the first to demonstrate stress-adjuncts to therapy can lead to greater benefits than standard exposure therapy up to 7-months follow-up and are the first to assess context renewal of fear within a clinical population. Moreover, the pilot study is the first to demonstrate stress-related treatment gains generalize to a novel context in the long-term and the RCT is the first to investigate potential cognitive processes that could underlie the therapeutic effects of stress. The specific long-term (but not short-term) mediation of stress effects by cortisol, is a particularly novel finding of this thesis.

2. Review of the Integrated Model of Stress-augmentation from Chapter 2

Based on the findings of the systematic review presented in Chapter 2, a hypothesis-generating model, the 'Integrated model of stress-augmentation,' was proposed to identify potential underlying mechanisms of the stress effects on extinction learning and memory (see Figure 1.). This model was used as a framework for testing unique and putative mechanisms of stress, and the findings of the empirical studies of this thesis will be discussed with reference to this model and prevailing literature. Briefly, the model proposes there are two pathways in which cortisol and noradrenaline are associated with the stress response to enhance long-term extinction memory. Firstly, stress can directly enhance memory consolidation by boosting synaptic

plasticity over time (Pathway 1). This pathway implies stress effects would be observed after some time has passed since extinction occurred. Secondly, stress can directly enhance extinction learning to strengthen memory in the long-term (Pathway 2). This pathway implies stress effects would be observed immediately during exposure/extinction learning and in the long-term. Within Pathway 2, there are also two ways in which stress may promote learning, depending on the level of cortisol and NE. Firstly, stress may enhance emotional arousal (driven by NE) which may increase expectancy of harm and attention to threat to maximize extinction learning. Secondly, stress may suppress fear memory to reduce avoidance and enhance maintenance of attention (driven by cortisol).

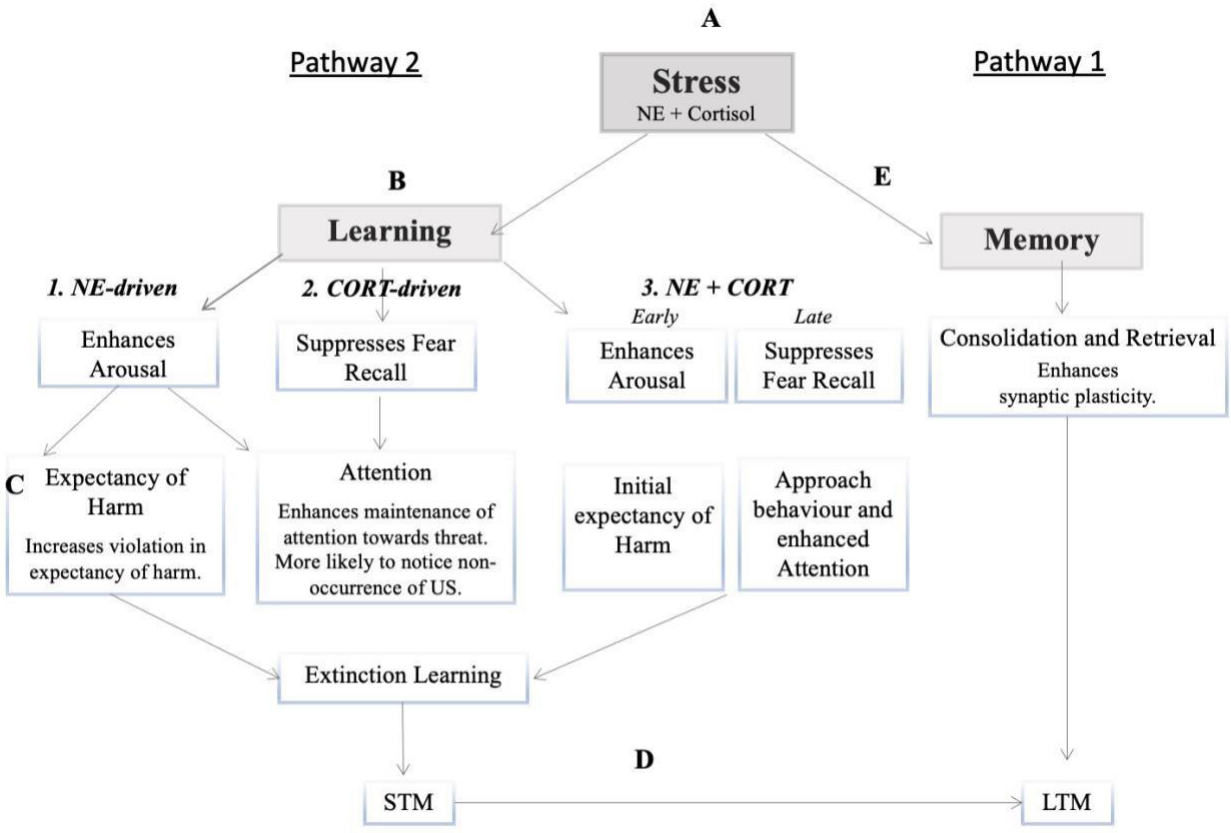

Figure 1. Integrated Model of Stress-augmentation

3. Effects of stress on spontaneous recovery of fear and long-term memory consolidation

This research has provided support for the memory-enhancing hypothesis of stress presented in the 'Integrated cognitive model of stress-augmentation' and other models of stress and memory, which posit stress enhances extinction consolidation (de Quervain, Schwabe, & Roozendaal, 2017; Maren & Holmes, 2016). It was demonstrated in the pilot study that the stress group improved in their treatment outcomes from 3- to 7-month follow-up, compared to the control group who showed a decline in their clinical outcomes, indicating stress prevented the spontaneous recovery of fear. These long-term effects of stress were also reflected in the time-dependent group differences in fear responding during the behavioural avoidance test (BAT). That is, group differences in subjective ratings of distress (SUDs) and heart rate during the BAT emerged in the long-term (7-months follow-up) but not the short-term (one week after treatment), suggesting stress may strengthen the effects on memory with time. In fact, the general finding of the systematic review (Chapter 2) that the benefits of stress are observed by all indices of fear in the long-term and less robustly observed in the short-term, supports this hypothesis. Further, the present findings revealed stress hormones, noradrenaline and cortisol, are related to long-term but not short-term treatment outcomes (in the pilot study) and mediated by cortisol only in the long-term (in the RCT), provide further support for the delayed effects of stress on long-term memory (Pathway 1).

The above findings are consistent with the timing of long-term changes in synaptic plasticity (Kandel, 2001), pertaining to the pathway in our model where stress has direct effects on long-term memory. Specifically, successful long-term stabilization and storage of memory requires alteration of synapses over weeks, months and years, and this process is enhanced by components of the stress response (McGaugh and Roozendaal, 2002). Growing evidence

indicates that stress enhances memory consolidation and synaptic plasticity by modulating cell signaling and structure as well as ion channel properties (Karstet al. 2002; Revestet al. 2005; Bisazet al. 2009). In turn, enhanced memory for events preceded by stress exposure results in greater retrieval, which may explain the pronounced differences between the groups at 7-months follow-up, relative to 3-months follow-up. However, as we were unable to test the return of fear at 7-months follow up in a larger sample (in the RCT) due to COVID-19 restrictions and attrition, this argument cannot be stated with confidence and requires further investigation.

Conversely, the other pathway of the 'Integrated cognitive model of stress-augmentation' suggests that stress modulates processes during extinction learning to produce a stronger memory in the short and long-term. This is plausible as findings of the RCT revealed group differences in clinical symptoms as early as one week after treatment and these differences were sustained at 3-months follow-up. This is consistent with clinical studies that have demonstrated stress-related changes during extinction learning enhance memory of this learning in the short and long-term (de Quervain et al., 2011; Soravia et al., 2006). Fundamentally, however, this pathway of the model suggests that stress-related changes during extinction learning, at least in part, account for the effects of stress on long-term treatment outcomes. There is some evidence in the present thesis that this could be the case. Specifically, the systematic review found that stress generally facilitated extinction learning, and this was indicated by reduced fear responding and US-expectancy ratings during extinction. Similarly, in the RCT, pre-exposure stress was shown to enhance expectancy of harm at the start of exposure therapy, indicating stress had some immediate effect on learning. However, stress-induced changes in expectancy of harm were not associated and did not mediate treatment outcomes in the RCT. Moreover, studies have observed enhanced long-term treatment outcomes following stress exposure without immediate group

differences in fear responding/ expectancies during exposure therapy. This will be discussed in more depth below under the subsection ‘Effects of stress during exposure.’

Taken together, acute stress has the potential to reduce the return of fear associated with the passage of time (i.e., spontaneous recovery) in the long-term. It is possible that stress exerts its effects both in the short and long-term, promoting the synergistic role of stress in both deepening extinction learning and directly influencing memory consolidation processes which are noticeable in the long-term. However, the robustness of stress effects in the long-term, largely suggests the benefits of pre-exposure stress are mostly accounted for by enhanced memory consolidation and long-term modification of synapses, which in turn promote memory retrieval (Pathway 1 of Integrated model of stress-augmentation).

4. Effects of stress on cognitive processes during exposure therapy

Based on the general findings of the systematic review in Chapter 2, it was hypothesized that stress would facilitate extinction learning via alterations in expectancy of harm and attention. The absence of an effect of stress on attention is consistent with a study that found acute stress did not influence patterns of eyegaze towards threat faces (Azulay, Guy, Shalev, Pertzov, & Israel, 2021), but does not support the attention component of the model and is inconsistent with other studies (Herten, Otto, & Wolf, 2017; Kofman, Meiran, Greenberg, Balas, & Cohen, 2006).

In contrast, there is some evidence of an effect of stress on expectancy of harm, but this does not appear to be driving the long-term benefits of stress. That is, the stress manipulation was shown to enhance expectancy of harm at the start of treatment but was not found to be a mediator of the therapeutic benefits of stress. This finding is partially consistent with our model and is in line with studies that demonstrate heightened expectancy of harm is linked to treatment

outcomes yet may not mediate them (Pittig et al.). However, it contradicts models of stress that posit acute stress suppresses fear memory to reduce fear responding (Bentz, Michael, de Quervain, & Wilhelm, 2010) and the stress-related attenuation of US-expectancy of harm found in another study (Bentz et al., 2013). Discrepancies could be accounted for by differences in the behavioural manifestation of cortisol and noradrenaline and their time-dependent effects on learning. This will be discussed under the subsection 'Role of NE and cortisol in stress-augmentation of therapy.' Thus, based on our findings, expectancy of harm and attention cannot be considered mechanisms of the effects of stress, but it cannot be ruled out that these or other cognitive processes have some role to play.

5. Effects of stress on mitigating renewal

Another major aim of this thesis was to determine whether pre-exposure stress could reduce the return of fear caused by a context change (i.e., mitigate renewal). Within the broader literature, context generalization and renewal have often been used synonymously, however for the purpose of disentangling the results of this thesis, we provide clear definitions for these two terms:

- *Generalization* refers to when the benefits observed in one context are maintained in another context.
- *Renewal* refers to the return of fear in another context, which is evident when fear responding is greater in the novel context relative to the extinction context.

In contrast to previous literature on stress hormone effects (namely cortisol) on the contextualization of memory (Drexler, Merz, & Oliver T. Wolf, 2018; Schwabe, Böhringer, & Wolf, 2009), stress did not reduce renewal and was not associated with in-session cortisol (in

both the pilot and RCT). The RCT found fear and avoidance behaviour increased in the novel context, relative to the extinction context across both stress and control groups. However, in the pilot study, a renewal effect was not established in either group to allow for any conclusions to be made regarding the effects of stress on renewal. These findings do not support the STAR model proposed by Drexler and colleagues, which posited that pre-extinction reduces the context-dependency of extinction memory to prevent renewal (Drexler, Merz, Jentsch, & Wolf, 2019). However, they do coincide with a study that revealed cortisol administration did not influence the context-dependency of extinction memory in conditioned healthy adults, and also found cortisol did not modulate the level of fear responding in a novel context (Merz, Hamacher-Dang, Stark, Wolf, & Hermann, 2018).

Possible explanations for the discrepancies (as discussed in Study 2 and 3) include differences in the testing context (novel vs acquisition context), type of stress (pharmacological or behavioural), timing of recall and relapse testing (short vs long-term recall) and characteristics of the samples (clinical vs non-clinical). Previously, it has been shown that pre-extinction stress can prevent fear renewal in the acquisition context (Drexler, Merz, & Wolf, 2018), suggesting stress could mitigate renewal in a familiar (i.e. acquisition) context but not an unfamiliar (i.e. novel) one. Pharmacological and various behavioural stress manipulations are shown to have different effects on NE arousal and cortisol reactivity (Dickerson & Kemeny, 2004; Harrewijn et al., 2020). In turn these unique stress hormones effect the context-dependency of memory differently and as such, variations in NE and cortisol release associated with the type of stressor could account for the differences. Moreover, renewal has generally been assessed at short-term follow-up periods in prior experimental studies, and there may well be differences in the short relative to the long-lasting effects of stress on renewal, which require further investigation.

In addition, individual variability and dispositional characteristics within clinical populations have been proposed to moderate the relationship between cortisol and memory (van Ast, Cornelisse, Marin, et al., 2013), and could explain variations in the current and previous findings. In fact, research supporting the STAR model is based on experimental studies involving conditioned healthy adults and animals which differ in their characteristics to clinical populations. Interestingly, individuals with greater levels of 'trait' emotional arousal (predisposition for anxiety disorders) are more sensitive to the effects of cortisol on memory (Abercrombie, Wirth, & Hoks, 2012). In accordance with this, noradrenergic arousal is shown to enhance memory accuracy including context-specificity of memory (Bahtiyar, Gulmez Karaca, Henckens, & Roozendaal, 2020). The finding of the RCT that higher noradrenergic arousal was associated with greater differences in behavioural avoidance between the extinction and novel context, provides some support for this account. In turn, it is possible the effects of stress hormones on the contextualization of memory may be less robust and more variable in clinical populations depending on dispositional characteristics. This could explain the discrepancies between the current renewal findings and previous experimental data. However, future research is needed to identify and assess plausible modulators of the effects of stress on renewal to further elucidate the potential benefits of stress on renewal within clinical populations.

Furthermore, it is interesting that a renewal effect was established in the RCT but not the pilot study. Possible reasons for this could be due to the small sample size in the pilot study preventing the detection of a possible renewal effect, or methodological differences and situational factors (such as COVID-19 related stress). Admittedly, participants in the pilot study were not assessed in the original treatment (i.e., extinction) context at post-treatment (as a comparison context against which to assess renewal in a novel context). Whilst group differences

could be assessed, this did not allow for context differences in the return of fear to be determined. However, both contexts were assessed at 7-months follow-up in the pilot study and no differences in the return of fear between contexts were observed in either group (i.e., no renewal), indicating testing in a comparison context would not have changed the results. Nevertheless, the RCT was altered to incorporate a comparison context at post treatment and ensure successful extinction retrieval. In addition, differences in situational factors between the two studies (pre-COVID-19 and during COVID-19) may have had a role to play in the renewal effects observed in the RCT. Previous adverse events or prolonged stress is shown to moderate the cortisol effects on memory (van Ast, Cornelisse, Marin, et al., 2013). Upon inspection, participants in the RCT exhibited higher basal cortisol levels on average (0.144)**,** relative to the pilot study (0.092). This suggests factors that affect absolute cortisol levels including moderate to major stress (Widmer et al., 2005) may affect treatment outcomes. In line with this, Van Ast, Cornelisse, Meeter, Joels, and Kindt (2012) demonstrated the slow effects of cortisol enhance the context-dependency of emotional memory the next day. Thus, COVID-19 related stress (including financial and personal stress), presumed to affect slow cortisol concentrations on non-treatment days may have contributed to the renewal effects observed in the RCT.

6. Time-dependent effects of stress on context generalization

The enhanced generalization of learning to a novel context in the pilot study may shed light on possible time-dependent effects of stress on context generalization. Specifically, pre-exposure stress led to less subjective distress and physiological arousal (measured by heart rate) across the extinction and novel context at 7-months follow-up, relative to the control condition (pilot study). However, the control group also showed a similar pattern of fear responding across contexts (i.e., no renewal), albeit fear was significantly higher than the stress group across

contexts. This demonstrates stress-enhanced benefits generalized to a novel context in the long-term, but we cannot argue this generalization mitigated renewal as no renewal effect was observed in the control group.

This generalization could be a result of an extremely effective treatment or perhaps due to the novel context being too similar to the extinction context**.** Alternatively, these findings may suggest stress exerts its effects on the contextualization of memory with time (van Ast, Cornelisse, Meeter, Joëls, & Kindt, 2013). This is consistent with studies showing that acute stress enhances generalization of older but not newly formed fear memories, suggesting stress may exerts its effects on memory generalization in the long-term (Dunsmoor, Otto, & Phelps, 2017). However, the fact that there was no difference in the behavioural avoidance test between the extinction and novel context in the control group (i.e., no renewal), makes it difficult to support this hypothesis. Another explanation is that stress strengthens long-term extinction memories (reducing fear in the extinction context) and these memories are easily retrievable, following exposure to retrieval cues. That is, perhaps the stress manipulation enhanced the consolidation of *context-specific* extinction memory to reduce fear responding in the extinction context, and the presentation of the extinction context prior to the novel one during testing, acted as a retrieval cue to promote generalization in both groups. This is consistent with Bouton et al. account of the role of retrieval cues in mitigating relapse. Specifically, a "booster" trial (e.g. re-exposure to the spider without harm) can enhance retrieval of extinction memory when the temporal or physical context has changed (Bouton, 2002). This may explain why both groups generalized their learning to a novel context, but the stress group displayed more pronounced fear reductions across contexts. However, these time-dependent effects require further investigation, especially considering this effect was not observed in the short-term (in the RCT),

and prior evidence indicates pre-learning stress impairs the context-dependency of memories tested in the short-term (Shira Meir Drexler et al., 2018). As a matter of fact, differences between these studies may be explained by the time-dependent paradoxical effects of cortisol and noradrenaline on the contextualization of memory, as discussed below.

7. Role of NE and cortisol in stress-augmentation of therapy

One possible explanation for the discrepancies between the current findings and previous studies in the context-dependency of memory and US-expectancies *during* extinction learning, is that distinct stress hormones (NE and cortisol) exert time-dependent effects on underlying brain systems, with contrasting effects on behaviour. Firstly, in both empirical studies, correlation and mediation analyses point towards a role of cortisol in the long-term enhancement of extinction memory, which as reported earlier, is consistent with previous literature (de Quervain, Schwabe, & Roozendaal, 2017; Maren & Holmes, 2016). However, the context-dependency of these memories (i.e., effects on renewal) was associated with greater NE levels during exposure therapy (in the RCT). Consistent with this finding, NE has been shown to enhance context-specificity of memories by boosting amygdala-hippocampal connectivity (Bahtiyar, Gulmez Karaca, Henckens, & Roozendaal, 2020). By contrast, cortisol exerts opposite effects on memory generalization, depending on the timing. *Rapid* cortisol effects lasting up to 60- 90 minutes impair the context-dependency of memories (i.e., enhances generalization of memories), whilst *delayed* effects of cortisol, emerging at least 60- 90 minutes after stress and lasting days/weeks, enhance the context-dependency of subsequent memories (van Ast, Cornelisse, Meeter, JoÎls, & Kindt, 2013). In turn, perhaps heightened NE levels or *delayed* cortisol effects (reflected in high basal cortisol levels in the RCT) may have affected renewal of fear in the RCT, preventing the detection of potential therapeutic benefits of *rapid* cortisol from the stressor. That is, the possible

delayed cortisol effects across the RCT sample could have trumped *rapid* cortisol effects on the contextualization of memory, leading to comparable renewal in both groups. These findings point towards the timing of pre-learning stress as a possible mediator of NE and cortisol effects on renewal. However, this requires more in-depth investigation as it does not explain the lack of renewal effects in the pilot study.

Another unresolved but related question is whether NE and cortisol have immediate effects on extinction learning and what is the nature of their roles. NE has been suggested to facilitate extinction learning by acting as an error detection signal when CS-US contingencies change, increasing neuronal excitability in the amygdala to later promote consolidation (Tully, Li, Tsvetkov, & Bolshakov, 2007; Wade, Blackley, & Felmingham, 2013). This is in line with the hypervigilant state associated with increased amygdala activity shortly after stress exposure (Joëls, Fernandez, & Roozendaal, 2011). There is evidence NE exerts immediate effects on extinction learning in addition to the well-established effects on consolidation, as it is shown to be a significant predictor of differential fear responding during the early, but not late extinction. However, during late extinction, NE has been found to not be associated with reduced extinction learning (Wade et al., 2013). These results suggest that the greater initial expectancy of harm violation observed in the stress group could be accounted for by NE levels. Indeed, exploratory analysis revealed higher basal NE levels were related to greater expectancy of harm violation at the start of treatment, potentially pointing towards a time-specific role of NE in extinction learning.

In contrast, cortisol, which is slow acting, is shown to have opposite effects on fear responding during learning compared to NE, and this may explain differences in stress-related US-expectancy effects between the current and previous studies. This is because cortisol has

been hypothesized to facilitate extinction learning within a different capacity to NE. A model by de Quervain, Schelling & Roozendaal (2009), posited that cortisol inhibits the retrieval of aversive memories, thereby reducing fear responding during exposure therapy to promote non-fearful association with the CS. For example, there is evidence that cortisol impairs memory retrieval processes 30 minutes after an electric footshock (which resulted in cortisol release), leading to impaired memory retrieval of spatial memory formed the day before (Bentz et al., 2010). This is also supported by studies revealing that cortisol suppresses amygdala activation during extinction learning to reduce fear responding (Merz, Hamacher-Dang, Stark, Wolf, & Hermann, 2018), which is partially consistent with Pathway 2.2 of the 'Integrated Model of Stress-augmentation'. Interestingly, some research points towards cortisol reducing amygdala responsivity, regardless of the timing of cortisol administration (Henckens, van Wingen, Joëls, & Fernández, 2010). This presumably allows for more cognitive control. In line with this, pre-extinction stress has led to reduced expectancy of harm during extinction learning (Bentz et al., 2010), which contradicts the RCT findings. However, this study did not investigate the relationship between expectancy of harm and cortisol/NE to inform the driver of this effect. It is possible differences in the timing of NE/cortisol elevations relative to the learning phase account for these inconsistencies. In particular, the duration of extinction leaning in experimental studies tends to be shorter than exposure therapy, which could affect the temporal effects of NE/cortisol. Further investigation into the role of timing in the distinct and interacting effects of NE and cortisol on learning and memory is required.

Below, an adaptation of a model proposed by Joels, Fernandez & Roozendaal (2011) is presented to summarize the time-specific effects of NE and cortisol on extinction learning and memory, from the broader literature and the current studies. Notably, the original model by Joel

et al. (2011) presents the timing of rapid and delayed NE/cortisol release following endogenous stress exposure, and their opportunities for interaction, but does not outline its effects on extinction processes at the behavioural level specifically. Thus, the proposed extension of this model provides the addition of time-specific NE/cortisol effects on extinction learning and contextualization of memory. It combines observations at the neural and behavioural level with the role of timing, offering a framework for disentangling the unique and interactive effects of NE and cortisol, for future testing and clinical use.

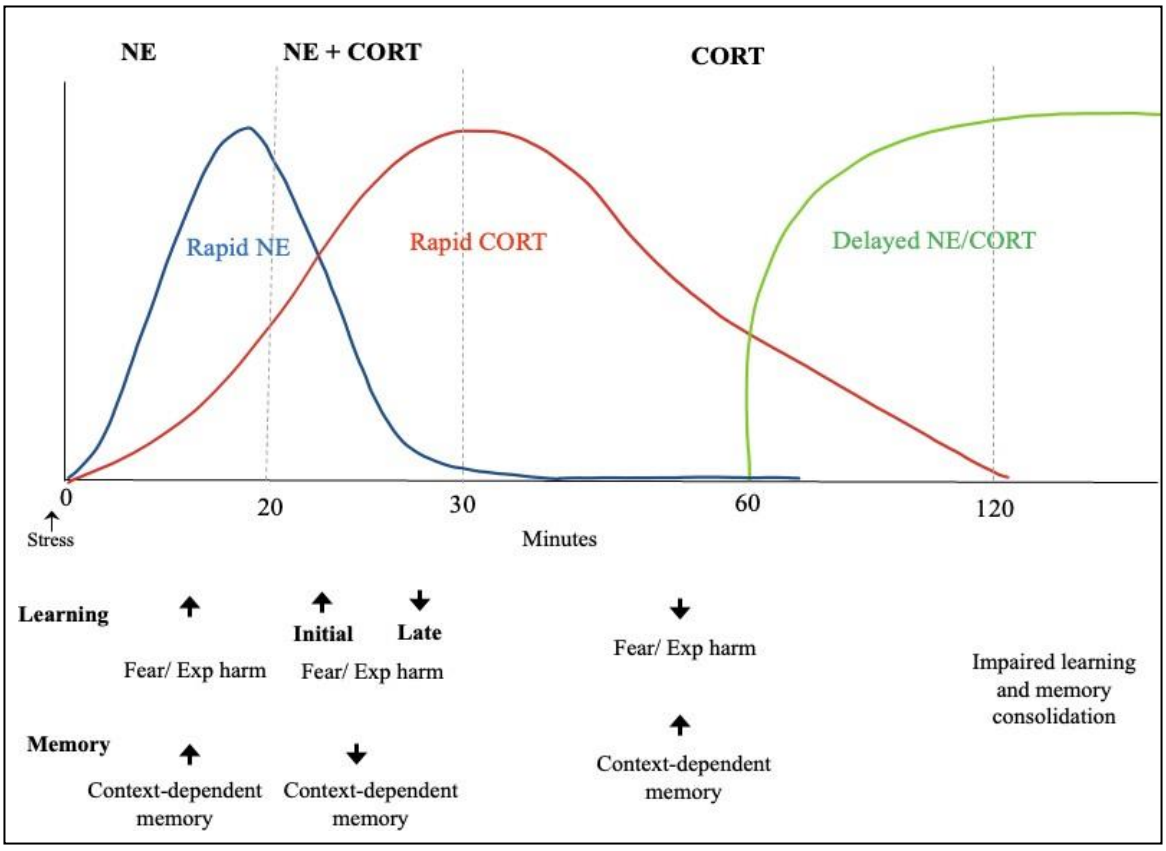

Figure 2. Time-dependent effects of NE and CORT on learning and memory. Soon after stress exposure, rapid NE levels (blue line) are elevated, with effects lasting up to 30 min. If learning primarily occurs during this phase, amygdala responding is elevated, increasing fear responding

and expectancies of harm, as well as the consolidation of memories in a context-dependent way. Cortisol (red line) is slower and peak levels are reached between 20 and 30 min after stress onset, lasting up to 60-120min (Droste et al., 2008). This is the window of time in which both NE and cortisol levels are elevated and interact to produce optimal memory enhancing effects. If learning occurs approximately 20-30 minutes after stress, the context-dependency of memory is reduced, and there may be an initial observation of enhanced fear responding and expectancies (due to higher NE), followed by reduced fear responding and expectancies (due to higher Cortisol). As such, these patterns will depend on the levels of NE and cortisol at the initial phase of learning. Later on, delayed cortisol and NE effects (green line) emerge approximately 60 -120 minutes after stress, in order to restore higher cognitive control and facilitate the consolidation of memory. However, if the onset of learning occurs more than 60 minutes after stress, delayed effects of cortisol will suppress memory retrieval and reduce fear responding and expectancies, and the context-dependency of memory will also be enhanced. However, if learning occurs several hours (i.e., more than 120 minutes) after stress exposure (once the rapid effects of cortisol and NE have subsided), NE and CORT will be 'out of sync' and learning and memory processes will be impaired.

8. Limitations and recommendations

The present thesis has several limitations. Firstly, the small sample sizes in the empirical studies potentially limits the generalizability of the findings and may have limited the ability to capture certain mediational effects and group differences in the context-dependency of memory. However, the power analysis conducted for both studies suggests the sample size would be adequate for the expected effects. In addition, due to attrition, data was imputed at follow-up periods. However, the pattern of results with and without the imputed data in both studies remained the same, suggesting imputation did not affect the results.

Moreover, there was no measure of VR immersion, which perhaps may have influenced fear ratings and eye gaze, depending on participants' perceived level of immersion. This is because there is evidence that participants' eye movements significantly decrease over time in an immersive condition, relative to a non-immersive one (Jenett et al., 2008). However, instructions were provided to refrain from using cognitive avoidance strategies (i.e., not telling themselves

the spider isn't real to reduce immersion). There were also no group differences in the rate of extinction learning and attention, and no evidence of impaired extinction learning, especially considering fear was heightened at the start of treatment which would suggest immersion. This suggests that degree of VR immersion was unlikely to have affected group differences in learning or attention but would be worth including in future studies to validate the efficacy of VR treatment and control for possible extraneous variables.

Methodological considerations in the timing of saliva sampling and type of stress intervention should also be taken into account for future research. Salivary alpha amylases (sAA; a biomarker of noradrenaline) were measured shortly prior and immediately after exposure therapy, but not during extinction learning. This may have prevented the detection of in-session NE levels as a mediator of stress effects. However, these times were selected to quantify stress-induced increases in NE levels, rather than NE elevations evoked by the phobic object (a natural consequence of exposure). There is evidence that stress enhances the sensitivity to a fear-eliciting stimulus, suggesting stress-induced NE can have longer-lasting effects during exposure therapy (Raio, 2015). Therefore, future studies could measure NE at different time points throughout exposure therapy to determine whether in-session NE levels predict treatment outcomes.

The socially evaluative cold presser task (SECPT) was chosen for the present study to maximize the induction of stress hormones, whilst also being an ecologically valid non-pharmacological treatment that could be applied in clinical settings. However, differences between the two empirical studies in the significance of a cortisol/NE change between groups, suggests SECPT may not have been a reliable method of stress induction. This is consistent with some studies that have produced stress effects using the SECPT without evidence of significant

cortisol increases (Antov, Melicherová, & Stockhorst, 2015). Notably, responsiveness to behavioural stressors is known to vary amongst individuals (Harrewijn et al 2020), which suggest pharmacological manipulations of stress may be more effective at elevating cortisol levels. Future studies should compare behavioural stressors that induce a natural physiological stress response with pharmacological manipulations of cortisol in their therapeutic efficacy and reliability. Subsequently, the delay between extinction learning and stress exposure varied across the first and second day of exposure as participants received psychoeducation after the first session, but not the second. This may have influenced the time-specific effects of cortisol and NE on attention and expectancy of harm during exposure therapy. Perhaps future studies could provide psychoeducation prior to stress exposure to ensure stress is directly influencing extinction learning processes and is having the desired effects throughout the learning phase (e.g., refer to model above).

Time-of-day effects are also an important consideration for future research. Whilst this was taken into consideration in the present study by scheduling all participants for the afternoon, participants nonetheless received exposure therapy across a wide window between 12pm and 6pm, which leaves open the possibility that the circadian rhythm of cortisol influenced stress effects. Further, exposure times and timing of follow-up tests were not randomly assigned, thus making it possible that third variables could have contributed the observed effects. However, exposure times did not vary between groups in either study, suggesting time of day effects would not have accounted for group differences. It would be interesting in future research to investigate if memory retrieval is affected by the time of testing.

There are also limitations in drawing inferences about the long-term effects of stress on spontaneous recovery of fear and the generalization of extinction memory. This is because

testing at 7-months follow-up was not able to be assessed in the RCT due to COVID-19 restrictions, increasing reliance on the smaller pilot study findings. In addition, the order of testing in each context was not counterbalanced at 7-months follow-up in the pilot study, making it possible that the order of retrieval testing was an extraneous variable that influenced the generalization of extinction memory to a novel context. Future studies should assess spontaneous recovery of fear with larger sample sizes and longer follow-up periods. To disentangle the effects of retrieval cues and the long-lasting effects of stress on memory generalization, studies could counterbalance the order of testing at follow-up periods and compare short-term and long-term effects of stress on memory generalization.

The empirical studies were also mostly composed of women, which again affects the generalizability of the findings. Differences in stress hormones are known to interact with cortisol to influence extinction learning memory. Studies show that females, especially on oral contraception (OC), show a blunted cortisol response which is linked to diminished effects of stress on extinction, relative to men (Merz & Wolf, 2017). As an attempt to mitigate this important third variable, participants on oral contraception were excluded from the RCT analysis, and gender was controlled in analyses. However, women on OC's (n=2) were not excluded from the pilot study due to the low sample size. Notably, the pattern and significance of results did not change with the exclusion of these participants.

A final limitation is that stringent exclusion criteria were applied (i.e., sample consisted of non-smoking participants, non-pregnant women, those not consuming psychotropic medications or having a more primary chronic condition). These stringent criteria were applied because they are known to interfere with cortisol concentrations. However, future studies should

investigate the effects of stress on less restrictive samples and individuals with comorbid conditions, to better represent real-life clinical settings.

9. Clinical implications

From a clinical perspective, current findings highlight the potential for pre-exposure stress to improve symptom remission and reduce relapse in the long-term. This is imperative as the development of more efficacious treatments are needed to address the problem of non-responders to treatment and relapse. This thesis extends knowledge about the mechanisms underlying the enhancing effects of stress on exposure therapy and points towards important avenues for future research. Understanding the mechanisms underlying the beneficial effects of stress will inform the precise methods required for optimising stress in the therapy room.

The specific long-term mediation effects of cortisol confirm its significant role in enhancing extinction memory consolidation. However, the finding that cortisol and other tested mechanisms did not predict the short-term effects of stress, suggest other mechanisms could account for the immediate effects. Further research into potential mechanisms is needed. Previous studies have typically applied stress to one off exposure sessions in only male or female samples. However, this thesis provides further support for the use of stress adjuncts to therapy within a more naturalistic clinical setting. We have demonstrated that the application of stress exposure to standard cognitive behavioural therapy procedures (i.e., across several sessions, with the inclusion of psychoeducation and cognitive strategies) can enhance clinical outcomes in both males and females.

Moreover, the use of behavioural stress interventions has rarely been investigated within a clinical sample. The current findings reveal that the Socially Evaluated Cold Presser Task

(SECPT) task can produce similar effects to pharmacological manipulations of cortisol. This means that clinicians could easily apply behavioural stressors as alternatives to pharmacological enhancers of psychotherapy. They could also consider utilizing other behavioural stressors such as the Maastricht Acute Stress Test (MAST) or the Trier Social Stress Test (TSST) which are known to elevate cortisol levels, or at the very least avoid relaxation strategies prior to exposure to maximize treatment outcomes. However, more studies are needed to further evaluate the therapeutic efficacy of combing specific behavioural stressors with cognitive behavioural therapy.

Finally, the findings shed light on the question of whether pre-exposure stress can enhance the generalization of extinction memory within a clinical sample. The findings suggest stress may have long but not short-term effects on memory generalization, and that there are likely other factors (such as clinical characteristics and methodological issues) that affect the renewal of fear in clinical populations. The adapted model proposed above, may provide some insights into how stress can reduce the context-dependency of memory to produce a more generalizable memory, and in other cases induce disparate effects. It is hypothesized that it is not only pre-learning stress exposure that plays an important role in modulating learning and memory, but also the timing of distinct NE and Cortisol elevations relative to the learning phase, and the duration of learning. This insight bears important implications for augmenting exposure therapy via stress. If delayed cortisol has detrimental effects on the context-dependency of long-term memory, then clinicians should take care to administer stress in close proximity to exposure therapy (approx. 20-30 min after), with exposure sessions lasting up to 30- 60 minutes, given delayed cortisol effects on the contextualization of memory are known to emerge 60- 90 minutes after stress. Whilst this study ties together clinical and experimental research, discrepancies in

renewal between the two empirical studies and other experimental findings, invite further research into the effects of stress timing and clinical characteristics on the generalization of extinction memories.

10. Concluding Remarks

In closing, the clinical utility of stress to enhance exposure therapy and address the problem of relapse is promising. This thesis provides evidence for the potential reduction and prevention of relapse associated with the passage of time (spontaneous recovery) and confirms cortisol as a partial driver of this effect. To this end, pre-exposure stress appears to largely affect long-term extinction processes including memory consolidation, but less consistently affects short-term processes (extinction learning and short-term retention). Noradrenaline appears to be associated with treatment outcomes but does not account for therapeutic benefits of stress, and similarly, cognitive processes including attention and expectancy of harm do not explain the enhancing effects of stress, but expectancy of harm may have a role to play as it is influenced by stress.

Given the limitations of this thesis, future research should include large-scale clinical studies to evaluate the therapeutic efficacy of stress-augmentation of treatment for different anxiety and fear-related disorders. The precise mechanisms through which cortisol might enhance the effectiveness of exposure therapy are still unclear, particularly short-term effects of stress and its impact on renewal. Future research is required to further examine the role of NE in stress-augmentation of therapy and investigate other mechanisms that could explain the immediate effects of stress and discrepancies in renewal findings. Using different pharmacological and behavioural stress interventions with various timing paradigms is a

necessary step towards identifying the conditions under which stress is most optimal for facilitation and clinical use. Such investigations are pivotal in supporting and extending the current body of evidence and paving the way for the future clinical use of stress-adjuncts to therapy.

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APPENDICES

APPENDIX A: Study Procedures and Materials

THE UNIVERSITY OF SYDNEY

School of Psychology
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Effects of acute stress on exposure therapy and relapse

PARTICIPANT INFORMATION STATEMENT

(1) What is this study about?

You are invited to take part in a research study that examines the role of stress in treatment and reducing relapse associated with anxiety and fear-based disorder. Research has shown that stress levels can influence learning. This treatment study involves two virtual reality exposure sessions (approx. 90 mins) to spiders. At various stages of the study you will be asked to participate in an interview, complete questionnaires, provide saliva samples, undergo various stress measurement procedures and attend three follow-up assessments (3-5 days, 3-months and 6-months after treatment has finished).

You have been invited to participate in this study because *you are between the ages of 18 and 60 and you have a clinically significant fear of spiders.* This Participant Information Statement tells you about the research study. Knowing what is involved will help you decide if you want to take part in the research. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about.

Participation in this research study is voluntary.

By giving your consent to take part in this study you are telling us that you:
- D Understand what you have read.
- D Agree to take part in the research study as outlined below.
- D Agree to the use of your personal information as described.

You will be given a copy of this Participant Information Statement to keep.

(2) Who is running the study?

The study is being carried out by the following researchers:
- D **Ms Elpiniki Andrew**
  PhD student at the University of Sydney
- D **Professor Mark Dadds**
  Professor of Clinical Psychology at the University of Sydney

- D **Professor Justin Harris**
  Professor of Behavioural Neuroscience at the University of Sydney
- D **Scientia Professor Richard Bryant**
  Professor of Clinical Psychology at the University of New South Wales

Ms Elpiniki Andrew is conducting this study as the basis for the degree of Masters of Clinical Psychology and Doctorate of Philosophy at The University of Sydney. This will take place under the supervision of Professor Mark Dadds.

(3) What will the study involve for me?

If you decide to take part in the research study, you will be asked to complete a diagnostic interview as well as several questionnaires about the severity of your fear of spiders, and a behavioural test that involves exposure to a virtual reality spider. These questions and the behavioural test are completed before the beginning of treatment, 1 week, 3 and 6 months after you have completed your final treatment session. At the end of treatment, you may receive feedback on the questionnaires and behavioural assessments, if you request it, which will tell you about the changes in your behaviour and feelings towards spiders. During assessment you will also be exposed to a virtual reality spider to test how

Treatment will involve two consecutive weekly sessions of virtual reality exposure therapy conducted in the afternoons between 12pm and 6pm. In these sessions you will be asked to complete several tasks that will involve observation and interaction with a virtual reality (VR) spider whilst wearing a VR headset. You will be required to complete a procedure before each treatment session that will involve you placing your right hand in water. Throughout the treatment you will wear a watch that measures your level of arousal and you will be asked to provide several saliva samples during the session.

After completion of treatment, you will be asked to return to the clinic to complete a post-treatment (1 week later) and follow-up assessments (3-months and 6-months later). Your participation will involve five visits to the clinic (see table below for summary).

Visit 1 *(Week 1)*	Interview, Questionnaires, Saliva samples, Hand in water procedure, VR exposure Test and VR exposure treatment Session 1
Visit 2 *(Week 2)*	Questionnaires, Saliva samples, Hand in Water Procedure, VR exposure treatment session 2
Visit 3 *(Week 2 or 3)*	VR exposure Test and Questionnaires
Visit 4 *(Week 14 or 15)*	VR exposure Test and Questionnaires
Visit 5 *(Week 26 or 27)*	VR exposure Test and Questionnaires

(4) How much of my time will the study take?

Your participation in the study will occur over a period of approximately 2- 3 weeks. There will also be a follow-up assessment and questions at 3 months and 6 months after completion.

You will be asked to answer a series of questionnaires at the start of the study, which will take around 20 minutes. Once you have completed these questions you will be shown how to use the VR headset and given time to habituate to the tool (approx. 10min). You will then be asked to approach a VR spider as close as you can (approx. 10min) using the VR headset, before beginning treatment. Saliva samples will be taken, and you will complete a task that requires you to place your hand in warm or ice cold water. Following this, treatment will begin which will involve psychoeducation, discussion of coping strategies and guided VR exposure tasks which will take approximately 60 min to complete. It is anticipated that your first visit will take a total of approximately 2.5 hours.

The following week you will be asked some questions about any stress you experienced in the past week. These questions will take approximately 5 minutes to complete and are part of the 90-minute treatment sessions. You will then be asked to complete a second guided exposure session. It is anticipated that your second visit will take a total of approximately 1.5 hour.

A few days later you will be asked to return to the clinic to answer some questions about any stress you experienced in the past week, complete the questionnaires you were given on the first day (15min) and complete two VR tests (asked to approach a spider as close as you can using the VR headset). The VR tests will take approximately 30min. This process will be repeated after 3-months. Your third and fourth visit is estimated to take approximately 1 hour each.

Your time involved in the research will depend on how long it takes for you to complete the exposure tasks and questionnaires, but will range from a total of approximately 6 hours to 7.5 hours (for 4 visits).

(5) Who can take part in the study?

Participants aged between 18 and 60 with a clinically diagnosed specific phobia of spiders (satisfy DSM-5 criteria) are eligible to participate in this study.

(6) Do I have to be in the study? Can I withdraw from the study once I've started?

Being in this study is completely voluntary and you do not have to take part. Your decision whether to participate will not affect your current or future relationship with the researchers or anyone else at the University of Sydney.

If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by informing the researcher via email or in person.

If you decide to withdraw from the study, we will not collect any more information from you. Any information that we have already collected, however, will be kept in our study records and may be included in the study results. Any information we retain will be de-identified and stored securely, and we will not publish any information that could be used to identify you.

(7) Are there any risks or costs associated with being in the study?

No major risks or difficulties are anticipated for you if you take part in this study. There is, however, the potential for you to experience some distress as a normal part of clinical processes. The nature of exposure therapy is to elicit some distress in order to assist you to manage your emotions when you are confronted with your fears. You should expect to feel some distress as you face your fears. However, you will be taught coping strategies before you begin, and you will also be guided and supported throughout the process by your psychologist.

If at any time you think you may be pregnant, it is important to let researchers, or your medical team know immediately.

(8) What happens if I suffer injury or complications as a result of the study?

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is caused by the drugs or procedures, or by the negligence of any of the parties involved in the study. If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

(9) Are there any benefits associated with being in the study?

You may expect to improve your anxiety symptoms related to spiders which may include less avoidance of spiders, and less physiological and emotional distress associated with spiders. You may also benefit by learning coping strategies to assist you to manage your distress and may benefit from feedback regarding clinical diagnoses and referral options should you request any further psychological support.

(10) What will happen to information about me that is collected during the study?

By providing your consent, you are agreeing to us collecting personal information about you for the purposes of this research study. Your information will only be used for the purposes outlined in this Participant Information Statement, unless you consent otherwise.

Your information will be stored securely in locked filing cabinets and password protected servers. Data collected will include your responses to questionnaires, saliva samples and your responses on measures throughout treatment. This information will be de-identified and kept strictly confidential, except as required by law. Study finding may be published, but you will not be individually identified in these publications. Any identifying data which includes your name and email address will be stored separately and will not be linked to your data files. Identifying information will only be able to be linked to your name by a specific code by the Chief Investigator and PhD student conducting the study.

(11) What will happen to my tissue sample after it has been used?

The saliva samples you provide during the study will be destroyed at the completion of the study.

(12) What will happen to my treatment when the study is finished?

No further treatment will be provided by the researcher, once you have finished. However, should you want or require further support, your treating psychologist will provide you with referral options for treatment elsewhere.

(13) Can I tell other people about the study?

Yes, you are welcome to tell other people about the study.

(14) What if I would like further information about the study?

When you have read this information, Ms Elpiniki Andrew will be available to discuss it with you further and answer any questions you may have. If you would like to know more at any stage during the study, please feel free to contact Ms Elpiniki Andrew, PhD Candidate and Registered Psychologist at elpiniki.andrew@sydney.edul.au

(15) Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback via ticking the relevant box on the consent form. This feedback will be in the form of a one page lay summary describing the general results of the study. This will be emailed to you. You will receive this feedback after the study is finished.

(16) What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney *2019/502.* As part of this process, we have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details outlined below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney:

- **Telephone:** +61 2 8627 8176
- **Email:** human.ethics@sydney.edu.au
- **Fax:** +61 2 8627 8177 (Facsimile)

This information sheet is for you to keep

Consent Form

PARTICIPANT CONSENT FORM

I, ...[PRINT NAME], agree to take part in this research study.

In giving my consent I state that:

D I understand the purpose of the study, what I will be asked to do, and any risks/benefits involved.

D I have read the Participant Information Statement and have been able to discuss my involvement in the study with the researchers if I wished to do so.

D The researchers have answered any questions that I had about the study and I am happy with the answers.

D I understand that being in this study is completely voluntary and I do not have to take part. My decision whether to be in the study will not affect my relationship with the researchers or anyone else at the University of Sydney now or in the future.

D I understand that I can withdraw from the study at any time.

D I understand that I may stop the interview at any time if I do not wish to continue, and that unless I indicate otherwise any recordings will then be erased and the information provided will not be included in the study. I also understand that I may refuse to answer any questions I don't wish to answer.

D I understand that personal information about me that is collected over the course of this project will be stored securely and will only be used for purposes that I have agreed to. I understand that information about me will only be told to others with my permission, except as required by law.

D I understand that the results of this study may be published, and that publications will not contain my name or any identifiable information about me.

I consent to:

D **Video-recording** YES ☐ NO ☐

I would like to receive feedback about the overall results of this study YES ☐ NO ☐

If you answered **YES**, please provide your email address:

☐ Email: _____

.....**Signature** .....**PRINT name**..... **Date**

Intake and Screening Forms Completed by Clinician

UNIVERSITY OF SYDNEY- STRESS AND SPIDER PHOBIA STUDY
INTAKE AND SCREENING RECORD

Full name: _____ Age: _____DOB:_____Sex: M/F

Phone: _____ Suburb: _____

Referral Source: _____

ASK: No eating, drinking (anything but water) 90 min prior to each testing session. No physical activity, caffeine or alcohol consumption 3 hours prior

Symptoms (Behavioural, physiological. Emotional)
Frequency (how often does this occur), intensity (how bad is it when they are confronted with spider), Ask for an example of what happened the last time they were anxious/fearful of a spider

_____

_____

_____

Avoidance or safety behaviours _____

_____

_____

Impact
School/ Work, Social relationships,

_____

_____

Current Health Problems **YES/NO**
How is their health? Any acute or severe medical problems?

_____

_____

_____

Current Treatment **YES/NO**
Medication, participating in any other psychological treatment

_____

_____

_____

Available Times and Dates (Between 11am and 6pm)

- Monday • Tuesday • Wednesday • Thursday. • Friday

_____

_____

Pregnant **YES/NO**
Oral Contraception **YES/NO**
Dominant Hand _____

Exclusion criteria: < 18 > 60 years old, severe medical or psychiatric disorder, currently receiving treatment for spider phobia, pregnant.

Stress/control Procedure Instructions for Experimenter

Experimenter Instructions

Control Procedure

1. **Wipe esky, surfaces, chairs w disinfectant wipe**
2. Confirm participants dominant hand, **ask them to sanitise** & then to **remove mask** for rest of session
3. Give them handout to read
4. Ask if they have any questions, **ask them to sanitize again** and leave the room for 3 minutes
5. Immediately after 3 minutes, take saliva sample, **ask them to place it in box** then complete Participant Rating sheet
6. After testing: **Sanitise saliva box** before placing it in the freezer (L3), desk & chairs. If no other sessions - dispose of ice water outside building

Control manipulation

Participants immerse their hands in warm water **(35–37 °C)**, they are **not videotaped/evaluated by experimenter.**

Stress Procedure

1. **Wipe esky, surfaces, chairs w disinfectant wipe**
2. Confirm participants dominant hand, **ask them to sanitise** & then to **remove mask** for rest of session
3. Give them handout to read
4. Ask if they have any questions, **ask them to sanitize again** and remind them to keep their entire wrist in without making a fist
5. State that you will be taking notes & tell them to keep their eyes on the video camera at all times
6. Stand close to the participant so they can see you taking notes & watching them
7. Immediately after 3 minutes, take saliva sample, **ask them to place it in box** then complete Participant Rating sheet
8. After testing: **Sanitise saliva box** before placing it in the freezer (L3), desk & chairs after testing. If no other sessions - dispose of ice water outside building

If Participant removes their hand before 3 min is up:

"Please place your hand back in the water up to your wrist as this is very important"

If Participant does not place their hand back in continue writing notes and evaluating:

"That's fine, please continue to look into the camera until I tell you to stop. When you are able to, please place your hand back into the water"

Uncertainty	Do not tell the participant how long the hand immersion will last & remove clock from wall.
Consistency	Ensure the same RA conducts S1 & S2. Avoid switching between roles: Be rather neutral from the beginning on.
Cold stress	Make sure the water is indeed cold enough **(0–2 °C)** and that the participant keeps his/her hand in the water all the time, without moving or making a fist.
Continuous evaluation	Take notes and make the participant feel being evaluated all the time during the hand immersion. Stand in their line of vision while doing this (do not sit).
Self-monitoring	Turn the camera screen towards the participant so that he/she can see his/her face on the screen. If possible, use a bigger screen in addition.
Lack of social support or reinforcement	Be reserved, keep the interaction to a minimum, and avoid any form of reinforcement (e.g. smiling). We're trying to stress them out.

Stress Group SECPT Handout

The following part of the experiment is aimed at increasing your stress levels, as research has shown stress can influence the success of treatment. As a result you will be asked to engage in a stress task where your facial expressions will be studied as well as your ability to tolerate pain. This is because these factors are known to influence the success of treatment. Specifically, participants who show the highest levels of stress, pain tolerance, and facial composure during this task report the greatest clinical achievements.

It is very important that you ***perform your best*** *in this task to maximise treatment outcomes. The entire procedure will be videotaped for further analysis by a research team.*

In the following part of the experiment, you are asked to immerse your dominant hand, including your wrist, into a tank containing ice water. Please keep your hand in the water and do not make a fist. When the experimenter says 'STOP' you are allowed to take your hand out of the water. Only if you are unable to tolerate the cold water any more, you are allowed to take your hand out of the water. However, please keep your hand in the water for ***as long as possible****!*

The experimenter will be taking notes.

Control Group Handout

The following part of the experiment is aimed at reducing your stress levels, as research has shown stress can influence the success of treatment. As a result you will be asked to engage in a relaxation task where you will place your hand in warm water and sit comfortably with your feet flat on the ground. This is because these factors are known to influence the success of treatment. Specifically, participants who have habituated to their surroundings and feel more relaxed during this task report the greatest clinical achievements.

Warm water has been shown to relax the body by increasing our body temperature and relaxing our muscles. Importantly it can soothe us mentally and physically.

Therefore, in the following part of the experiment, you are asked to immerse your dominant hand, including the wrist, for 3 minutes into a tank containing warm water. The experimenter will let you know when the 3 minutes are over and you are allowed to take your hand out of the water.

The experimenter will leave the room.

Stress/Control Procedure Subjective Ratings

Participant Rating

Date: _____Session: _____

Participant's name: _____/ ID Number:_____

Condition(Stress or Control):_____Experimenter's name:_____

Saliva start time:_____ Saliva end time:_____

How stressful was that experience?

0	1	2	3	4	5	6	7	8	9	10
Not at all			A bit Stressful		Somewhat Stressful			Very Stressful		Extremely Stressful

How painful was that experience?

0	1	2	3	4	5	6	7	8	9	10
Not at all			A bit Painful		Somewhat Painful			Very Painful		Extremely Painful and intolerable

How unpleasant was that experience?

0	1	2	3	4	5	6	7	8	9	10
Not at all		A Bit unpleasant			Moderately unpleasant			Very unpleasant		Extremely unpleasant

Comments:

_____
_____
_____
_____
_____

Specific Phobia Screening Questions

H. SPECIFIC PHOBIA

(® MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO,** AND MOVE TO THE NEXT MODULE)

®
HI In the past month, have you been excessively afraid of things like: flying,
NO
YES
driving, heights, storms, animals, insects, or seeing blood or needles?

®
H2 Is this fear excessive or unreasonable?
NO
YES

®
H3 Do you fear these situations so much that you avoid them or suffer through
NO
YES
them?

H4 Does this fear disrupt your normal work or social functioning or cause you significant distress?

NO **YES**

SPECIFIC PHOBIA
CURRENT

CHRONOLOGY

H5 How old were you when you first began to fear or avoid this situation? Dage

H6 During the past year, how many times have you had significant fear of this situation? ☐

Depression Anxiety Stress Scale (DASS)

DASS21

Name: Date:

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you **over the past week**. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree or a good part of time
3 Applied to me very much or most of the time

1 (s)	I found it hard to wind down	0	1	2	3
2 (a)	I was aware of dryness of my mouth	0	1	2	3
3 (d)	I couldn't seem to experience any positive feeling at all	0	1	2	3
4 (a)	I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5 (d)	I found it difficult to work up the initiative to do things	0	1	2	3
6 (s)	I tended to over-react to situations	0	1	2	3
7 (a)	I experienced trembling (e.g. in the hands)	0	1	2	3
8 (s)	I felt that I was using a lot of nervous energy	0	1	2	3
9 (a)	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10 (d)	I felt that I had nothing to look forward to	0	1	2	3
11 (s)	I found myself getting agitated	0	1	2	3
12 (s)	I found it difficult to relax	0	1	2	3
13 (d)	I felt down-hearted and blue	0	1	2	3
14 (s)	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15 (a)	I felt I was close to panic	0	1	2	3
16 (d)	I was unable to become enthusiastic about anything	0	1	2	3
17 (d)	I felt I wasn't worth much as a person	0	1	2	3
18 (s)	I felt that I was rather touchy	0	1	2	3
19 (a)	I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat)	0	1	2	3
20 (a)	I felt scared without any good reason	0	1	2	3
21 (d)	I felt that life was meaningless	0	1	2	3

State-Trait Anxiety Inventory (STAI)

State-Trait Anxiety Inventory
STAI Form Y-1

Name……Date……..Age..... Sex: Male

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then write the number in the blank at the end of the statement that indicates how you feel right now, that is, at this moment. There is no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best

S. No.		Not at all	Some What	Moderately so	Very much so
1.	I feel calm	1	2	3	4
2.	I feel secure	1	2	3	4
3.	I am tense	1	2	3	4
4.	I feel Strained	1	2	3	4
5.	I feel at ease	1	2	3	4
6.	I feel upset	1	2	3	4
7.	I am presently worrying over possible misfortunes	1	2	3	4
8.	I feel satisfied	1	2	3	4
9.	I feel frightened	1	2	3	4
10.	I feel comfortable	1	2	3	4
11	I feel self confident	1	2	3	4
12.	I feel nervous	1	2	3	4
13.	I am Jittery	1	2	3	4
14.	I feel indecisive	1	2	3	4
15.	I am relaxed	1	2	3	4
16.	I feel content	1	2	3	4
17.	I am worried	1	2	3	4
18.	I feel confused	1	2	3	4
19.	I feel steady	1	2	3	4
20.	I feel pleasant	1	2	3	4

Spider-related Questionnaires

SPQ

SPQ-15

Please mark the following statements as either "true" or "false" as you feel that they generally apply to you. If a statement is true most of the time or is mostly true for you, you should answer true. If it is mostly false or false most of the time, mark it false. Indicate your answer by placing an "X" in the appropriate column.

True	False	
____	____	1. I avoid going to parks or on camping trips because there may be spiders about.
____	____	2. I would feel some anxiety holding a toy spider in my hand.
____	____	3. I dislike looking at pictures of spiders in a magazine.
____	____	4. If there is a spider on the ceiling over my bed, I cannot go to sleep unless someone kills it for me.
____	____	5. I am terrified by the thought of touching a harmless spider.
____	____	6. If someone says that there are spiders anywhere about, I become alert and edgy.
____	____	7. I would not go down to the basement to get something if I thought there might be spiders down there.
____	____	8. I would feel uncomfortable if a spider crawled out of my shoe as I took it out of the closet to put it on.
____	____	9. When I see a spider, I feel tense and restless.
____	____	10. I feel sick when I see a spider.
____	____	11. I shudder when I think of spiders.
____	____	12. The way spiders move is repulsive.
____	____	13. If I came upon a spider while cleaning the attic I would probably run.
____	____	14. I would prefer not to finish a story if something about spiders was introduced into the plot.
____	____	15. Even if I was late for a very important appointment, the thought of spiders would stop me from taking a shortcut through an underpass.

FSQ

1. If I came across a spider now, I would get help from someone else to remove it.
2. Currently, I am sometimes on the look out for spiders.
3. If I saw a spider now, I would think it will harm me.
4. I now think a lot about spiders.
6. I would be somewhat afraid to enter a room now, where I have seen a spider before.
7. I now would do anything to try to avoid a spider.
8. Currently, I sometimes think about getting bit by a spider.
9. If I encountered a spider now, I wouldn't be able to deal effectively with it.
10. If I encountered a spider now, it would take a long time to get it out of my mind.
11. If I came across a spider now, I would leave the room.
13. If I saw a spider now, I would think it will try to jump on me.
14. If I saw a spider now, I would ask someone else to kill it.
15. If I encountered a spider now, I would have images of it trying to get me.
16. If I saw a spider now I would be afraid of it.
18. If I saw a spider now, I would feel very panicky.
20. Spiders are one of my worst fears.
21. I would feel very nervous if I saw a spider now.
22. If I saw a spider now I would probably break out in a sweat and my heart would beat faster.

Behavioural Avoidance Test (BAT)

MEASURES DURING BAT

Date: _____
Session: ____
Participant's name/ID: _____
Clinician: _____

Kitchen/Garden

BEFORE BAT (with headset) .

Expectancy Ratings

How much fear/distress/disgust will you experience when you see this spider?

0	1	2	3	4	5	6	7	8	9	10
No fear etc.					Moderate Fear etc.					Extreme fear etc.

What is the worst thing that could happen?_____

How likely do you think you this will occur?

0	1	2	3	4	5	6	7	8	9	10
Certainly not		Very unlikely	Unlikely		Uncertain		Likely	Very Likely		Certainly

How well do you think you will cope?

0	1	2	3	4	5	6	7	8	9	10
Not at all			A bit		Somewhat			Very well		Extremely well

AFTER THEY SAY STOP .

SUDs

How distressed/disgusted do you feel?

0	1	2	3	4	5	6	7	8	9	10
Total	Alert &	Minimal	Mild		Moderate		Quite	Very	Extre	Highest
ly Relaxed	awake; concentrating well	anxiety	anxiety		anxiety, uncomfortable but can continue to performance		anxious interfering with performance	anxious, can't concentrate	mely anxious	distress/fear/ discomfort ever felt

Lifted Lid: YES / NO

Comments: _____

_____

_____

_____

US-expectancy Ratings

Rate the following on scale of 0 -10.

1) How much fear will you experiencing when you see this spider? (0- no fear at all, 100- very
2) How likely do you think your feared outcome will occur? (e.g., the spider will jump out at you)

Feared outcomes will be determined at the start

Form Completed During Exposure Therapy

MEASURES DURING EXPOSURE THERAPY

Date: _____ START TIME:__:____
Session: ____ END TIME:___:____
Participant's name/ID: _____ SALIVA TIME AFTER CPT:____
Clinician: _____ TOTAL ET DURATION:____

Talk about spider, Prompt coping strategies 8/10 SUDs, Increase immersion and check for cog avoidance

1	2	3	4	5
Approach spider at arm's length	Lift Lid and stay at arm's length	Touch spider	Lift Vase	Touch spider with tactile feedback

TASK:_____. TRIAL_____

Explain task and ask ratings before they see spider

Expectancy Ratings ___/10
Worst that could happen: _____
Likelihood ___/10
Coping___ /10
SUDS __ /10

During Task (Ask every 1-5 min)

SUDs 2:00m: ____ Likilhood 2:00m: ____
SUDs 4:00m: ____ Likilhood 4:00m: ____
SUDs 6:00m: ____ Likilhood 6:00m: ____
SUDs 8.00m: ____ Likilhood 8:00m: ____
SUDs 10.00m: ____ Likilhood 10:00m: ___
SUDs 12.00m: ____ Likilhood 12:00m: ___
SUDs 14.00m: ____ Likilhood 14:00m: ___
SUDs 16.00m: ____ Likilhood 16:00m: ____
SUDs 16.00m: _____ Likilhood 16:00m: _____

Move on if SUDS < 30 or Anxiety has reduced by 50%

Comments:

Saliva Questionnaire

Saliva sample collection procedure: Passive drool method

Before collection, complete the following survey with the participant:

D Was today a typical day for you?

- o Yes
- o No (explain) _____

D Have you been feeling healthy and well today?

- o Yes
- o No (explain) _____

D Did you participate in any vigorous physical activity today before the samples were collected (e.g., soccer practice, swimming)?

- o Yes (explain) _____At what time? _____a.m./p.m.
- o No

D Did you have an emotional event today before sampling (such as fighting with someone, prolonged crying for more than 10 minutes)?

- o Yes (explain) _____At what time? _____a.m./p.m.
- o No

D Did you eat or drink anything with caffeine today before sampling?

- o Yes (explain) _____At what time? _____a.m./p.m.
- o No

D Did you have anything to eat in the last 30 minutes?

- o Yes (explain) _____At what time? _____a.m./p.m.
- o No

D Did you have milk products in the last 30 minutes?

- o Yes (explain) _____At what time? _____a.m./p.m.
- o No

D Have you been experiencing/ experienced any stress in the past week?

Saliva Collection Steps

- Put on gloves.

Spit Protocol Script

Give participants a glass of water whilst completing the first questionnaire. Instruct them to stop drinking once they have started their second questionnaire, i.e. at least 5 minutes prior to saliva sampling. Introduce spitting and leave the room till they have indicated they have finished.

[To participant] We are going to ask you to provide some saliva samples now by **spitting into a mouth piece**. This is to determine your cortisol or stress levels

- Open the vial.
- Place the mouthpiece into the vial.

Now what I want you to do is to spit into this **tube** here. [*Make sure they take the cap off now*]. You can do this by spitting **through this mouthpiece** here into the tube [*Demonstrate as you explain this*]. Try to pull as much saliva as you can into your mouth,, until you feel spit gathering up in your mouth. You may want to tilt your head forward to allow gravity to let the saliva fall towards the front of your mouth.. Wait until it feels like there is a lot of saliva pooled at the front of your mouth, then you can spit through the mouthpiece. Go ahead and **try** that now?

- **Let it fall** through the mouthpiece into the tube and make sure the end of the mouthpiece is near the top of the tube.

Sometimes spitting can seem a little messy, so you can use some **tissues** to stay neat [*hand tissue box*]. I want you to spit **all the way up to this line** here [*Show them 0.5ml line*]. You might get a lot of bubbles, but **bubbles don't count**. If you see lots of bubbles, I want you to **tap** the tube lightly on the table until the bubbles settle.

- If necessary, demonstrate/instruct participant to direct saliva through the tube into the vial.
- If no saliva appears in the vial, have the participant gently blow saliva out of the mouthpiece.
- Fill the vial one thirds full.
- Close the vial tightly.
- Clearly label the vial on the side and on the top of the vial.
- ID Number, Timepoint, analyte type, Session number (e.g., 1, Baseline sAA/cort, S1)
- Ask participant to place each sample in the saliva storage tube boxes.

Appendix B: Pilot Study Supplementary File

VR Tasks

On the first treatment day, exposure tasks included approaching a virtual spider in a clear enclosed container within a virtual kitchen. Participants were asked to approach the spider as closely as they could by walking towards it in the VR environment (Task 1). They were then required to walk towards the spider and lift the lid of the container using their real hand which mimicked a VR hand in the VR world (Task 2). The third task (Task 3) required participants to touch the virtual spider with their VR hand and the spider would respond by fleeing (without tactile feedback). On the second treatment day, participants were encouraged to lift a vase where an animated spider with wiggly legs would drift to the floor of the virtual kitchen and a scream sound would be heard through the speakers of the headset (Task 4). They were then required to touch the VR spider with their VR hand to explore the virtual spider. Simultaneously, their real hand would explore a model spider attached to a stand in order to allow the spider to feel more realistic and tangible (Task 5) (Garcia-Palacios et al., 2002).

Study Timeline

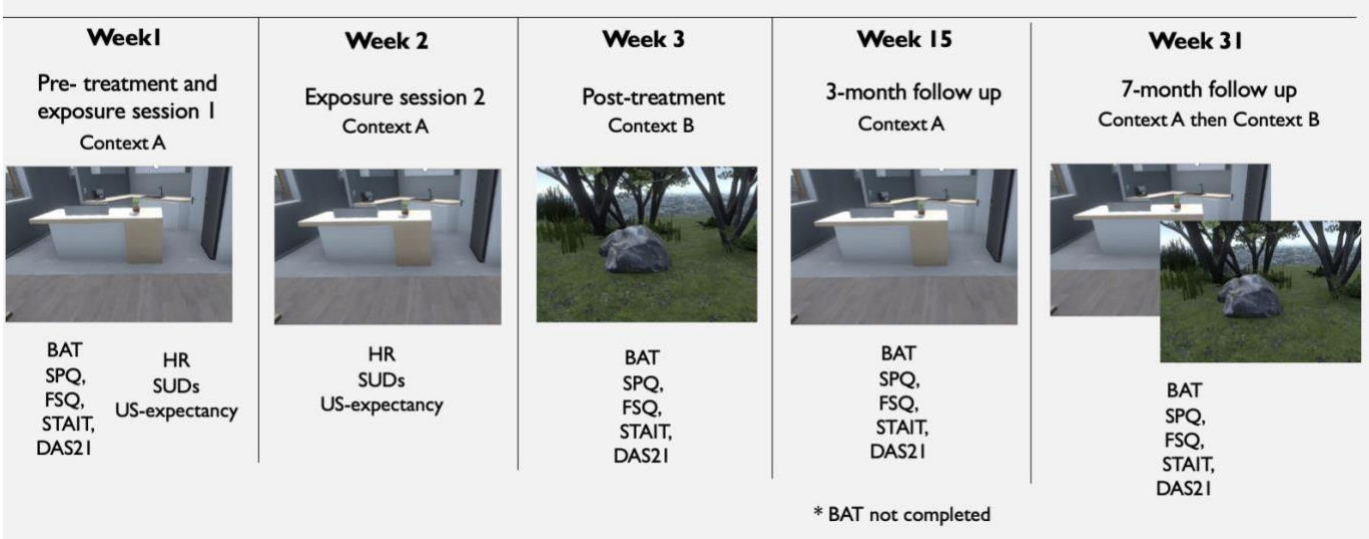


Figure 1. *Study timeline of procedures and implementation of measures*. Participants completed exposure sessions in a virtual kitchen (Context A) during week 1 and 2. The behavioural avoidance test (BAT) was completed at pre-treatment (Week 1) and 7-month follow-up (Week 31) in Context A to assess spontaneous recovery of fear. Participants were tested for renewal of fear in a virtual garden (Context B) at post-treatment (Week 3) and in both contexts at 7-month follow-up (Week 31). The BAT was not completed at 3-month follow-up (Week 15) due to COVID-19 lockdowns. Measures implemented at each visit are reported in the figure.

Note: BAT; Behavioural Avoidance Test; DASS21, Depression, Anxiety, Stress Scale-21; FSQ, Fear Spider Questionnaire; SPQ, Spider Phobia Questionnaire; STAIT, State- trait anxiety inventory; SUDs, Subjective Units of Discomfort

Saliva sampling Times

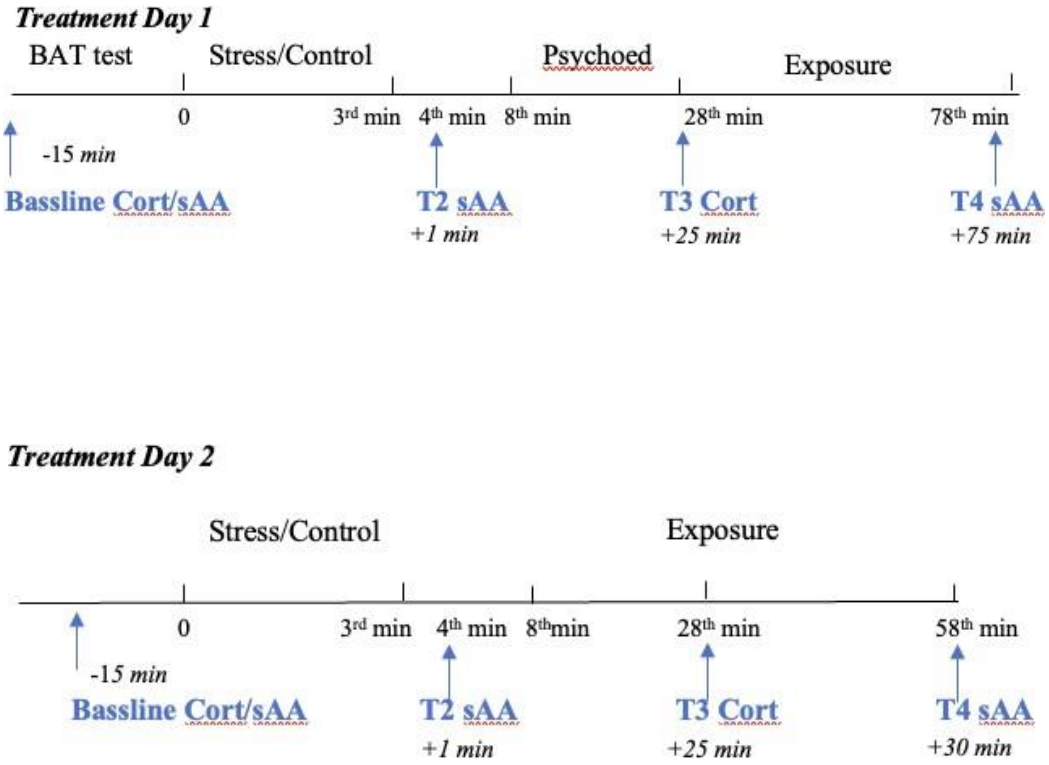


Figure 2. represents the timing of saliva samples on the first and second treatment day. The writing in blue indicates whether cortisol (cort) or alpha amylase (sAA) was sampled at a time point; Baseline, Time 2 (T2), Time 3 (T3) or Time 4 (T4). Time 0 begins with the start of the stress/control procedure and ends at the 3rd minute. Baseline cortisol and alpha amylase samples were collected 15 min prior to the stress/control task on both treatment days. Cortisol was sampled 25 min (T3 Cort) after the stress/control task on the first and second treatment day. Salivary alpha amylase was sampled 1min (T2 sAA) after the stress/control task on both days, and immediately after exposure therapy (T4 sAA); 75 min after the stress/control task on day 1 and 30min after stress/control task on day 2. The addition of psychoeducation on the first

treatment day meant the timing of saliva sampling after exposure therapy differed between treatment days.

Table 1. Procedures at each study visit

First point of contact	Inclusion/exclusion questions Brief study description and availability
Visit 1	Assessment /VR Preparation (1 – 1.5 hours) Information and Consent (included rationale for the study and stress/control procedure) Diagnostic assessment and demographic information Pre-treatment assessments (SPQ, FSQ, DAS-21, STAIT) Baseline EDA/ HR measured Taught to use and habituate to virtual reality headset then Baseline BAT test conducted in Context A (Kitchen) Treatment (1.5 – 2 hours) Stress or control procedure and saliva samples Psychoeducation about exposure therapy and discussion of coping strategies (20 min) Up to three guided exposure tasks (US-expectancy ratings before during and after; SUDs, SCR, HR throughout) (50min)
Visit 2	Assessment (15 min) Questions about the past week Treatment (1.5 -2 hours) Stress or Control Procedure and saliva samples Guided exposure tasks (US-expectancy ratings before during and after; SUDs, SCR, HR throughout) in Context A (Kitchen) (up to 50min)
Visit 3	Assessment (30 min) Questions about the past week Post-treatment assessment (SPQ, FSQ, DAS-21, STAIT) BAT in Context B
Visit 4	Assessment (30 min) Questions about the past week Follow-up assessment (SPQ, FSQ, DAS-21, STAIT) BAT in Context A
Visit 5	Assessment (30 min) Questions about the past week Follow-up assessment (SPQ, FSQ, DAS-21, STAIT) BAT in Context A BAT in Context B

Table 2: Participant outcome measures and treatment implementation measures

	Initial Phone Screening	Week 1 Pre-treatment /Exposure session 1 (Baseline)	Week 2 Exposure Session 2	Week 3 Post-treatment assessment	Week 14 3-months Follow Up	Week 30 7-months Follow Up
Informed Consent		X				
Inclusion / Exclusion criteria	X					
MINI-Dips		X				
General info/ demographics	X					
FSQ		X		X	X	X
SPQ		X		X	X	X
BAT		X		X	X	X
SCR		X	X	X	X	X
US-expectancy Rating		X	X	X	X	X
DASS-21		X		X	X	X
STAIT		X		X	X	X
SUDs		X	X	X	X	X
Saliva sample		X	X			
Questionnaires about the past week		X	X	X	X	X

Cortisol Response to Stress

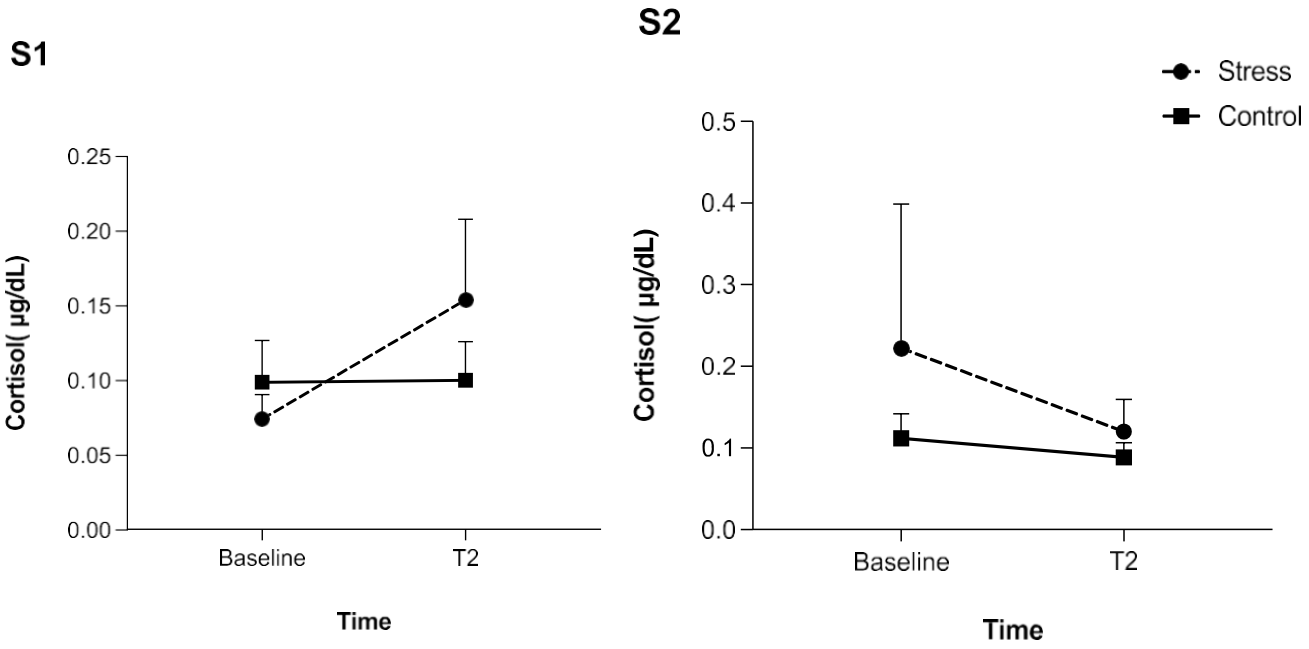


Figure 2. Cortisol Response at Session 1 (S1) and Session (S2), across time points; Baseline, and 25min. after stress or control procedure (T2). Note: Error bars represent standard error of means.

Renewal of Fear at Post-treatment

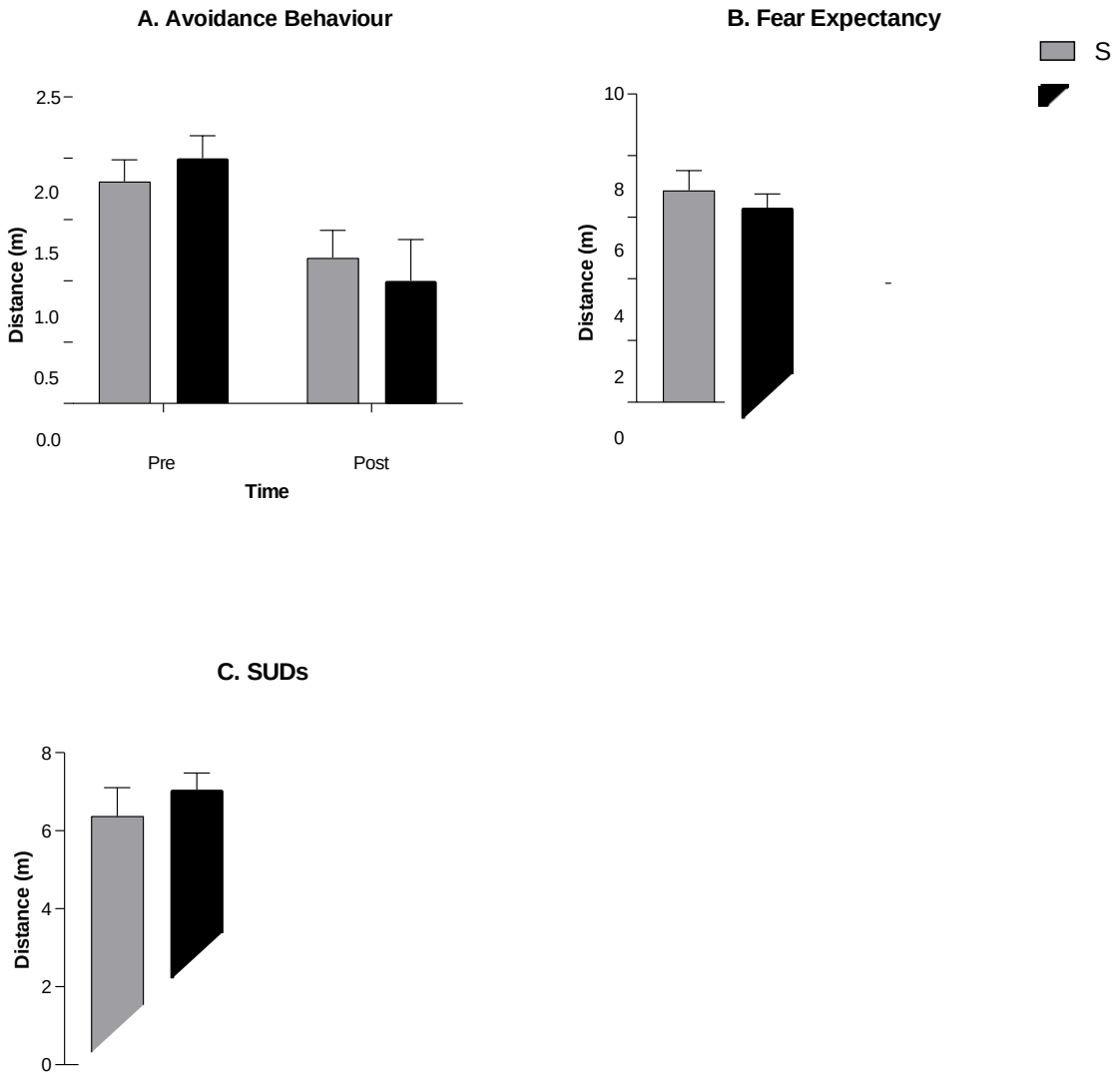


Figure 6. Presents participants avoidance behaviour (A), fear expectancy (B) subjective units of distress (SUDs)(C) and mean heart rate (D) during the behavioural avoidance test (BAT) at pre- and post-treatment. Participants were tested in the original treatment context at pre- and in the novel context at post-treatment. Group differences at post-treatment were compared, controlling for pre-treatment values as values at post-treatment assess renewal of fear. Note: Error bars represent standard error of the mean.

Table 5.1 Pearson correlations matrix with cortisol and treatment outcome variables (SPQ, FSQ, BAT)

		Day1 Cortisol T2	**Day2 Cortisol Baseline**	**Day2 Cortisol T2**	**Pre-Post diff SPQ**	**Pre-3mFU diff SPQ**	**Pre-7mFU diff SPQ**	**Pre-Post diff FSQ**	**Pre-3mFU diff FSQ**	**Pre-7mFU-diff FSQ**	**Pre_Post diff BATDist**	**Pre-7mFU diff BATDist**
Day1 Cortisol T2	Pearson Correlation	1	.200	.438	.137	-.240	-.016	.037	-.193	-.053	-.180	-.403
	Sig. (2-tailed)		.426	.069	.589	.338	.949	.884	.442	.834	.476	.098
	N	18	18	18	18	18	18	18	18	18	18	18
Day2 Cortisol Baseline	Pearson Correlation	.200	1	.847**	-.157	.282	.599**	.072	.280	.515*	.252	.388
	Sig. (2-tailed)	.426		<.001	.534	.256	.009	.777	.261	.029	.312	.112
	N	18	18	18	18	18	18	18	18	18	18	18
Day2 Cortisol T2	Pearson Correlation	.438	.847**	1	-.073	.269	.516*	.156	.263	.408	.060	.100
	Sig. (2-tailed)	.069	<.001		.774	.280	.029	.537	.292	.093	.814	.692
	N	18	18	18	18	18	18	18	18	18	18	18
Pre-Post diff. SPQ	Pearson Correlation	.137	-.157	-.073	1	.563*	.498*	.547*	.255	.406	-.372	-.127
	Sig. (2-tailed)	.589	.534	.774		.015	.036	.019	.306	.095	.128	.615
	N	18	18	18	18	18	18	18	18	18	18	18

Pre-3mFU diff SPQ	Pearson Correlation	-.240	.282	.269	.563*	1	.610**	.528*	.565*	.536*	-.204	.098
	Sig. (2-tailed)	.338	.256	.280	.015		.007	.024	.014	.022	.416	.698
	N	18	18	18	18	18	18	18	18	18	18	18
Pre-7mFU diff SPQ	Pearson Correlation	-.016	.599**	.516*	.498*	.610**	1	.432	.483*	.833**	.177	.364
	Sig. (2-tailed)	.949	.009	.029	.036	.007		.073	.042	<.001	.481	.138
	N	18	18	18	18	18	18	18	18	18	18	18
Pre-Post diff FSQ	Pearson Correlation	.037	.072	.156	.547*	.528*	.432	1	.850**	.630**	-.117	.212
	Sig. (2-tailed)	.884	.777	.537	.019	.024	.073		<.001	.005	.644	.398
	N	18	18	18	18	18	18	18	18	18	18	18
Pre-3mFU diff FSQ	Pearson Correlation	-.193	.280	.263	.255	.565*	.483*	.850**	1	.781**	.069	.344
	Sig. (2-tailed)	.442	.261	.292	.306	.014	.042	<.001		<.001	.785	.162
	N	18	18	18	18	18	18	18	18	18	18	18
Pre-7mFU-diff FSQ	Pearson Correlation	-.053	.515*	.408	.406	.536*	.833**	.630**	.781**	1	.221	.334
	Sig. (2-tailed)	.834	.029	.093	.095	.022	<.001	.005	<.001		.377	.175
	N	18	18	18	18	18	18	18	18	18	18	18

Pre_Post diff BATDist	Pearson Correlation	-.180	.252	.060	-.372	-.204	.177	-.117	.069	.221	1	.369
	Sig. (2-tailed)	.476	.312	.814	.128	.416	.481	.644	.785	.377		.132
	N	18	18	18	18	18	18	18	18	18	18	18
Pre-7mFU diff BATDist	Pearson Correlation	-.403	.388	.100	-.127	.098	.364	.212	.344	.334	.369	1
	Sig. (2-tailed)	.098	.112	.692	.615	.698	.138	.398	.162	.175	.132	
	N	18	18	18	18	18	18	18	18	18	18	18

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Note: Difference scores calculated from pre- to post-treatment(pre- post diff), pre-treatment to 3-month follow-up (pre-3mfu diff), pre-treatment to 7-month follow-up. FSQ, Fear Spider Questionnaire; SPQ, Spider Phobia Questionnaire; BAtDist, Behavioural Avoidance test minimum distance. Cortisol concentrations at baseline on the second day, and 25min after the stress or control procedure (T2) on both treatment days are presented. Significant correlations between cortisol and treatment outcomes are highlighted in bold.

Appendix C: RCT Study Supplementary File

Table 1. Treatment scores across groups.

	PRE-TREATMENT	POST-TREATMENT	3-MONTHS FOLLOW-UP
FSQ	95.62(18.82)	53.68(16.02)	52.44(18.35)
SPQ	11.66 (2.41)	6.90(2.68)	6.85(2.63)
BAT SCORE	2.32 (0.14)	5.14 (0.09)	4.97(0.06)

Note. Means (SD) of each primary outcome, across the treatment phases (pre-treatment, post-treatment and 3-month follow up). Lower scores on the FSQ and SPQ reflect less phobic symptoms. Higher scores on the BAT reflect less avoidance.

Renewal Test at Post-treatment

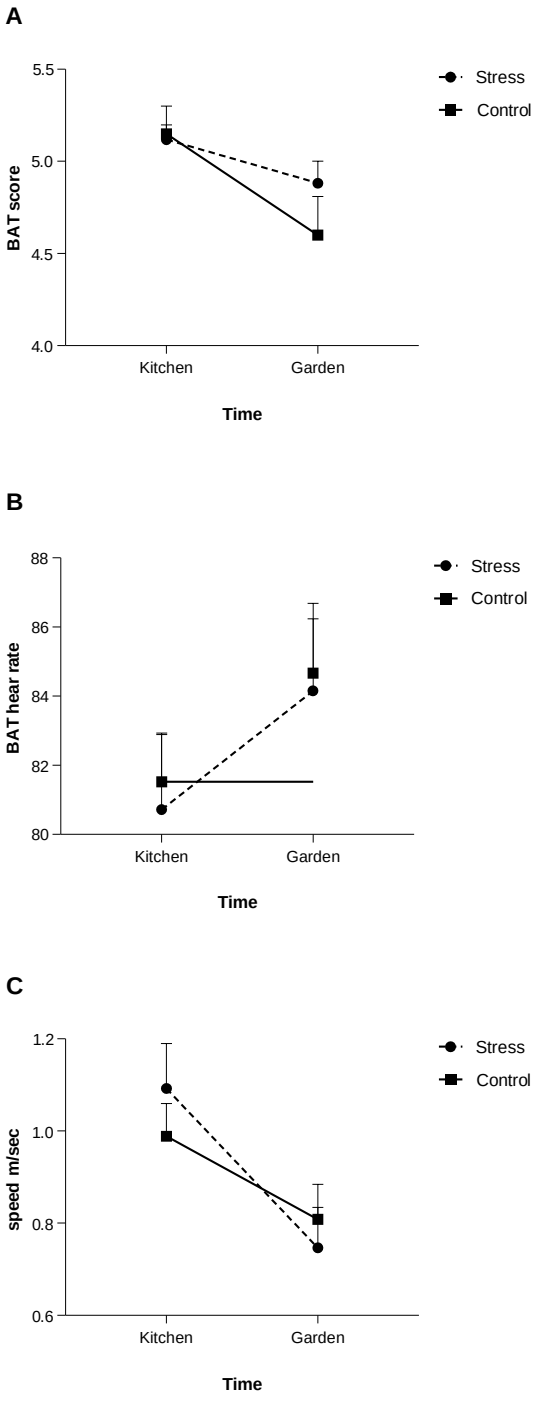


Figure 1. Performance during the Behavioural avoidance test (BAT) during testing in the Kitchen (original treatment context) and the Garden (novel context), measured by (A) behavioural score (B) heart rate, and (C) speed approaching the spider. Error bars represent standard error of the means. Higher BAT scores and speed reflect less fear-related avoidance and lower heart rate indicates less fear responding.

Effects of Stress on Attention

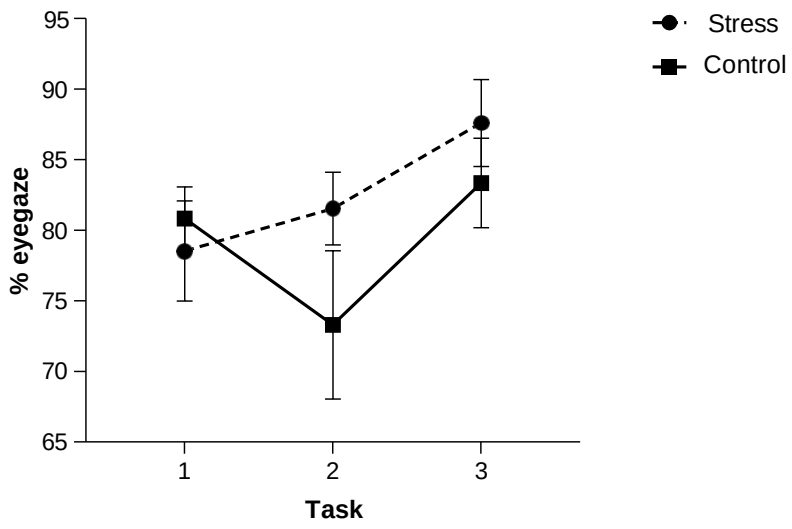


Figure 2. Percentage of eyegaze, during the first 3 tasks; Group differences were analysed during Task 1, Task 2, and Task 3. Note: Error bars represent standard error of means.

Mediation Models

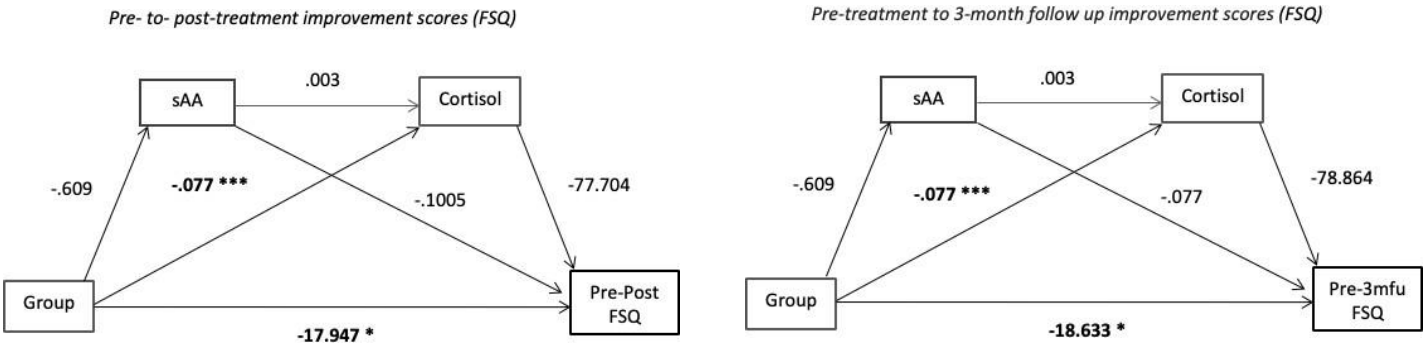


Figure 3. Mediation Model 1 for NE and cortisol mediating the effect of group on symptom improvement from pre- to post-treatment (Pre-Post) on the left, and pre-treatment to 3-month follow-up (Pre-3FU), on the right, measured by the Fear of Spider Questionnaire (FSQ). Note control variables were age and gender. *** P<.001** P<.01, *P<.05, (*) indicates p-value is approaching significance.

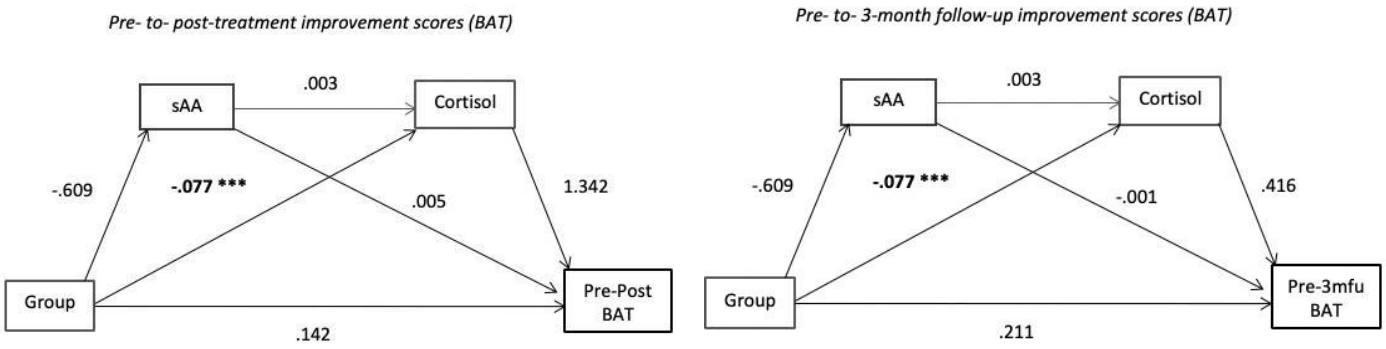


Figure 4. Mediation Model 1 for NE and cortisol mediating the effect of group on symptom improvement from pre- to post-treatment (Pre-Post) on the left, and pre-treatment to 3-month follow-up (Pre-3FU), on the right, measured by the difference in scores on the behavioural avoidance (BAT). Note control variables were age and gender. *** P<.001** P<.01, *P<.05, (*) indicates p-value is approaching significance.

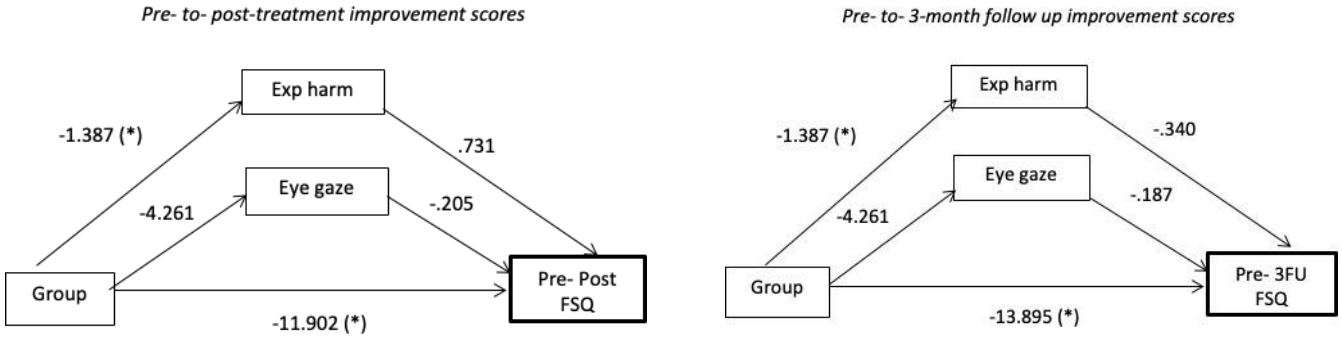


Figure 5. Mediation Model 2 for expectancy of harm violation and eyegaze separately mediating the effect of group on symptom improvement from pre- to post-treatment (Pre-Post), pre-treatment to 3-month follow-up (Pre-3FU) measured by the Fear of Spider Questionnaire (FSQ). Note control variables were age and gender. (*) indicates p-value is approaching significance

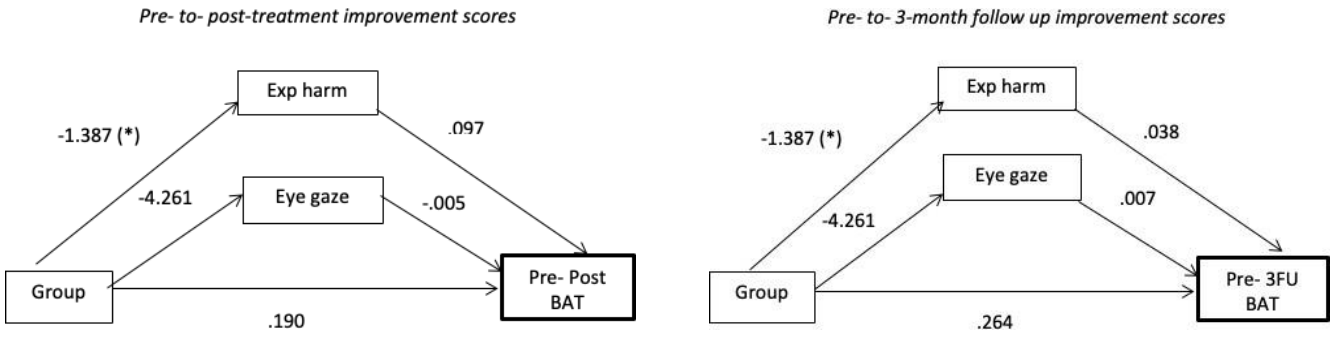


Figure 6. Mediation Model 2 for expectancy of harm violation and eyegaze separately mediating the effect of group on symptom improvement from pre- to post-treatment (Pre-Post), pre-treatment to 3-month follow-up (Pre-3FU) measured by the difference in scores on the Behavioural Avoidance Test (BAT). Note control variables were age and gender. (*) indicates p-value is approaching significance

Appendix D: SPSS Output

Pilot Study

Multiple Imputations Analysis

Independent Sample T-Tests: STAIT

N=18
Group 1= Stress =8
Group 2= Control =10
Covariate: none
Exclusions: none
Outcome: No sig. difference in STAIT scores (p=.414) between stress and control groups at pre-treatment.
Comment: equal variance assumed

Group Statistics

	Mean Group	N	Mean	Std. Deviation	Std. Error Mean
Mean Pre_Stait_Total	1.00	8	42.6250	5.55331	1.96339
	2.00	10	44.8694	5.70500	1.80408

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
Mean Pre_Stait_Total	Equal variances assumed	.000	.988	-.839	16	.414	-2.24441	2.67488	-7.91490	3.42607
	Equal variances not assumed			-.842	15.318	.413	-2.24441	2.66639	-7.91744	3.42861

Independent Sample T-Tests: Age
N=18
Group 1= Stress =8
Group 2= Control =10

Covariate: none
Exclusions: None
Outcome: No sig. difference in age (p=.401) between stress and control groups.
Comment: equal variance assumed

Group Statistics

	Mean Group	N	Mean	Std. Deviation	Std. Error Mean
Mean Age	1.00	8	32.6250	9.59073	3.39084
	2.00	10	29.3590	6.47421	2.04733

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Mean Age	Equal variances assumed	1.276	.275	.862	16	.401	3.26598	3.78938	-4.76716	11.29911
	Equal variances not assumed			.825	11.813	.426	3.26598	3.96097	-5.37942	11.91137

Effects of VR Exposure Therapy

One-way Repeated Measures: FSQ
N =18
Group 1= Stress= 8
Group 2 = Control=10

Covariate: Nil
Exclusions: none
Outcome: Significant differences across time points in FSQ scores. Post-hoc tests revealed a reduction in FSQ scores from pre to post, pre to 3FU, pre to 7mfu and post to 3mFU across groups.

Descriptive Statistics

	Mean	Std. Deviation	N
Mean Pre_fsq_Total	95.5556	16.49322	18

Mean Post_fsq_Total	52.3009	12.82356	18
Mean 3mFU_fsq_Total	43.5121	10.55715	18
Mean 7mFU_fsq_Total	50.0216	12.85620	18

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
Time	Pillai's Trace	.884	38.006[b]	3.000	15.000	.000
	Wilks' Lambda	.116	38.006[b]	3.000	15.000	.000
	Hotelling's Trace	7.601	38.006[b]	3.000	15.000	.000
	Roy's Largest Root	7.601	38.006[b]	3.000	15.000	.000

a. Design: Intercept
Within Subjects Design: Time
b. Exact statistic

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	30499.393	3	10166.464	73.507	.000
	Greenhouse-Geisser	30499.393	2.226	13699.813	73.507	.000
	Huynh-Feldt	30499.393	2.577	11834.977	73.507	.000
	Lower-bound	30499.393	1.000	30499.393	73.507	.000
Error(Time)	Sphericity Assumed	7053.594	51	138.306		
	Greenhouse-Geisser	7053.594	37.846	186.374		
	Huynh-Feldt	7053.594	43.810	161.004		
	Lower-bound	7053.594	17.000	414.917		

Post-hoc

Pairwise Comparisons
Measure: MEASURE_1

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b] Lower Bound	Upper Bound
Pre_fsq	Post_fsq	43.255*	4.123	.000	34.557	51.953
	3mFU_fsq	52.043*	4.776	.000	41.967	62.120
	7mfU_fsq	45.534*	4.667	.000	35.687	55.381
Post_fsq	Pre_fsq	-43.255*	4.123	.000	-51.953	-34.557
	3mfu_fsq	8.789*	2.516	.003	3.481	14.097
	7mfU_fsq	2.279	3.812	.558	-5.763	10.321
3mfu_fsq	Pre_fsq	-52.043*	4.776	.000	-62.120	-41.967
	Post_fsq	-8.789*	2.516	.003	-14.097	-3.481

	7mfU_fsq	-6.509	3.124	.053	-13.100	.081
7mfU_fsq	Pre_fsq	-45.534*	4.667	.000	-55.381	-35.687
	Post_fsq	-2.279	3.812	.558	-10.321	5.763
	3mfu_fsq	6.509	3.124	.053	-.081	13.100

Based on estimated marginal means
*. The mean difference is significant at the .05 level.
b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

One-way Repeated Measures: SPQ

N =18
Group 1= Stress= 8
Group 2 = Control=10
Covariate: Nil
Exclusions: None
Outcome: Significant differences across time points in SPQ scores. Post-hoc tests revealed a reduction in SPQ scores from pre to post, pre to 3mfU, and pre to 6mfu.

Descriptive Statistics

	Mean	Std. Deviation	N
Mean Pre_spq_Total	11.2222	2.34033	18
Mean Post_spq_Total	8.10642	3.475863	18
Mean FU_spq_Total	6.8706	2.45948	18
Mean 7mFU_spq_Total	7.6368	3.26617	18

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
Time	Pillai's Trace	.762	15.968[b]	3.000	15.000	.000
	Wilks' Lambda	.238	15.968[b]	3.000	15.000	.000
	Hotelling's Trace	3.194	15.968[b]	3.000	15.000	.000
	Roy's Largest Root	3.194	15.968[b]	3.000	15.000	.000

a. Design: Intercept
Within Subjects Design: Time
b. Exact statistic

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	197.257	3	65.752	14.971	.000
	Greenhouse-Geisser	197.257	2.698	73.104	14.971	.000
	Huynh-Feldt	197.257	3.000	65.752	14.971	.000

	Lower-bound	197.257	1.000	197.257	14.971	.001
Error(Time)	Sphericity Assumed	223.984	51	4.392		
	Greenhouse-Geisser	223.984	45.871	4.883		
	Huynh-Feldt	223.984	51.000	4.392		
	Lower-bound	223.984	17.000	13.176		

Post Hoc

Pairwise Comparisons
Measure: MEASURE_1

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b] Lower Bound	Upper Bound
Pre_spq	Post_spq	3.116*	.716	.000	1.605	4.626
	3mFU_spq	4.352*	.591	.000	3.105	5.599
	7mfU_spq	3.585*	.813	.000	1.869	5.302
Post_spq	Pre_spq	-3.116*	.716	.000	-4.626	-1.605
	3mfu_spq	1.236	.621	.063	-.074	2.545
	7mfU_spq	.470	.771	.551	-1.158	2.097
3mfu_spq	Pre_spq	-4.352*	.591	.000	-5.599	-3.105
	Post_spq	-1.236	.621	.063	-2.545	.074
	7mfU_spq	-.766	.651	.256	-2.140	.608
7mfU_spq	Pre_spq	-3.585*	.813	.000	-5.302	-1.869
	Post_spq	-.470	.771	.551	-2.097	1.158
	3mfu_spq	.766	.651	.256	-.608	2.140

Based on estimated marginal means
*. The mean difference is significant at the .05 level.
b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Effects of Stress on Exposure Therapy

Two-way Repeated Measures ANCOVA Analysis: FSQ
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 3mFU_FSQ, 7mFU_ FSQ

Covariate: Pre_FSQ
Exclusions: None

Outcome: Significant difference between stress and control groups across time points in FSQ scores. Stress group showed sig. less phobic symptoms on average across follow-up periods (3mFU, 7mFU) , relative to control group.

Descriptive Statistics

	Mean Group	Mean	Std. Deviation	N
Mean FU_fsq_Total	1.00	37.6075	10.38312	8
	2.00	48.2358	8.41951	10
	Total	43.5121	10.55715	18
Mean 7mFU_fsq_Total	1.00	41.6041	10.96217	8
	2.00	56.7555	10.26491	10
	Total	50.0216	12.85620	18

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	6.807	1	6.807	.072	.792	.005
	Greenhouse-Geisser	6.807	1.000	6.807	.072	.792	.005
	Huynh-Feldt	6.807	1.000	6.807	.072	.792	.005
	Lower-bound	6.807	1.000	6.807	.072	.792	.005
factor1 * Mean_Pre_fsq_Total	Sphericity Assumed	33.485	1	33.485	.355	.560	.023
	Greenhouse-Geisser	33.485	1.000	33.485	.355	.560	.023
	Huynh-Feldt	33.485	1.000	33.485	.355	.560	.023
	Lower-bound	33.485	1.000	33.485	.355	.560	.023
factor1 * Mean_Group	Sphericity Assumed	38.072	1	38.072	.404	.535	.026
	Greenhouse-Geisser	38.072	1.000	38.072	.404	.535	.026
	Huynh-Feldt	38.072	1.000	38.072	.404	.535	.026
	Lower-bound	38.072	1.000	38.072	.404	.535	.026
Error(factor1)	Sphericity Assumed	1413.808	15	94.254			
	Greenhouse-Geisser	1413.808	15.000	94.254			
	Huynh-Feldt	1413.808	15.000	94.254			

Lower-bound	1413.808	15.000	94.254			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	2262.479	1	2262.479	19.608	.000	.567
Mean_Pre_fsq_Total	4.041	1	4.041	.035	.854	.002
Mean_Group	1478.352	1	1478.352	12.812	.003	.461
Error	1730.823	15	115.388			

Two-way Repeated Measures ANCOVA Analysis: SPQ
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 3mFU_SPQ, 7mFU_ SPQ

Covariate: Pre_SPQ
Exclusions: None
Outcome: Stress group showed sig. less phobic symptoms at 3-month follow-up, relative to control group.

Descriptive Statistics

	Mean Group	Mean	Std. Deviation	N
Mean FU_spq_Total	1.00	6.3585	2.59666	8
	2.00	7.2803	2.40044	10
	Total	6.8706	2.45948	18
Mean 7mFU_spq_Total	1.00	5.7833	2.89707	8
	2.00	9.1195	2.85062	10
	Total	7.6368	3.26617	18

Multivariate Tests[a]

Effect	Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared

factor1	Pillai's Trace	.079	1.287[b]	1.000	15.000	.274	.079
	Wilks' Lambda	.921	1.287[b]	1.000	15.000	.274	.079
	Hotelling's Trace	.086	1.287[b]	1.000	15.000	.274	.079
	Roy's Largest Root	.086	1.287[b]	1.000	15.000	.274	.079
factor1 * Mean_Pre_spq_Total	Pillai's Trace	.057	.904[b]	1.000	15.000	.357	.057
	Wilks' Lambda	.943	.904[b]	1.000	15.000	.357	.057
	Hotelling's Trace	.060	.904[b]	1.000	15.000	.357	.057
	Roy's Largest Root	.060	.904[b]	1.000	15.000	.357	.057
factor1 * Mean_Group	Pillai's Trace	.241	4.751[b]	1.000	15.000	.046	.241
	Wilks' Lambda	.759	4.751[b]	1.000	15.000	.046	.241
	Hotelling's Trace	.317	4.751[b]	1.000	15.000	.046	.241
	Roy's Largest Root	.317	4.751[b]	1.000	15.000	.046	.241

a. Design: Intercept + Mean_Pre_spq_Total + Mean_Group
Within Subjects Design: factor1

b. Exact statistic

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	16.193	1	16.193	1.511	.238	.092
Mean_Pre_spq_Total	18.250	1	18.250	1.703	.212	.102
Mean_Group	23.743	1	23.743	2.215	.157	.129
Error	160.751	15	10.717			

Post Hoc: Univariate Tests

Group differences at 3mFU

Descriptive Statistics
Dependent Variable: Mean FU_spq_Total

Mean Group	Mean	Std. Deviation	N
1.00	6.3585	2.59666	8
2.00	7.2803	2.40044	10

Total	6.8706	2.45948	18

Tests of Between-Subjects Effects
Dependent Variable: Mean FU_spq_Total

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	3.776[a]	1	3.776	.610	.446	.037
Intercept	826.743	1	826.743	133.537	.000	.893
Mean_Group	3.776	1	3.776	.610	.446	.037
Error	99.057	16	6.191			
Total	952.530	18				
Corrected Total	102.834	17				

a. R Squared = .037 (Adjusted R Squared = -.023)

Group differences at 7mFU

Descriptive Statistics
Dependent Variable: Mean 7mFU_spq_Total

Mean Group	Mean	Std. Deviation	N
1.00	5.7833	2.89707	8
2.00	9.1195	2.85062	10
Total	7.6368	3.26617	18

Tests of Between-Subjects Effects
Dependent Variable: Mean 7mFU_spq_Total

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	49.468[a]	1	49.468	6.001	.026	.273
Intercept	987.088	1	987.088	119.751	.000	.882
Mean_Group	49.468	1	49.468	6.001	.026	.273
Error	131.886	16	8.243			
Total	1231.118	18				
Corrected Total	181.354	17				

a. R Squared = .273 (Adjusted R Squared = .227)

One-way Repeated Measures: BAT Distance
N =18
Group 1= Stress= 8
Group 2 = Control=10

Dependent variables: Pre-treatment Bat distance, 7mFU BAT distance tested in Kitchen
Covariate: Nil
Exclusions: None
Outcome: p<.001. Significant reduction in min distance during BAT from pre to 7mfu

Within-Subjects Factors
Measure: MEASURE_1

factor1	Dependent Variable
1	Mean_Pre_BAT_ Distance
2	Mean_FU7_BAT _DIstance_K

Means
Measure: MEASURE_1

			95% Confidence Interval	
factor1	Mean	Std. Error	Lower Bound	Upper Bound
1	1.874	.125	1.609	2.139
2	.817	.053	.705	.928

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
factor1	Pillai's Trace	.770	56.985[b]	1.000	17.000	.000
	Wilks' Lambda	.230	56.985[b]	1.000	17.000	.000
	Hotelling's Trace	3.352	56.985[b]	1.000	17.000	.000
	Roy's Largest Root	3.352	56.985[b]	1.000	17.000	.000

a. Design: Intercept
Within Subjects Design: factor1
b. Exact statistic

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	10.061	1	10.061	56.985	.000
	Greenhouse-Geisser	10.061	1.000	10.061	56.985	.000
	Huynh-Feldt	10.061	1.000	10.061	56.985	.000
	Lower-bound	10.061	1.000	10.061	56.985	.000
Error(factor1)	Sphericity Assumed	3.001	17	.177		
	Greenhouse-Geisser	3.001	17.000	.177		
	Huynh-Feldt	3.001	17.000	.177		
	Lower-bound	3.001	17.000	.177		

One-way Repeated Measures: BAT Expectancy Ratings
N =18
Group 1= Stress= 8
Group 2 = Control=10

Dependent variables: Pre-treatment Bat Expectancy ratings, 7mFU BAT expectancy ratings tested in Kitchen
Covariate: Nil
Exclusions: None
Outcome: p<.001. Significant reduction in expectancy ratings from pre to 7mfu.

Within-Subjects Factors

Measure: MEASURE_1

factor1	Dependent Variable
1	Mean_Pre_BAT_Expectancy
2	Mean_7mFU_BAT_Expectancy

2. Means
Measure: MEASURE_1

factor1	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
1	7.167	.373	6.380	7.953
2	4.058	.391	3.232	4.884

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
factor1	Pillai's Trace	.609	26.531[b]	1.000	17.000	.000
	Wilks' Lambda	.391	26.531[b]	1.000	17.000	.000
	Hotelling's Trace	1.561	26.531[b]	1.000	17.000	.000
	Roy's Largest Root	1.561	26.531[b]	1.000	17.000	.000

1. Design: Intercept
Within Subjects Design: factor1
2. Exact statistic

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	86.977	1	86.977	26.531	.000
	Greenhouse-Geisser	86.977	1.000	86.977	26.531	.000
	Huynh-Feldt	86.977	1.000	86.977	26.531	.000
	Lower-bound	86.977	1.000	86.977	26.531	.000
Error(factor1)	Sphericity Assumed	55.730	17	3.278		
	Greenhouse-Geisser	55.730	17.000	3.278		
	Huynh-Feldt	55.730	17.000	3.278		
	Lower-bound	55.730	17.000	3.278		

One-way Repeated Measures: BAT SUDs Ratings
N =18
Group 1= Stress= 8
Group 2 = Control=10

Dependent variables: Pre-treatment Bat SUDs ratings, 7mFU BAT SUDs ratings tested in Kitchen
Covariate: Nil
Exclusions: None
Outcome: p<.001. Significant reduction in expectancy ratings from pre to 7mfu.

Within-Subjects Factors
Measure:
MEASURE_1

factor1	Dependent Variable
1	Mean_Pre_BAT_suds
2	Mean_7mFU_BAT_suds

2. factor1
Measure: MEASURE_1

			95% Confidence Interval	
factor1	Mean	Std. Error	Lower Bound	Upper Bound
1	6.750	.397	5.913	7.587
2	2.886	.301	2.251	3.520

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
factor1	Pillai's Trace	.742	48.818[b]	1.000	17.000	.000
	Wilks' Lambda	.258	48.818[b]	1.000	17.000	.000
	Hotelling's Trace	2.872	48.818[b]	1.000	17.000	.000
	Roy's Largest Root	2.872	48.818[b]	1.000	17.000	.000

a. Design: Intercept
Within Subjects Design: factor1
b. Exact statistic

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	134.407	1	134.407	48.818	.000
	Greenhouse-Geisser	134.407	1.000	134.407	48.818	.000
	Huynh-Feldt	134.407	1.000	134.407	48.818	.000
	Lower-bound	134.407	1.000	134.407	48.818	.000
Error(factor1)	Sphericity Assumed	46.805	17	2.753		
	Greenhouse-Geisser	46.805	17.000	2.753		
	Huynh-Feldt	46.805	17.000	2.753		
	Lower-bound	46.805	17.000	2.753		

Univariate Analysis of Variance: BAT Distance 7mFU
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 7mFU_ BAT_distance

Covariate: Pre_BAT_distance
Exclusions: None
Outcome: No sig, diff between stress and control groups in avoidance behaviour at 7mfu.

Descriptive Statistics

Dependent Variable: Mean FU7_BAT_DIstance_K

Mean Group	Mean	Std. Deviation	N
1.00	.721460	.1748395	8
2.00	.892775	.2390365	10
Total	.816635	.2247438	18

Mean Group
Dependent Variable: Mean FU7_BAT_DIstance_K

Tests of Between-Subjects Effects
Dependent Variable: Mean FU7_BAT_DIstance_K

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.144[a]	2	.072	1.510	.253
Intercept	1.040	1	1.040	21.829	.000
Mean_Pre_BAT_Distance	.013	1	.013	.282	.603
Mean_Group	.138	1	.138	2.899	.109
Error	.715	15	.048		
Total	12.863	18			
Corrected Total	.859	17			

a. R Squared = .168 (Adjusted R Squared = .057)

Univariate Analysis of Variance: BAT SUDs 7mFU

N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 7mFU_ BAT_SUDs

Covariate: Pre_BAT_SUDs
Exclusions: None
Outcome: Sig less SUDs ratings in stress group relative to control group at 7mfu.

Descriptive Statistics
Dependent Variable: Mean 7mFU_BAT_suds

Mean Group	Mean	Std. Deviation	N
1.00	2.3030	1.19560	8
2.00	3.3516	1.18996	10
Total	2.8855	1.27503	18

Tests of Between-Subjects Effects
Dependent Variable: Mean 7mFU_BAT_suds

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	8.047[a]	2	4.023	3.081	.076	.291
Intercept	20.336	1	20.336	15.571	.001	.509
Mean_Pre_BAT_suds	3.160	1	3.160	2.420	.141	.139
Mean_Group	6.392	1	6.392	4.894	.043	.246
Error	19.590	15	1.306			

Total	177.510	18				
Corrected Total	27.637	17				

a. R Squared = .291 (Adjusted R Squared = .197)

Univariate Analysis of Variance: BAT Expectancy Ratings 7mFU
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 7mFU_ BAT_Expectancy Ratings

Covariate: Pre_BAT_Expectancy Ratings
Exclusions: None
Outcome: No sig, diff between stress and control groups in Expectancy ratings during the BAT at 7mfu.

Descriptive Statistics
Dependent Variable: Mean 7mFU_BAT_Expectancy

Mean Group	Mean	Std. Deviation	N
1.00	3.4298	1.47049	8
2.00	4.5605	1.70207	10
Total	4.0579	1.66084	18

Tests of Between-Subjects Effects
Dependent Variable: Mean 7mFU_BAT_Expectancy

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	10.212[a]	2	5.106	2.088	.158
Intercept	31.339	1	31.339	12.816	.003
Mean_Pre_BAT_Expectancy	4.529	1	4.529	1.852	.194
Mean_Group	7.347	1	7.347	3.004	.104
Error	36.681	15	2.445		
Total	343.297	18			
Corrected Total	46.892	17			

a. R Squared = .218 (Adjusted R Squared = .113)

Univariate Analysis of Variance: BAT avg HR 7mFU
N =17
Group 1= Stress= 7

Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 7mFU_ BAT_avg HR

Covariate: Pre_BAT_avg HR
Exclusions: None
Outcome: Sig lower HR in stress group relative to control group at 7mfu.

Descriptive Statistics
Dependent Variable:
SCR_7mFUBAT_K_avg_HR

Mean Group	Mean	Std. Deviation	N
1.00	75.7866	4.96885	7
2.00	84.0971	6.26068	10
Total	80.6751	7.00573	17

Tests of Between-Subjects Effects
Dependent Variable: SCR_7mFUBAT_K_avg_HR

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	327.330[a]	2	163.665	5.003	.023
Intercept	929.287	1	929.287	28.409	.000
SCR_PreBAT_avg_HR	42.947	1	42.947	1.313	.271
Mean_Group	314.667	1	314.667	9.620	.008
Error	457.955	14	32.711		
Total	111429.400	17			
Corrected Total	785.285	16			

a. R Squared = .417 (Adjusted R Squared = .334)

Context Renewal Test

Univariate Analysis of Variance: BAT Garden Distance Post-Treatment
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: Post_ BAT_Distance

Covariate: Pre_BAT_Distance
Exclusions: None
Outcome: No sig, diff between stress and control groups in avoidance behaviour when tested in a novel context at post-treatment.

Descriptive Statistics
Dependent Variable: Mean Post_BAT_Distance

Mean Group	Mean	Std. Deviation	N
1.00	1.187814	.6291641	8
2.00	1.275035	1.0659235	10
Total	1.236270	.8754991	18

Tests of Between-Subjects Effects
Dependent Variable: Mean Post_BAT_Distance

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.692[a]	2	.346	.421	.664
Intercept	.364	1	.364	.443	.516
Mean_Pre_BAT_Distance	.658	1	.658	.800	.385
Mean_Group	.009	1	.009	.011	.919
Error	12.338	15	.823		
Total	40.541	18			
Corrected Total	13.030	17			

a. R Squared = .053 (Adjusted R Squared = -.073)

Univariate Analysis of Variance: BAT Expectancy Ratings Post-treatment Garden
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: Post_ BAT_Expectancy Ratings

Covariate: Pre_BAT_Expectancy Ratings
Exclusions: None
Outcome: No sig, diff between stress and control groups in Expectancy ratings during the renewal BAT test at post-treatment.

Descriptive Statistics
Dependent Variable: Mean Post_BAT_Expectancy

Mean Group	Mean	Std. Deviation	N
1.00	4.4291	1.49830	8
2.00	4.7666	1.22777	10
Total	4.6166	1.32371	18

Tests of Between-Subjects Effects
Dependent Variable: Mean Post_BAT_Expectancy

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.520[a]	2	.260	.133	.876
Intercept	17.301	1	17.301	8.867	.009
Mean_Pre_BAT_Expectancy	.013	1	.013	.007	.936
Mean_Group	.519	1	.519	.266	.613
Error	29.268	15	1.951		
Total	413.419	18			
Corrected Total	29.787	17			

a. R Squared = .017 (Adjusted R Squared = -.114)

Univariate Analysis of Variance: BAT SUDs Ratings Post-treatment Garden
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: Post_ BAT_SUDs Ratings

Covariate: Pre_BAT_SUDs Ratings
Exclusions: None
Outcome: No sig, diff between stress and control groups in SUDs ratings during the renewal BAT test at post-treatment.

Descriptive Statistics
Dependent Variable: Mean Post_BAT_suds

Mean Group	Mean	Std. Deviation	N
1.00	3.0546	1.77953	8
2.00	3.5560	1.25708	10
Total	3.3332	1.48536	18

Tests of Between-Subjects Effects
Dependent Variable: Mean Post_BAT_suds

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.296[a]	2	.648	.268	.768
Intercept	8.065	1	8.065	3.341	.088
Mean_Pre_BAT_suds	.179	1	.179	.074	.789
Mean_Group	.898	1	.898	.372	.551

Error	36.211	15	2.414		
Total	237.490	18			
Corrected Total	37.507	17			

a. R Squared = .035 (Adjusted R Squared = -.094)

Univariate Analysis of Variance: BAT HR Post-treatment Garden

N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: Post_ BAT_HR avg

Covariate: Pre_BAT_HR avg
Exclusions: None
Outcome: No sig, diff between stress and control groups in avg HR during the renewal BAT test at post-treatment, controlling for pre-BAT avg HR

Descriptive Statistics
Dependent Variable: SCR_PostBAT_avg_HR

Mean Group	Mean	Std. Deviation	N
1.00	78.1527	3.85697	8
2.00	79.8251	6.29527	10
Total	79.0818	5.27613	18

Tests of Between-Subjects Effects

Dependent Variable: SCR_PostBAT_avg_HR

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	51.416[a]	2	25.708	.914	.422
Intercept	1087.923	1	1087.923	38.687	.000
SCR_PreBAT_avg_HR	38.985	1	38.985	1.386	.257
Mean_Group	36.547	1	36.547	1.300	.272
Error	421.822	15	28.121		
Total	113044.034	18			

Corrected Total	473.238	17			

a. R Squared = .109 (Adjusted R Squared = -.010)

Two-way Repeated Measures ANOVA Analysis: 7mFU BAT Garden Distance
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 7mfu BAT distance Kitchen, 7mfu BAT distance Garden

Exclusions: None
Outcome: No sig group differences in BAT distance at 7mfu.

Descriptive Statistics

	Mean Group	Mean	Std. Deviation	N
Mean FU7_BAT_Distance_G	1.00	.782349	.1707439	8
	2.00	.812948	.1274943	10
	Total	.799348	.1444113	18
Mean FU7_BAT_DIstance_K	1.00	.721460	.1748395	8
	2.00	.892775	.2390365	10
	Total	.816635	.2247438	18

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
factor	Pillai's Trace	.002	.026[b]	1.000	16.000	.873
	Wilks' Lambda	.998	.026[b]	1.000	16.000	.873
	Hotelling's Trace	.002	.026[b]	1.000	16.000	.873
	Roy's Largest Root	.002	.026[b]	1.000	16.000	.873
factor * Mean_Group	Pillai's Trace	.084	1.462[b]	1.000	16.000	.244
	Wilks' Lambda	.916	1.462[b]	1.000	16.000	.244
	Hotelling's Trace	.091	1.462[b]	1.000	16.000	.244
	Roy's Largest Root	.091	1.462[b]	1.000	16.000	.244

a. Design: Intercept + Mean_Group
Within Subjects Design: factor
b. Exact statistic

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor	Sphericity Assumed	.001	1	.001	.026	.873
	Greenhouse-Geisser	.001	1.000	.001	.026	.873
	Huynh-Feldt	.001	1.000	.001	.026	.873
	Lower-bound	.001	1.000	.001	.026	.873
factor * Mean_Group	Sphericity Assumed	.044	1	.044	1.462	.244
	Greenhouse-Geisser	.044	1.000	.044	1.462	.244
	Huynh-Feldt	.044	1.000	.044	1.462	.244
	Lower-bound	.044	1.000	.044	1.462	.244
Error(factor)	Sphericity Assumed	.481	16	.030		
	Greenhouse-Geisser	.481	16.000	.030		
	Huynh-Feldt	.481	16.000	.030		
	Lower-bound	.481	16.000	.030		

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	22.891	1	22.891	613.334	.000
Mean_Group	.091	1	.091	2.427	.139
Error	.597	16	.037		

Two-way Repeated Measures ANOVA Analysis: 7mFU BAT Garden Expectancy Ratings
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 7mfu BAT Exp Kitchen, 7mfu BAT Exp Garden

Exclusions: None
Outcome: No group differences across context. Sig less fear responding across groups observed in garden context, relative to kitchen.

Descriptive Statistics

	Mean Group	Mean	Std. Deviation	N
Mean	1.00	3.8635	1.50279	8
7mFU_BAT_Expectancy	2.00	4.8765	1.06716	10
	Total	4.4263	1.34206	18
	1.00	2.5102	1.32711	8

Mean 7mfu_BAT_Expectancy_G	2.00	3.5748	1.44542	10
	Total	3.1017	1.45863	18

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
factor	Pillai's Trace	.613	25.304[b]	1.000	16.000	.000
	Wilks' Lambda	.387	25.304[b]	1.000	16.000	.000
	Hotelling's Trace	1.581	25.304[b]	1.000	16.000	.000
	Roy's Largest Root	1.581	25.304[b]	1.000	16.000	.000
factor * Mean_Group	Pillai's Trace	.001	.010[b]	1.000	16.000	.923
	Wilks' Lambda	.999	.010[b]	1.000	16.000	.923
	Hotelling's Trace	.001	.010[b]	1.000	16.000	.923
	Roy's Largest Root	.001	.010[b]	1.000	16.000	.923

a. Design: Intercept + Mean_Group
Within Subjects Design: factor
b. Exact statistic

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	488.403	1	488.403	165.263	.000
Mean_Group	9.592	1	9.592	3.246	.090
Error	47.285	16	2.955		

Two-way Repeated Measures ANOVA Analysis: 7mFU BAT Garden SUDs Ratings
N =18
Group 1= Stress= 8
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 7mfu SUDs Kitchen, 7mfu SUDs Garden

Exclusions: None
Outcome: Stress group reported sig. less anxiety across contexts, relative to control group.

Descriptive Statistics

	Mean Group	Mean	Std. Deviation	N
Mean 7mFU_BAT_suds	1.00	2.3030	1.19560	8
	2.00	3.3516	1.18996	10
	Total	2.8855	1.27503	18
Mean 7mfFU_BAT_suds_G	1.00	2.1156	1.16894	8
	2.00	3.6024	1.61188	10
	Total	2.9416	1.58622	18

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.001	.016[b]	1.000	16.000	.902	.001
	Wilks' Lambda	.999	.016[b]	1.000	16.000	.902	.001
	Hotelling's Trace	.001	.016[b]	1.000	16.000	.902	.001
	Roy's Largest Root	.001	.016[b]	1.000	16.000	.902	.001
factor1 * Mean_Group	Pillai's Trace	.045	.746[b]	1.000	16.000	.400	.045
	Wilks' Lambda	.955	.746[b]	1.000	16.000	.400	.045
	Hotelling's Trace	.047	.746[b]	1.000	16.000	.400	.045
	Roy's Largest Root	.047	.746[b]	1.000	16.000	.400	.045

a. Design: Intercept + Mean_Group
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	.009	1	.009	.016	.902	.001
	Greenhouse-Geisser	.009	1.000	.009	.016	.902	.001
	Huynh-Feldt	.009	1.000	.009	.016	.902	.001
	Lower-bound	.009	1.000	.009	.016	.902	.001
factor1 * Mean_Group	Sphericity Assumed	.427	1	.427	.746	.400	.045
	Greenhouse-Geisser	.427	1.000	.427	.746	.400	.045
	Huynh-Feldt	.427	1.000	.427	.746	.400	.045
	Lower-bound	.427	1.000	.427	.746	.400	.045
Error(factor1)	Sphericity Assumed	9.150	16	.572			
	Greenhouse-Geisser	9.150	16.000	.572			
	Huynh-Feldt	9.150	16.000	.572			
	Lower-bound	9.150	16.000	.572			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	287.411	1	287.411	98.791	.000	.861
Mean_Group	14.285	1	14.285	4.910	.042	.235
Error	46.549	16	2.909			

Two-way Repeated Measures ANOVA Analysis: 7mFU BAT HEART RATE
N =17
Group 1= Stress= 7
Group 2 = Control= 10

Between factor: Stress group, Control group
Within factor: 7mfu SUDs Kitchen, 7mfu SUDs Garden

Exclusions: Excluded one sig outlier in stress group
Outcome: Stress group reported sig. less anxiety across contexts, relative to control group.

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	232676.934	1	232676.934	7953.279	.000
Mean_Group	464.323	1	464.323	15.871	.001
Error	438.832	15	29.255		

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	554.342	1	554.342	15.009	.001
	Greenhouse-Geisser	554.342	1.000	554.342	15.009	.001
	Huynh-Feldt	554.342	1.000	554.342	15.009	.001
	Lower-bound	554.342	1.000	554.342	15.009	.001
factor1 * Mean_Group	Sphericity Assumed	5.293	1	5.293	.143	.710
	Greenhouse-Geisser	5.293	1.000	5.293	.143	.710
	Huynh-Feldt	5.293	1.000	5.293	.143	.710
	Lower-bound	5.293	1.000	5.293	.143	.710
Error(factor1)	Sphericity Assumed	553.998	15	36.933		
	Greenhouse-Geisser	553.998	15.000	36.933		
	Huynh-Feldt	553.998	15.000	36.933		
	Lower-bound	553.998	15.000	36.933		

Saliva Analysis

Independent Samples T-test: cort Day1 + Day 2

N =18

Group 1= Stress= 8

Group 2 = Control= 10

Group Statistics

	Mean Group	N	Mean	Std. Deviation	Std. Error Mean
Mean Day1_cort_Baseline	1.00	8	.089949	.0735713	.0260114
	2.00	10	.094641	.0603063	.0190705
Mean Day1_cort_2	1.00	8	.115466	.1339012	.0473412
	2.00	10	.094558	.0753373	.0238237
Mean Day2_cort_Baseline	1.00	8	.161711	.3102438	.1096878
	2.00	10	.107382	.0648938	.0205212
Mean Day2_cort_2	1.00	8	.103917	.0975610	.0344930
	2.00	10	.082861	.0528910	.0167256

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
Mean Day1_cort_Baseline	Equal variances assumed	.001	.978	-.149	16	.884	-.0046916	.0315136	-.0714974	.0621142
	Equal variances not assumed			-.145	13.511	.886	-.0046916	.0322533	-.0741035	.0647203
Mean Day1_cort_2	Equal variances assumed	.695	.417	.420	16	.680	.0209073	.0498324	-.0847327	.1265473
	Equal variances not assumed			.394	10.472	.701	.0209073	.0529978	-.0964616	.1382762
Mean Day2_cort_Baseline	Equal variances assumed	3.319	.087	.543	16	.595	.0543291	.1000385	-.1577432	.2664013

	Equal variances not assumed			.487	7.491	.640	.0543291	.1115909	-.2060725	.3147306
Mean Day2_cort_2	Equal variances assumed	2.713	.119	.586	16	.566	.0210566	.0359304	-.0551125	.0972257
	Equal variances not assumed			.549	10.239	.595	.0210566	.0383342	-.0640884	.1062016

Independent Samples T-test: sAA Day1 + Day 2

N =18

Group 1= Stress= 8

Group 2 = Control= 10

Group Statistics

	Mean Group	N	Mean	Std. Deviation	Std. Error Mean
Mean Day1_sAA_Baseline	1.00	8	111.159830	88.1942407	31.1813728
	2.00	10	92.873178	78.1571599	24.7154641
Mean Day1_sAA_2	1.00	8	131.848724	87.4467135	30.9170820
	2.00	9	60.042222	42.8836830	14.2945610
Mean Day1_sAA_3	1.00	8	166.674522	123.4391036	43.6423136
	2.00	10	82.777186	76.7757373	24.2786199
Mean Day2_sAA_Baseline	1.00	8	151.413000	73.3145120	25.9205943
	2.00	10	86.460800	61.9457426	19.5889638
Mean Day2_sAA_2	1.00	8	112.791000	74.4319870	26.3156814
	2.00	10	38.513925	30.6920400	9.7056752
Mean Day2_sAA_3	1.00	8	118.080000	61.7407805	21.8286623
	2.00	10	61.483600	51.8501417	16.3964545

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Mean Day1_sAA_Baseline	Equal variances assumed	.004	.949	.466	16	.647	18.2866522	39.2273022	-64.8715136	101.4448180

	Equal variances not assumed			.460	14.200	.653	18.2866522	39.7885936	-66.9390434	103.5123479
Mean Day1_sAA_2	Equal variances assumed	.660	.429	2.191	15	.045	71.8065016	32.7743377	1.9496543	141.6633489
	Equal variances not assumed			2.108	9.916	.061	71.8065016	34.0617151	-4.1748099	147.7878130
Mean Day1_sAA_3	Equal variances assumed	1.878	.190	1.770	16	.096	83.8973362	47.3913230	-16.5677805	184.3624529
	Equal variances not assumed			1.680	11.171	.121	83.8973362	49.9409944	-25.8171213	193.6117937
Mean Day2_sAA_Baseline	Equal variances assumed	.003	.959	2.039	16	.058	64.9522000	31.8552731	-2.5779622	132.4823622
	Equal variances not assumed			1.999	13.782	.066	64.9522000	32.4900710	-4.8353962	134.7397962
Mean Day2_sAA_2	Equal variances assumed	2.659	.122	2.881	16	.011	74.2770751	25.7794040	19.6271799	128.9269703
	Equal variances not assumed			2.648	8.906	.027	74.2770751	28.0484441	10.7245485	137.8296016
Mean Day2_sAA_3	Equal variances assumed	.092	.766	2.116	16	.050	56.5964000	26.7486747	-.1082573	113.3010573
	Equal variances not assumed			2.073	13.728	.057	56.5964000	27.3008098	-2.0669169	115.2597169

Correlations

sAA vs Treatment outcomes (SPQ, FSQ)

Correlations

	Mean Day1_sAA_Baseline	Mean Day1_sAA_2	Mean Day1_sAA_3	Mean Day2_sAA_Baseline	Mean Day2_sAA_2	Mean Day2_sAA_3	Pre_Post_SPQ	Pre_Post_FSQ	Pre_Post_BATDist	Pre_3mFU_SPQ	Pre_7mFU_SPQ	Pre_3mFU_FSQ	Pre_7mFU_FSQ

Mean Day1_sAA_Baseline	Pearson Correlation	1	.432	.391	.167	.155	.582*	.142	-.494*	-.063	-.114	-.070	-.515*	-.253
	Sig. (2-tailed)		.073	.109	.507	.538	.011	.573	.037	.805	.651	.784	.029	.312
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Mean Day1_sAA_2	Pearson Correlation	.432	1	.254	.065	.345	.758**	-.229	-.356	.028	-.040	-.140	-.061	-.048
	Sig. (2-tailed)	.073		.310	.797	.161	.000	.361	.147	.912	.875	.580	.811	.851
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Mean Day1_sAA_3	Pearson Correlation	.391	.254	1	.392	.514*	.417	.138	-.003	-.192	.029	.190	-.097	-.050
	Sig. (2-tailed)	.109	.310		.108	.029	.085	.586	.990	.446	.908	.449	.702	.844
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Mean Day2_sAA_Baseline	Pearson Correlation	.167	.065	.392	1	.421	.175	.056	-.052	.078	.160	.375	.125	.314
	Sig. (2-tailed)	.507	.797	.108		.082	.488	.825	.838	.759	.527	.125	.622	.205
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Mean Day2_sAA_2	Pearson Correlation	.155	.345	.514*	.421	1	.547*	-.189	.000	.128	.169	.506*	.240	.422
	Sig. (2-tailed)	.538	.161	.029	.082		.019	.454	.998	.612	.502	.032	.338	.081
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Mean Day2_sAA_3	Pearson Correlation	.582*	.758**	.417	.175	.547*	1	.139	-.086	.027	-.006	.170	.033	.245
	Sig. (2-tailed)	.011	.000	.085	.488	.019		.582	.734	.914	.982	.499	.897	.328
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_Post_SPQ	Pearson Correlation	.142	-.229	.138	.056	-.189	.139	1	.547*	-.372	.563*	.498*	.255	.406
	Sig. (2-tailed)	.573	.361	.586	.825	.454	.582		.019	.128	.015	.036	.306	.095
	N	18	18	18	18	18	18	18	18	18	18	18	18	18

Pre_Post_FSQ	Pearson Correlation	-.494*	-.356	-.003	-.052	.000	-.086	.547*	1	-.117	.528*	.432	.850**	.630**
	Sig. (2-tailed)	.037	.147	.990	.838	.998	.734	.019		.644	.024	.073	.000	.005
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_Post_BATDist	Pearson Correlation	-.063	.028	-.192	.078	.128	.027	-.372	-.117	1	-.204	.177	.069	.221
	Sig. (2-tailed)	.805	.912	.446	.759	.612	.914	.128	.644		.416	.481	.785	.377
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_3mFU_SPQ	Pearson Correlation	-.114	-.040	.029	.160	.169	-.006	.563*	.528*	-.204	1	.610**	.565*	.536*
	Sig. (2-tailed)	.651	.875	.908	.527	.502	.982	.015	.024	.416		.007	.014	.022
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_7mFU_SPQ	Pearson Correlation	-.070	-.140	.190	.375	.506*	.170	.498*	.432	.177	.610**	1	.483*	.833**
	Sig. (2-tailed)	.784	.580	.449	.125	.032	.499	.036	.073	.481	.007		.042	.000
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_3mFU_FSQ	Pearson Correlation	-.515*	-.061	-.097	.125	.240	.033	.255	.850**	.069	.565*	.483*	1	.781**
	Sig. (2-tailed)	.029	.811	.702	.622	.338	.897	.306	.000	.785	.014	.042		.000
	N	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_7mFU_FSQ	Pearson Correlation	-.253	-.048	-.050	.314	.422	.245	.406	.630**	.221	.536*	.833**	.781**	1
	Sig. (2-tailed)	.312	.851	.844	.205	.081	.328	.095	.005	.377	.022	.000	.000	
	N	18	18	18	18	18	18	18	18	18	18	18	18	18

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Cort vs Treatment outcomes (SPQ, FSQ BAT)

Correlations

		Mean Day1_cort_2	Mean Day2_cort_Baseline	Mean Day2_cort_2	Pre_Post_SPQ	Pre_3mFU_SPQ	Pre_7mFU_SPQ	Pre_Post_FSQ	Pre_3mFU_FSQ	Pre_7mFU_FSQ	Pre_Post_BATDist	Pre_7mFU_BATDist
Mean Day1_cort_2	Pearson Correlation	1	.200	.438	.137	-.240	-.016	.037	-.193	-.053	-.180	-.403
	Sig. (2-tailed)		.426	.069	.589	.338	.949	.884	.442	.834	.476	.098
	N	18	18	18	18	18	18	18	18	18	18	18
Mean Day2_cort_Baseline	Pearson Correlation	.200	1	.847**	-.157	.282	.599**	.072	.280	.515*	.252	.388
	Sig. (2-tailed)	.426		<.001	.534	.256	.009	.777	.261	.029	.312	.112
	N	18	18	18	18	18	18	18	18	18	18	18
Mean Day2_cort_2	Pearson Correlation	.438	.847**	1	-.073	.269	.516*	.156	.263	.408	.060	.100
	Sig. (2-tailed)	.069	<.001		.774	.280	.029	.537	.292	.093	.814	.692
	N	18	18	18	18	18	18	18	18	18	18	18
Pre_Post_SPQ	Pearson Correlation	.137	-.157	-.073	1	.563*	.498*	.547*	.255	.406	-.372	-.127
	Sig. (2-tailed)	.589	.534	.774		.015	.036	.019	.306	.095	.128	.615
	N	18	18	18	18	18	18	18	18	18	18	18
Pre_3mFU_SPQ	Pearson Correlation	-.240	.282	.269	.563*	1	.610**	.528*	.565*	.536*	-.204	.098
	Sig. (2-tailed)	.338	.256	.280	.015		.007	.024	.014	.022	.416	.698
	N	18	18	18	18	18	18	18	18	18	18	18
Pre_7mFU_SPQ	Pearson Correlation	-.016	.599**	.516*	.498*	.610**	1	.432	.483*	.833**	.177	.364
	Sig. (2-tailed)	.949	.009	.029	.036	.007		.073	.042	<.001	.481	.138
	N	18	18	18	18	18	18	18	18	18	18	18

Pre_Post_FSQ	Pearson Correlation	.037	.072	.156	.547*	.528*	.432	1	.850**	.630**	-.117	.212
	Sig. (2-tailed)	.884	.777	.537	.019	.024	.073		<.001	.005	.644	.398
	N	18	18	18	18	18	18	18	18	18	18	18
Pre_3mFU_FSQ	Pearson Correlation	-.193	.280	.263	.255	.565*	.483*	.850**	1	.781**	.069	.344
	Sig. (2-tailed)	.442	.261	.292	.306	.014	.042	<.001		<.001	.785	.162
	N	18	18	18	18	18	18	18	18	18	18	18
Pre_7mFU_FSQ	Pearson Correlation	-.053	.515*	.408	.406	.536*	.833**	.630**	.781**	1	.221	.334
	Sig. (2-tailed)	.834	.029	.093	.095	.022	<.001	.005	<.001		.377	.175
	N	18	18	18	18	18	18	18	18	18	18	18
Pre_Post_BATDist	Pearson Correlation	-.180	.252	.060	-.372	-.204	.177	-.117	.069	.221	1	.369
	Sig. (2-tailed)	.476	.312	.814	.128	.416	.481	.644	.785	.377		.132
	N	18	18	18	18	18	18	18	18	18	18	18
Pre_7mFU_BATDist	Pearson Correlation	-.403	.388	.100	-.127	.098	.364	.212	.344	.334	.369	1
	Sig. (2-tailed)	.098	.112	.692	.615	.698	.138	.398	.162	.175	.132	
	N	18	18	18	18	18	18	18	18	18	18	18

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

sAA vs Treatment outcomes (BAT)

Correlations

	Mean Day1_cort_Baseline	Mean Day1_cort_2	Mean Day2_cort_Baseline	Mean Day2_cort_2	Crt_Day 1diff	Crt_Day 2diff	Pre_Post_BATDist	Pre_7mFU_BATDist	BAT 7mFU_Dist_K_G	Pre_Post_BATExp	Pre_Post_BATSUDs	Pre_7mfu_BATExp	Pre_7mfu_BATsuds	BAT 7mfu_suds_G_K	BAT 7mfu_exp_G_K

Mean Day1_cort_Baseline	Pearson Correlation	1	.175	.257	.486*	.419	.114	.016	.071	.120	-.084	.270	.016	-.102	-.146	.281
	Sig. (2-tailed)		.488	.303	.041	.084	.653	.950	.781	.635	.740	.278	.950	.688	.563	.258
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Mean Day1_cort_2	Pearson Correlation	.175	1	.200	.438	-.821**	.059	-.180	-.403	-.078	-.437	.220	-.338	.213	-.309	.173
	Sig. (2-tailed)	.488		.426	.069	.000	.817	.476	.098	.758	.070	.381	.170	.397	.212	.492
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Mean Day2_cort_Baseline	Pearson Correlation	.257	.200	1	.847**	-.035	.964**	.252	.388	-.072	-.138	.380	.370	.457	-.120	.677**
	Sig. (2-tailed)	.303	.426		.000	.889	.000	.312	.112	.776	.584	.120	.130	.057	.635	.002
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Mean Day2_cort_2	Pearson Correlation	.486*	.438	.847**	1	-.122	.676**	.060	.100	.075	-.105	.335	.192	.320	-.368	.454
	Sig. (2-tailed)	.041	.069	.000		.630	.002	.814	.692	.767	.677	.174	.445	.196	.133	.059
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Crt_Day1diff	Pearson Correlation	.419	-.821**	-.035	-.122	1	.012	.175	.412	.142	.354	-.046	.321	-.255	.200	.003
	Sig. (2-tailed)	.084	.000	.889	.630		.963	.488	.089	.574	.149	.857	.194	.307	.426	.989
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Crt_Day2diff	Pearson Correlation	.114	.059	.964**	.676**	.012	1	.320	.487*	-.138	-.139	.359	.417	.474*	.017	.712**
	Sig. (2-tailed)	.653	.817	.000	.002	.963		.195	.040	.586	.582	.143	.085	.047	.947	.001
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18

Pre_Post_BATDist	Pearson Correlation	.016	-.180	.252	.060	.175	.320	1	.369	-.092	-.014	.297	.233	-.032	.319	.247
	Sig. (2-tailed)	.950	.476	.312	.814	.488	.195		.132	.716	.956	.232	.351	.899	.197	.324
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_7mFU_BAT Dist	Pearson Correlation	.071	-.403	.388	.100	.412	.487*	.369	1	-.218	.317	.192	.554*	.199	.136	.271
	Sig. (2-tailed)	.781	.098	.112	.692	.089	.040	.132		.385	.199	.444	.017	.428	.591	.276
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
BAT7mFU_Dist_K_G	Pearson Correlation	.120	-.078	-.072	.075	.142	-.138	-.092	-.218	1	.266	.065	.158	-.042	-.163	-.015
	Sig. (2-tailed)	.635	.758	.776	.767	.574	.586	.716	.385		.286	.797	.532	.867	.518	.954
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_Post_BATexp	Pearson Correlation	-.084	-.437	-.138	-.105	.354	-.139	-.014	.317	.266	1	.182	.656**	.168	-.097	-.074
	Sig. (2-tailed)	.740	.070	.584	.677	.149	.582	.956	.199	.286		.469	.003	.505	.702	.771
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_Post_BATSUnDs	Pearson Correlation	.270	.220	.380	.335	-.046	.359	.297	.192	.065	.182	1	.366	.753**	-.370	.540*
	Sig. (2-tailed)	.278	.381	.120	.174	.857	.143	.232	.444	.797	.469		.135	.000	.131	.021
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Pre_7mfu_BATexp	Pearson Correlation	.016	-.338	.370	.192	.321	.417	.233	.554*	.158	.656**	.366	1	.369	.270	.279
	Sig. (2-tailed)	.950	.170	.130	.445	.194	.085	.351	.017	.532	.003	.135		.132	.279	.261
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18

Pre_7mfu_BATsuds	Pearson Correlation	-.102	.213	.457	.320	-.255	.474*	-.032	.199	-.042	.168	.753**	.369	1	-.428	.647**
	Sig. (2-tailed)	.688	.397	.057	.196	.307	.047	.899	.428	.867	.505	.000	.132		.077	.004
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
BAT7mfu_suds_G_K	Pearson Correlation	-.146	-.309	-.120	-.368	.200	.017	.319	.136	-.163	-.097	-.370	.270	-.428	1	-.093
	Sig. (2-tailed)	.563	.212	.635	.133	.426	.947	.197	.591	.518	.702	.131	.279	.077		.712
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
BAT7mfu_exp_G_K	Pearson Correlation	.281	.173	.677**	.454	.003	.712**	.247	.271	-.015	-.074	.540*	.279	.647**	-.093	1
	Sig. (2-tailed)	.258	.492	.002	.059	.989	.001	.324	.276	.954	.771	.021	.261	.004	.712	
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

RCT

Multiple Imputations Analysis
Demographics

Independent Sample T-Tests: Age
N=37
Group 1= Stress =17
Group 2= Control =20

Covariate: none
Exclusions: none
Exclusions: none
Outcome: No sig. difference in age between groups.

Group Statistics

	Mean Grooup	N	Mean	Std. Deviation	Std. Error Mean
Age	1.00	17	27.6471	8.97873	2.17766
	2.00	20	29.4000	9.35499	2.09184

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
Age	Equal variances assumed	.652	.425	-.579	35	.567	-1.75294	3.02995	-7.90407	4.39819
	Equal variances not assumed			-.581	34.450	.565	-1.75294	3.01960	-7.88656	4.38068

Chi-squared: Gender
N=37
Group 1= Stress =17
Group 2= Control =20

Covariate: none
Exclusions: none
Exclusions: none

Outcome: No sig. difference in the number of males and females between groups.

Gender * Grooup Crosstabulation
Count

		Mean Grooup		
		1.00	2.00	Total
Mean Gender	.00	6	5	11
	1.00	11	15	26
Total		17	20	37

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.466[a]	1	.495		
Continuity Correction[b]	.104	1	.748		
Likelihood Ratio	.465	1	.495		
Fisher's Exact Test				.719	.373
Linear-by-Linear Association	.454	1	.501		
N of Valid Cases	37				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.05.
b. Computed only for a 2x2 table

Clinical Characteristics

Independent Sample T-Tests: Pre-treatment scores and exposure therapy trials

N=37
Group 1= Stress =17
Group 2= Control =20

Covariate: none
Exclusions: none
Outcome: No sig. difference in pre-treatment measures, except cortisol. Participants in stress group showed higher baseline cortisol levels than control participants
Comment: equal variance assumed

Group Statistics

	Grooup	N	Mean	Std. Deviation	Std. Error Mean
Age	1.00	17	27.6471	8.97873	2.17766

	2.00	20	29.4000	9.35499	2.09184
Pre_DAS21_Depression_total	1.00	17	2.8824	2.54662	.61765
	2.00	20	5.1500	5.16338	1.15457
Pre_DAS21_Anxitety_total	1.00	17	3.4706	3.06426	.74319
	2.00	20	3.2000	2.54641	.56939
Pre_DAS21_Stress_total	1.00	17	6.7647	4.81572	1.16798
	2.00	20	7.3500	4.52217	1.01119
Pre_Stait_Total	1.00	17	43.0000	5.31507	1.28909
	2.00	20	44.3000	5.39103	1.20547
Pre_fsq_Total	1.00	17	96.633217993079580	17.360162124367594	4.210457771565569
	2.00	20	94.750000000000000	20.388012473793980	4.558898181751699
Pre_spq_Total	1.00	17	11.778280542986424	1.933793668765843	.469013856145427
	2.00	20	11.567857143000001	2.813432086534790	.629102539557086
Day1cortT1	1.00	15	.162312000	.066374588	.017137845
	2.00	20	.126382000	.0428384677	.0095789726
Day1_ssaa_T1	1.00	17	89.946000000000000	45.049109684598655	10.926013974684455
	2.00	20	77.875300000000010	53.886348362085190	12.049353799685692
Day1estradiol	1.00	17	.438655294	.6290344593	.1525632658
	2.00	20	.460051844	.6415319193	.1434508981
Exp_steps_total	1.00	17	4.2006	.72709	.17634
	2.00	20	4.1675	.92622	.20711
Total_Trials	1.00	17	9.1176	3.35191	.81296
	2.00	20	8.2909	3.40467	.76131
pre_BAT_Expectancy	1.00	17	7.4118	1.54349	.37435
	2.00	20	6.5000	1.79179	.40066
pre_BAT_suds	1.00	17	6.4706	1.84112	.44654
	2.00	20	6.1000	1.29371	.28928

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means					
	F	Sig.	t	df	Significance	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference

						One-Sided p	Two-Sided p			Lower	Upper
Age	Equal variances assumed	.652	.425	-.579	35	.283	.567	-1.75294	3.02995	-7.90407	4.39819
	Equal variances not assumed			-.581	34.450	.283	.565	-1.75294	3.01960	-7.88656	4.38068
Pre_DAS21_Depression_total	Equal variances assumed	9.057	.005	-1.646	35	.054	.109	-2.26765	1.37754	-5.06420	.52891
	Equal variances not assumed			-1.732	28.645	.047	.094	-2.26765	1.30939	-4.94710	.41181
Pre_DAS21_Anxitety_total	Equal variances assumed	.828	.369	.293	35	.385	.771	.27059	.92205	-1.60127	2.14245
	Equal variances not assumed			.289	31.234	.387	.774	.27059	.93624	-1.63831	2.17948
Pre_DAS21_Stress_total	Equal variances assumed	.012	.914	-.381	35	.353	.706	-.58529	1.53682	-3.70520	2.53461
	Equal variances not assumed			-.379	33.246	.354	.707	-.58529	1.54489	-3.72752	2.55693
Pre_Stait_Total	Equal variances assumed	.116	.735	-.736	35	.233	.467	-1.30000	1.76700	-4.88721	2.28721
	Equal variances not assumed			-.737	34.197	.233	.466	-1.30000	1.76491	-4.88598	2.28598
Pre_fsq_Total	Equal variances assumed	.112	.740	.299	35	.383	.766	1.88321799307958 3	6.28878477231472 8	-10.88369383225495 4	14.650129818414120
	Equal variances not assumed			.303	34.999	.382	.763	1.88321799307958 3	6.20576403658049 5	-10.71517119824618 5	14.481607184405352
Pre_spq_Total	Equal variances assumed	.129	.722	.260	35	.398	.796	.21042339998642 3	.80848154085170 3	-1.43088138594046 4	1.8517281859133 10

	Equal variances not assumed			.268	33.647	.395	.790	.21042339998 6423	.78469357237 9422	-1.3848822130 57606	1.8057290130 30452
Day1cortT1	Equal variances assumed	5.618	.024	1.945	33	.	.060	.03593 00000	.01847 4939	-.00165 755	.07351 7546
	Equal variances not assumed			1.830	22.496	.	.081	.35930 00000	.19633 197	-.01963 3197	.07659 4765
Day1_ssaa_T1	Equal variances assumed	.406	.528	.731	35	.235	.470	12.070 699999 999988	16.507 564309 482920	-21.441 437180 779430	45.582 837180 779410
	Equal variances not assumed			.742	34.995	.231	.463	12.070 699999 999988	16.265 445224 923910	-20.950 075977 692535	45.091 475977 692510
Day1estradiol	Equal variances assumed	.023	.880	-.102	35	.460	.919	-.02139 65496	.20975 65752	-.44722 50358	.40443 19366
	Equal variances not assumed			-.102	34.252	.460	.919	-.02139 65496	.20941 27748	-.44685 91641	.40406 60649
Exp_steps_total	Equal variances assumed	2.164	.150	.119	35	.453	.906	.03314	.27745	-.53012	.59639
	Equal variances not assumed			.122	34.809	.452	.904	.03314	.27201	-.51919	.58546
Total_Trials	Equal variances assumed	.376	.544	.741	35	.232	.463	.82679	1.11522	-1.43724	3.09081
	Equal variances not assumed			.742	34.211	.231	.463	.82679	1.11377	-1.43616	3.08973
pre_BAT_Expectancy	Equal variances assumed	.014	.907	1.642	35	.055	.109	.91176	.55514	-.21523	2.03876
	Equal variances not assumed			1.663	34.989	.053	.105	.91176	.54833	-.20142	2.02494
pre_BAT_suds	Equal variances assumed	.966	.332	.717	35	.239	.478	.37059	.51721	-.67940	1.42058

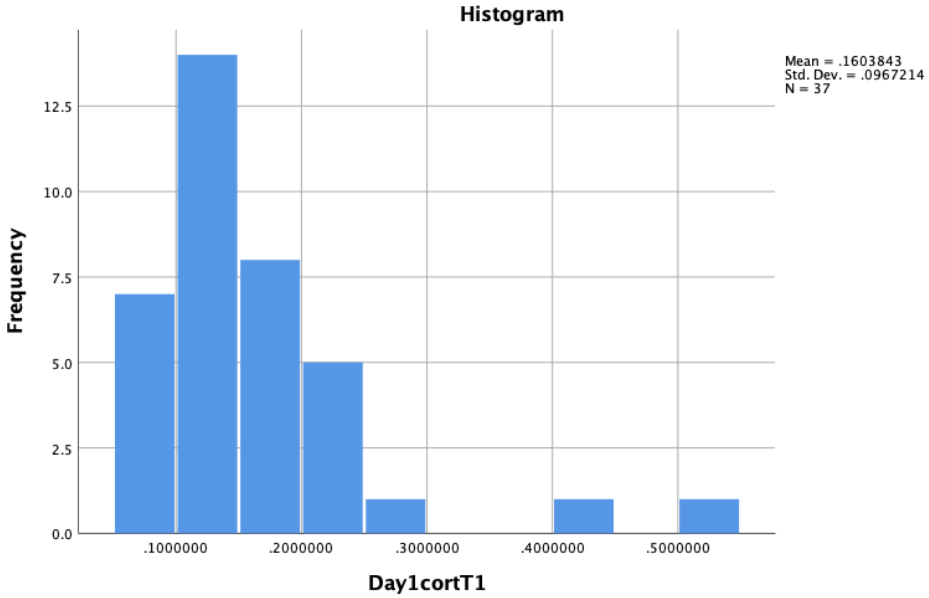
	Equal variances not assumed			.697	28.083	.246	.492	.37059	.53205	-.71912	1.46030

All p's on OC's excluded.

Saliva Analysis

Independent Samples T-test : Cortisol Day 1 and Day 2

N =37
Group 1= Stress= 17
Group 2 = Control=20
Exclusions: 2 sig outliers removed from baseline cort on Day 1
Outcome: Stress demonstrated sig higher cortisol levels after stress/control procedure at Session 1 only.



Group Statistics

	Mean Grooup	N	Mean	Std. Deviation	Std. Error Mean
Day1-cortT1_1	1.00	15	.162312000	.0663745876	.0171378448
	2.00	20	.126382000	.0428384677	.0095789726
Day1_cort_T2_1	1.00	17	.202028235	.1012451787	.0245555627
	2.00	20	.100029000	.0388187895	.0086801452
Day2_cort_T1_2	1.00	17	.150142776	.0592874545	.0143793198
	2.00	20	.138124264	.0493774687	.0110411377
Day2_cort_T3_2	1.00	17	.174382382	.1167184728	.0283083878

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Day1-cortT1_	Equal variances assumed	5.618	.024	1.945	33	.060	.0359300000	.0184749391	-.0016575461	.0735175461
	Equal variances not assumed			1.830	22.496	.081	.0359300000	.0196331974	-.0047347651	.0765947651
Day1_cort_T2_1	Equal variances assumed	7.894	.008	4.168	35	.000	.1019992353	.0244737840	.0523148124	.1516836582
	Equal variances not assumed			3.916	19.986	.001	.1019992353	.0260445883	.0476686676	.1563298030
Day2_cort_T1_2	Equal variances assumed	.561	.459	.673	35	.505	.0120185117	.0178577240	-.0242345953	.0482716187
	Equal variances not assumed			.663	31.274	.512	.0120185117	.0181293011	-.0249433185	.0489803419
Day2_cort_T3_2	Equal variances assumed	3.360	.075	1.270	35	.212	.0384022557	.0302392142	-.0229866129	.0997911243
	Equal variances not assumed			1.213	23.749	.237	.0384022557	.0316494555	-.0269555100	.1037600214
	2.00		20	.135980126		.0632966374		.0141535584		

Independent Samples T-test : sAA Day 1 and Day 2

N =37

Group 1= Stress= 17

Group 2 = Control=20

Exclusions:Nil

Outcome: No group differences at baseline, after stress/control procedure or after exposure therapy at Session 1 or Session 2 were found.

Group Statistics

	Mean Grooup	N	Mean	Std. Deviation	Std. Error Mean
Day1_ssaa_T1	1.00	17	89.946000000000000	45.049109684598655	10.926013974684455
	2.00	20	77.875300000000010	53.886348362085190	12.049353799685692
Day1_saa_T2	1.00	17	101.614176470588220	54.262216946088850	13.160520702876758
	2.00	20	115.601699999999980	87.139320618191650	19.484944441542552
Day1_saa_T3	1.00	17	86.070000000000000	54.366656988681950	13.185851133885900
	2.00	20	91.607495864396330	54.032188048897660	12.081964545038690
Day2_saa_T1	1.00	17	91.878854028631240	40.958772899576270	9.933961585919944
	2.00	20	70.687124684765080	27.521729841374320	6.154045878369748
Day2_saa_T2	1.00	17	79.759818464964780	40.691334383460024	9.869098218254903
	2.00	20	62.432246922720786	37.664261521440940	8.421984908427160
Day3_saa_T3	1.00	17	92.375489416419070	37.383513128794840	9.066833722746216
	2.00	20	79.805389555209050	47.535526799415760	10.629266926975665

Independent Samples Test

	Levene's Test for Equality of Variances	t-test for Equality of Means

		F	Sig.	t	df	Significance One-Sided p	Significance Two-Sided p	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	95% Confidence Interval of the Difference Upper
Day1_ssaa_T1	Equal variances assumed	.406	.528	.731	35	.235	.470	12.070699999999988	16.507564309482920	-21.441437180779430	45.582837180779410
	Equal variances not assumed			.742	34.995	.231	.463	12.070699999999988	16.265445224923910	-20.950075977692535	45.091475977692510
Day1_saa_T2	Equal variances assumed	1.402	.244	-.573	35	.285	.570	-13.987523529411760	24.393724963351357	-63.509417977063370	35.534370918239850
	Equal variances not assumed			-.595	32.306	.278	.556	-13.987523529411760	23.513025434019493	-61.864223673521494	33.889176614697970
Day1_saa_T3	Equal variances assumed	.023	.881	-.310	35	.379	.759	-5.537495864396334	17.874884360958880	-41.825440322132415	30.750448593339748
	Equal variances not assumed			-.310	33.977	.379	.759	-5.537495864396334	17.884086149215790	-41.883257487350250	30.808265758557580
Day2_saa_T1	Equal variances assumed	1.362	.251	1.872	35	.035	.070	21.191729343866143	11.322751484753956	-1.794678214938290	44.178136902670570
	Equal variances not assumed			1.813	27.257	.040	.081	21.191729343866143	11.685712364405209	-2.774809078124491	45.158267765856780
Day2_saa_T2	Equal variances assumed	.002	.969	1.344	35	.094	.188	17.327571542243994	12.890938598959117	-8.842425110087959	43.497568194575940
	Equal variances not assumed			1.336	33.035	.095	.191	17.327571542243994	12.974163920628447	-9.067486747528832	43.722629832016820

Day3_saa_T3	Equal variances assumed	.164	.688	.882	35	.192	.384	12.570099861210040	14.248258954447246	-16.355403605973590	41.495603328393670
	Equal variances not assumed			.900	34.818	.187	.374	12.570099861210040	13.970998144757830	-15.797822352379974	40.938022074800050

Independent samples T-test: Subjective ratings after stress/control procedure

N =37
Group 1= Stress= 17
Group 2 = Control=20
Exclusions: none
Outcome: Stress group rated stress procedure sig more stressful, unpleasant and painful at Session 1 and 2, relative to control.

Group Statistics

	Mean Grooup	N	Mean	Std. Deviation	Std. Error Mean
Stressful S1	1.00	17	7.0000	2.44949	.59409
	2.00	20	.9000	1.88903	.42240
Painful S1	1.00	17	8.0588	2.04544	.49609
	2.00	20	.2500	.63867	.14281
Unpleasant S1	1.00	17	8.0588	2.70348	.65569
	2.00	20	1.1485	2.13225	.47679
Stressful S2	1.00	17	5.4866	2.42618	.58844
	2.00	20	1.0589	1.65918	.37100
Painful S2	1.00	17	6.3949	2.40395	.58304
	2.00	20	.8583	1.56544	.35004
Unpleasant S2	1.00	17	6.8040	2.42553	.58828
	2.00	20	1.1090	1.87711	.41973

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means							
					Significance				95% Confidence Interval of the Difference	
	F	Sig.	t	df	One-Sided p	Two-Sided p	Mean Difference	Std. Error Difference	Lower	Upper

Stressful S1	Equal variances assumed	1.735	.196	8.548	35	<.001	<.001	6.10000	.71365	4.65122	7.54878
	Equal variances not assumed			8.368	29.843	<.001	<.001	6.10000	.72895	4.61097	7.58903
Painful S1	Equal variances assumed	10.367	.003	16.204	35	<.001	<.001	7.80882	.48191	6.83050	8.78714
	Equal variances not assumed			15.126	18.654	<.001	<.001	7.80882	.51624	6.72697	8.89068
Unpleasant S1	Equal variances assumed	.141	.709	8.691	35	<.001	<.001	6.91029	.79510	5.29615	8.52443
	Equal variances not assumed			8.524	30.267	<.001	<.001	6.91029	.81071	5.25520	8.56537
Stressful S2	Equal variances assumed	1.819	.186	6.561	35	<.001	<.001	4.42771	.67488	3.05764	5.79779
	Equal variances not assumed			6.365	27.579	<.001	<.001	4.42771	.69563	3.00180	5.85363
Painful S2	Equal variances assumed	5.492	.025	8.421	35	<.001	<.001	5.53661	.65747	4.20188	6.87134
	Equal variances not assumed			8.141	26.693	<.001	<.001	5.53661	.68005	4.14051	6.93271
Unpleasant S2	Equal variances assumed	1.166	.288	8.047	35	<.001	<.001	5.69505	.70769	4.25836	7.13175
	Equal variances not assumed			7.881	29.910	<.001	<.001	5.69505	.72267	4.21899	7.17112

Effects of VR Exposure Therapy

Repeated Measures Analysis: Pre-, Post-treatment, 3mfu FSQ Scores

N =37

Between factor: None

Within factor: Pre_FSQ, Post_ FSQ, 3mfu_ FSQ

Covariate: None

Exclusions: None

Outcome: Sig reduction in fear across time. Post-hoc tests show sig. fear symptom change from pre- post but not post- 3mfu.

Descriptive Statistics

	Mean	Std. Deviation	N
Pre_fsq_Total	95.615262321144670	18.821045560155014	37
Post_fsq_Total	53.678730300690050	16.015914717080683	37
FU_fsq_Total	52.435958834556510	18.350270208434180	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.794	67.423[b]	2.000	35.000	.000	.794
	Wilks' Lambda	.206	67.423[b]	2.000	35.000	.000	.794
	Hotelling's Trace	3.853	67.423[b]	2.000	35.000	.000	.794
	Roy's Largest Root	3.853	67.423[b]	2.000	35.000	.000	.794

a. Design: Intercept
Within Subjects Design: factor1
b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	44704.257	2	22352.128	111.604	.000	.756
	Greenhouse-Geisser	44704.257	1.451	30803.134	111.604	.000	.756
	Huynh-Feldt	44704.257	1.496	29875.108	111.604	.000	.756
	Lower-bound	44704.257	1.000	44704.257	111.604	.000	.756
Error(factor1)	Sphericity Assumed	14420.212	72	200.281			
	Greenhouse-Geisser	14420.212	52.246	276.004			
	Huynh-Feldt	14420.212	53.869	267.689			
	Lower-bound	14420.212	36.000	400.561			

Post-Hocs

Pairwise Comparisons
Measure: MEASURE_1

(I) factor1	(J) factor1	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b] Lower Bound	Upper Bound
Pre	Post	41.937*	3.774	.000	34.283	49.590
	3mfu	43.179*	3.750	.000	35.573	50.786
Post	Pre	-41.937*	3.774	.000	-49.590	-34.283
	3mfu	1.243	2.042	.547	-2.899	5.384
3mfu	Pre	-43.179*	3.750	.000	-50.786	-35.573
	Post	-1.243	2.042	.547	-5.384	2.899

Based on estimated marginal means
*. The mean difference is significant at the .05 level.
b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Repeated Measures Analysis: Pre-, Post-treatment . 3mfu SPQ Scores
N =37
Between factor: None
Within factor: Pre_SPQ, Post_SPQ, 3mfu_ SPQ
Covariate: None
Exclusions: None
Outcome: Sig reduction in fear across time. Post-hoc tests show sig. fear symptom change from pre- post but not post- 3mfu.

Descriptive Statistics

	Mean	Std. Deviation	N
Pre_spq_Total	11.664538164615381	2.418863416776552	37
Post_spq_Total	6.896911180799489	2.676970680622036	37
FU_spq_Total	6.851452648594332	2.625551658403959	37

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	566.077	2	283.038	75.917	.000	.678
	Greenhouse-Geisser	566.077	1.780	317.973	75.917	.000	.678
	Huynh-Feldt	566.077	1.866	303.289	75.917	.000	.678
	Lower-bound	566.077	1.000	566.077	75.917	.000	.678
Error(factor 1)	Sphericity Assumed	268.436	72	3.728			
	Greenhouse-Geisser	268.436	64.090	4.188			
	Huynh-Feldt	268.436	67.193	3.995			
	Lower-bound	268.436	36.000	7.457			

Post-hocs

Pairwise Comparisons
Measure: MEASURE_1

(I) factor1	(J) factor1	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
Pre	Post	4.768*	.476	.000	3.801	5.734
	3mfu	4.813*	.496	.000	3.807	5.819
Post	Pre	-4.768*	.476	.000	-5.734	-3.801
	3mfu	.045	.363	.901	-.690	.781
3mfu	Pre	-4.813*	.496	.000	-5.819	-3.807
	Post	-.045	.363	.901	-.781	.690

Based on estimated marginal means
*. The mean difference is significant at the .05 level.
b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Repeated Measures Analysis: Pre-, Post-treatment 3mfu BAT Scores
Missing data imputed

N =37
Between factor: None
Within factor: BAT pre, post, 3mfu (in the kitchen)
Covariate: None

Exclusions: none
Outcome: Sig reduction in avoidance across time. Post-hoc tests show sig. fear symptom change from pre- post but not post- 3mfu.

Descriptive Statistics

	Mean	Std. Deviation	N
BAT_dis_score_pre	2.3243	.81833	37
BAT_post_K_score	5.1351	.53552	37
BAT_score_K3mfu	4.97	.372	37

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	184.288	2	92.144	305.567	.000	.895
	Greenhouse-Geisser	184.288	1.491	123.633	305.567	.000	.895
	Huynh-Feldt	184.288	1.540	119.649	305.567	.000	.895
	Lower-bound	184.288	1.000	184.288	305.567	.000	.895
Error(factor 1)	Sphericity Assumed	21.712	72	.302			
	Greenhouse-Geisser	21.712	53.662	.405			
	Huynh-Feldt	21.712	55.448	.392			
	Lower-bound	21.712	36.000	.603			

Post-hocs

Pairwise Comparisons

Measure: MEASURE_1

(I) factor1	(J) factor1	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b] Lower Bound	Upper Bound
Pre	Post	-2.811*	.144	.000	-3.103	-2.518
	3mfu	-2.649*	.146	.000	-2.945	-2.352
Post	Pre	2.811*	.144	.000	2.518	3.103
	3mfu	.162	.082	.057	-.005	.329

3mfu	Pre	2.649*	.146	.000	2.352	2.945
	Post	-.162	.082	.057	-.329	.005

Based on estimated marginal means
*. The mean difference is significant at the .05 level.
b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Effects of Stress on Exposure Therapy

Two-way repeated measures ANOVA: Post and 3mfu SPQ Scores
N =37
Group 1= Stress= 17
Group 2 = Control= 20
Between factor: Stress group, Control group
Within factor: Post_SPQ score, 3mfu_SPQscore
Covariate: Pre_SPQ, Age, Gender
Exclusions: none
Outcome: Sig. main effect of group.

Descriptive Statistics

	Mean Grooup	Mean	Std. Deviation	N
Mean Post_spq_Total	1.00	5.766506242536256	2.536887788711072	17
	2.00	7.857755378323240	2.458306075999541	20
	Total	6.896911180799489	2.676970680622036	37
FU_spq_Total	1.00	6.246973578154922	2.191419103766004	17
	2.00	7.365259858467827	2.900435723255194	20
	Total	6.851452648594332	2.625551658403959	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.009	.299[b]	1.000	32.000	.588	.009
	Wilks' Lambda	.991	.299[b]	1.000	32.000	.588	.009
	Hotelling's Trace	.009	.299[b]	1.000	32.000	.588	.009

	Roy's Largest Root	.009	.299[b]	1.000	32.000	.588	.009
factor1 * Mean_Pre_spq_Total	Pillai's Trace	.032	1.057[b]	1.000	32.000	.312	.032
	Wilks' Lambda	.968	1.057[b]	1.000	32.000	.312	.032
	Hotelling's Trace	.033	1.057[b]	1.000	32.000	.312	.032
	Roy's Largest Root	.033	1.057[b]	1.000	32.000	.312	.032
factor1 * Age	Pillai's Trace	.020	.646[b]	1.000	32.000	.427	.020
	Wilks' Lambda	.980	.646[b]	1.000	32.000	.427	.020
	Hotelling's Trace	.020	.646[b]	1.000	32.000	.427	.020
	Roy's Largest Root	.020	.646[b]	1.000	32.000	.427	.020
factor1 * Gender	Pillai's Trace	.190	7.489[b]	1.000	32.000	.010	.190
	Wilks' Lambda	.810	7.489[b]	1.000	32.000	.010	.190
	Hotelling's Trace	.234	7.489[b]	1.000	32.000	.010	.190
	Roy's Largest Root	.234	7.489[b]	1.000	32.000	.010	.190
factor1 * Grooup	Pillai's Trace	.037	1.239[b]	1.000	32.000	.274	.037
	Wilks' Lambda	.963	1.239[b]	1.000	32.000	.274	.037
	Hotelling's Trace	.039	1.239[b]	1.000	32.000	.274	.037
	Roy's Largest Root	.039	1.239[b]	1.000	32.000	.274	.037

a. Design: Intercept + Mean_Pre_spq_Total + Age + Gender + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	.611	1	.611	.299	.588	.009
	Greenhouse-Geisser	.611	1.000	.611	.299	.588	.009
	Huynh-Feldt	.611	1.000	.611	.299	.588	.009

	Lower-bound	.611	1.000	.611	.299	.588	.009
factor1 * Mean_Pre_spq_Total	Sphericity Assumed	2.162	1	2.162	1.057	.312	.032
	Greenhouse-Geisser	2.162	1.000	2.162	1.057	.312	.032
	Huynh-Feldt	2.162	1.000	2.162	1.057	.312	.032
	Lower-bound	2.162	1.000	2.162	1.057	.312	.032
factor1 * Age	Sphericity Assumed	1.321	1	1.321	.646	.427	.020
	Greenhouse-Geisser	1.321	1.000	1.321	.646	.427	.020
	Huynh-Feldt	1.321	1.000	1.321	.646	.427	.020
	Lower-bound	1.321	1.000	1.321	.646	.427	.020
factor1 * Gender	Sphericity Assumed	15.311	1	15.311	7.489	.010	.190
	Greenhouse-Geisser	15.311	1.000	15.311	7.489	.010	.190
	Huynh-Feldt	15.311	1.000	15.311	7.489	.010	.190
	Lower-bound	15.311	1.000	15.311	7.489	.010	.190
factor1 * Grooup	Sphericity Assumed	2.534	1	2.534	1.239	.274	.037
	Greenhouse-Geisser	2.534	1.000	2.534	1.239	.274	.037
	Huynh-Feldt	2.534	1.000	2.534	1.239	.274	.037
	Lower-bound	2.534	1.000	2.534	1.239	.274	.037
Error(factor1)	Sphericity Assumed	65.421	32	2.044			
	Greenhouse-Geisser	65.421	32.000	2.044			
	Huynh-Feldt	65.421	32.000	2.044			
	Lower-bound	65.421	32.000	2.044			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	.782	1	.782	.082	.776	.003
Mean_Pre_spq_Total	64.569	1	64.569	6.808	.014	.175
Age	4.900	1	4.900	.517	.477	.016

Gender	5.376	1	5.376	.567	.457	.017
Grooup	52.619	1	52.619	5.548	.025	.148
Error	303.488	32	9.484			

Age and Gender did not impact the results (below is without controlling age, gender)

Descriptive Statistics

	Mean Grooup	Mean	Std. Deviation	N
Mean Post_spq_Total	1.00	5.766506242536256	2.536887788711072	17
	2.00	7.857755378323240	2.458306075999541	20
	Total	6.896911180799489	2.676970680622036	37
Mean FU_spq_Total	1.00	6.246973578154922	2.191419103766004	17
	2.00	7.365259858467827	2.900435723255194	20
	Total	6.851452648594332	2.625551658403959	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
measure	Pillai's Trace	.010	.350[b]	1.000	34.000	.558
	Wilks' Lambda	.990	.350[b]	1.000	34.000	.558
	Hotelling's Trace	.010	.350[b]	1.000	34.000	.558
	Roy's Largest Root	.010	.350[b]	1.000	34.000	.558
measure * Mean_Pre_spq_Total	Pillai's Trace	.011	.369[b]	1.000	34.000	.548

	Wilks' Lambda	.989	.369[b]	1.000	34.000	.548
	Hotelling's Trace	.011	.369[b]	1.000	34.000	.548
	Roy's Largest Root	.011	.369[b]	1.000	34.000	.548
measure * Grooup	Pillai's Trace	.052	1.864[b]	1.000	34.000	.181
	Wilks' Lambda	.948	1.864[b]	1.000	34.000	.181
	Hotelling's Trace	.055	1.864[b]	1.000	34.000	.181
	Roy's Largest Root	.055	1.864[b]	1.000	34.000	.181

a. Design: Intercept + Mean_Pre_spq_Total + Grooup
Within Subjects Design: measure

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
measure	Sphericity Assumed	.848	1	.848	.350	.558
	Greenhouse-Geisser	.848	1.000	.848	.350	.558
	Huynh-Feldt	.848	1.000	.848	.350	.558
	Lower-bound	.848	1.000	.848	.350	.558
measure * Mean_Pre_spq_Total	Sphericity Assumed	.894	1	.894	.369	.548
	Greenhouse-Geisser	.894	1.000	.894	.369	.548
	Huynh-Feldt	.894	1.000	.894	.369	.548

	Lower-bound	.894	1.000	.894	.369	.548
measure * Grooup	Sphericity Assumed	4.516	1	4.516	1.864	.181
	Greenhouse-Geisser	4.516	1.000	4.516	1.864	.181
	Huynh-Feldt	4.516	1.000	4.516	1.864	.181
	Lower-bound	4.516	1.000	4.516	1.864	.181
Error(measure)	Sphericity Assumed	82.385	34	2.423		
	Greenhouse-Geisser	82.385	34.000	2.423		
	Huynh-Feldt	82.385	34.000	2.423		
	Lower-bound	82.385	34.000	2.423		

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	18.641	1	18.641	2.018	.165
Mean_Pre_spq_Total	57.058	1	57.058	6.176	.018
Grooup	51.912	1	51.912	5.619	.024
Error	314.133	34	9.239		

Two-way repeated measures ANCOVA: Post and 3mfu FSQ Scores

N =37
Group 1= Stress= 17
Group 2 = Control= 20
Between factor: Stress group, Control group
Within factor: Post_FSQ score, 3mfu_FSQ score
Covariate: Pre_FSQ, Age, Gender
Exclusions: none
Outcome: Sig. main effect of group.

Descriptive Statistics

	Mean Grooup	Mean	Std. Deviation	N
Mean Post_fsq_Total	1.00	47.434036023756995	12.068285161182860	17
	2.00	58.986720436083154	17.286465753098800	20

	Total	53.678730300690050	16.015914717080683	37
Mean FU_fsq_Total	1.00	46.954675883019660	14.058606567914962	17
	2.00	57.095049343362845	20.538997501559420	20
	Total	52.435958834556510	18.350270208434180	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.011	.367[b]	1.000	32.000	.549	.011
	Wilks' Lambda	.989	.367[b]	1.000	32.000	.549	.011
	Hotelling's Trace	.011	.367[b]	1.000	32.000	.549	.011
	Roy's Largest Root	.011	.367[b]	1.000	32.000	.549	.011
factor1 * Age	Pillai's Trace	.002	.056[b]	1.000	32.000	.814	.002
	Wilks' Lambda	.998	.056[b]	1.000	32.000	.814	.002
	Hotelling's Trace	.002	.056[b]	1.000	32.000	.814	.002
	Roy's Largest Root	.002	.056[b]	1.000	32.000	.814	.002
factor1 * Gender	Pillai's Trace	.172	6.640[b]	1.000	32.000	.015	.172
	Wilks' Lambda	.828	6.640[b]	1.000	32.000	.015	.172
	Hotelling's Trace	.208	6.640[b]	1.000	32.000	.015	.172
	Roy's Largest Root	.208	6.640[b]	1.000	32.000	.015	.172
factor1 * Mean_Pre_fsq_Total	Pillai's Trace	.073	2.537[b]	1.000	32.000	.121	.073
	Wilks' Lambda	.927	2.537[b]	1.000	32.000	.121	.073
	Hotelling's Trace	.079	2.537[b]	1.000	32.000	.121	.073
	Roy's Largest Root	.079	2.537[b]	1.000	32.000	.121	.073
factor1 * Grooup	Pillai's Trace	.000	.003[b]	1.000	32.000	.958	.000
	Wilks' Lambda	1.000	.003[b]	1.000	32.000	.958	.000
	Hotelling's Trace	.000	.003[b]	1.000	32.000	.958	.000

	Roy's Largest Root	.000	.003[b]	1.000	32.000	.958	.000

a. Design: Intercept + Age + Gender + Mean_Pre_fsq_Total + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	25.403	1	25.403	.367	.549	.011
	Greenhouse-Geisser	25.403	1.000	25.403	.367	.549	.011
	Huynh-Feldt	25.403	1.000	25.403	.367	.549	.011
	Lower-bound	25.403	1.000	25.403	.367	.549	.011
factor1 * Age	Sphericity Assumed	3.882	1	3.882	.056	.814	.002
	Greenhouse-Geisser	3.882	1.000	3.882	.056	.814	.002
	Huynh-Feldt	3.882	1.000	3.882	.056	.814	.002
	Lower-bound	3.882	1.000	3.882	.056	.814	.002
factor1 * Gender	Sphericity Assumed	459.456	1	459.456	6.640	.015	.172
	Greenhouse-Geisser	459.456	1.000	459.456	6.640	.015	.172
	Huynh-Feldt	459.456	1.000	459.456	6.640	.015	.172
	Lower-bound	459.456	1.000	459.456	6.640	.015	.172
factor1 * Mean_Pre_fsq_Total	Sphericity Assumed	175.527	1	175.527	2.537	.121	.073
	Greenhouse-Geisser	175.527	1.000	175.527	2.537	.121	.073
	Huynh-Feldt	175.527	1.000	175.527	2.537	.121	.073
	Lower-bound	175.527	1.000	175.527	2.537	.121	.073
factor1 * Grooup	Sphericity Assumed	.193	1	.193	.003	.958	.000
	Greenhouse-Geisser	.193	1.000	.193	.003	.958	.000
	Huynh-Feldt	.193	1.000	.193	.003	.958	.000

	Lower-bound	.193	1.000	.193	.003	.958	.000
Error(factor1)	Sphericity Assumed	2214.166	32	69.193			
	Greenhouse-Geisser	2214.166	32.000	69.193			
	Huynh-Feldt	2214.166	32.000	69.193			
	Lower-bound	2214.166	32.000	69.193			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	454.732	1	454.732	.976	.331	.030
Age	541.230	1	541.230	1.162	.289	.035
Gender	.619	1	.619	.001	.971	.000
Mean_Pre_fsq_Total	1345.483	1	1345.483	2.889	.099	.083
Grooup	2049.915	1	2049.915	4.401	.044	.121
Error	14904.319	32	465.760			

Age and gender did not impact results (see below not controlling age/gender)

Descriptive Statistics

	Mean Grooup	Mean	Std. Deviation	N
Mean Post_fsq_Total	1.00	47.434036023756995	12.068285161182860	17
	2.00	58.986720436083154	17.286465753098800	20
	Total	53.678730300690050	16.015914717080683	37
Mean FU_fsq_Total	1.00	46.954675883019660	14.058606567914962	17
	2.00	57.095049343362845	20.538997501559420	20
	Total	52.435958834556510	18.350270208434180	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
measure	Pillai's Trace	.039	1.383[b]	1.000	34.000	.248
	Wilks' Lambda	.961	1.383[b]	1.000	34.000	.248
	Hotelling's Trace	.041	1.383[b]	1.000	34.000	.248
	Roy's Largest Root	.041	1.383[b]	1.000	34.000	.248
measure * Mean_Pre_fsq_Total	Pillai's Trace	.034	1.180[b]	1.000	34.000	.285
	Wilks' Lambda	.966	1.180[b]	1.000	34.000	.285
	Hotelling's Trace	.035	1.180[b]	1.000	34.000	.285
	Roy's Largest Root	.035	1.180[b]	1.000	34.000	.285
measure * Grooup	Pillai's Trace	.002	.082[b]	1.000	34.000	.777
	Wilks' Lambda	.998	.082[b]	1.000	34.000	.777
	Hotelling's Trace	.002	.082[b]	1.000	34.000	.777
	Roy's Largest Root	.002	.082[b]	1.000	34.000	.777

a. Design: Intercept + Mean_Pre_fsq_Total + Grooup
Within Subjects Design: measure

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
measure	Sphericity Assumed	108.789	1	108.789	1.383	.248
	Greenhouse-Geisser	108.789	1.000	108.789	1.383	.248
	Huynh-Feldt	108.789	1.000	108.789	1.383	.248
	Lower-bound	108.789	1.000	108.789	1.383	.248
measure * Mean_Pre_fsq_Total	Sphericity Assumed	92.880	1	92.880	1.180	.285

	Greenhouse-Geisser	92.880	1.000	92.880	1.180	.285
	Huynh-Feldt	92.880	1.000	92.880	1.180	.285
	Lower-bound	92.880	1.000	92.880	1.180	.285
measure * Grooup	Sphericity Assumed	6.432	1	6.432	.082	.777
	Greenhouse-Geisser	6.432	1.000	6.432	.082	.777
	Huynh-Feldt	6.432	1.000	6.432	.082	.777
	Lower-bound	6.432	1.000	6.432	.082	.777
Error(measure)	Sphericity Assumed	2675.186	34	78.682		
	Greenhouse-Geisser	2675.186	34.000	78.682		
	Huynh-Feldt	2675.186	34.000	78.682		
	Lower-bound	2675.186	34.000	78.682		

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	3092.206	1	3092.206	6.804	.013
Mean_Pre_fsq_Total	964.341	1	964.341	2.122	.154
Grooup	2304.910	1	2304.910	5.071	.031
Error	15452.973	34	454.499		

Two-way repeated measures ANCOVA: Post and 3mfu BAT distance
N =37
Group 1= Stress= 17
Group 2 = Control= 20
Between factor: Stress group, Control group
Within factor: Post_BATdist, 3mfu_BATdist
Covariate: Pre_BATdistscore Age, Gender
Exclusions: none
Outcome: No sig difference between groups.

Descriptive Statistics

	Mean Grooup	Mean	Std. Deviation	N

BAT_post_K_score	1.00	5.1176	.33211	17
	2.00	5.1500	.67082	20
	Total	5.1351	.53552	37
BAT_score_K3mfu	1.00	4.88	.332	17
	2.00	5.05	.394	20
	Total	4.97	.372	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.021	.685[b]	1.000	32.000	.414	.021
	Wilks' Lambda	.979	.685[b]	1.000	32.000	.414	.021
	Hotelling's Trace	.021	.685[b]	1.000	32.000	.414	.021
	Roy's Largest Root	.021	.685[b]	1.000	32.000	.414	.021
factor1 * Age	Pillai's Trace	.016	.510[b]	1.000	32.000	.480	.016
	Wilks' Lambda	.984	.510[b]	1.000	32.000	.480	.016
	Hotelling's Trace	.016	.510[b]	1.000	32.000	.480	.016
	Roy's Largest Root	.016	.510[b]	1.000	32.000	.480	.016
factor1 * Gender	Pillai's Trace	.002	.056[b]	1.000	32.000	.815	.002
	Wilks' Lambda	.998	.056[b]	1.000	32.000	.815	.002
	Hotelling's Trace	.002	.056[b]	1.000	32.000	.815	.002
	Roy's Largest Root	.002	.056[b]	1.000	32.000	.815	.002
factor1 * BAT_dis_score_pre	Pillai's Trace	.051	1.725[b]	1.000	32.000	.198	.051
	Wilks' Lambda	.949	1.725[b]	1.000	32.000	.198	.051
	Hotelling's Trace	.054	1.725[b]	1.000	32.000	.198	.051
	Roy's Largest Root	.054	1.725[b]	1.000	32.000	.198	.051
factor1 * Grooup	Pillai's Trace	.022	.718[b]	1.000	32.000	.403	.022
	Wilks' Lambda	.978	.718[b]	1.000	32.000	.403	.022

	Hotelling's Trace	.022	.718[b]	1.000	32.000	.403	.022
	Roy's Largest Root	.022	.718[b]	1.000	32.000	.403	.022

a. Design: Intercept + Age + Gender + BAT_dis_score_pre + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	.089	1	.089	.685	.414	.021
	Greenhouse-Geisser	.089	1.000	.089	.685	.414	.021
	Huynh-Feldt	.089	1.000	.089	.685	.414	.021
	Lower-bound	.089	1.000	.089	.685	.414	.021
factor1 * Age	Sphericity Assumed	.067	1	.067	.510	.480	.016
	Greenhouse-Geisser	.067	1.000	.067	.510	.480	.016
	Huynh-Feldt	.067	1.000	.067	.510	.480	.016
	Lower-bound	.067	1.000	.067	.510	.480	.016
factor1 * Gender	Sphericity Assumed	.007	1	.007	.056	.815	.002
	Greenhouse-Geisser	.007	1.000	.007	.056	.815	.002
	Huynh-Feldt	.007	1.000	.007	.056	.815	.002
	Lower-bound	.007	1.000	.007	.056	.815	.002
factor1 * BAT_dis_score_pre	Sphericity Assumed	.225	1	.225	1.725	.198	.051
	Greenhouse-Geisser	.225	1.000	.225	1.725	.198	.051
	Huynh-Feldt	.225	1.000	.225	1.725	.198	.051
	Lower-bound	.225	1.000	.225	1.725	.198	.051
factor1 * Grooup	Sphericity Assumed	.094	1	.094	.718	.403	.022

	Greenhouse-Geisser	.094	1.000	.094	.718	.403	.022
	Huynh-Feldt	.094	1.000	.094	.718	.403	.022
	Lower-bound	.094	1.000	.094	.718	.403	.022
Error(factor1)	Sphericity Assumed	4.177	32	.131			
	Greenhouse-Geisser	4.177	32.000	.131			
	Huynh-Feldt	4.177	32.000	.131			
	Lower-bound	4.177	32.000	.131			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	55.772	1	55.772	183.509	.000	.852
Age	.062	1	.062	.205	.653	.006
Gender	.397	1	.397	1.307	.261	.039
BAT_dis_score_pre	.263	1	.263	.867	.359	.026
Grooup	.237	1	.237	.781	.383	.024
Error	9.725	32	.304			

Two-way repeated measures ANCOVA: Post and 3mfu BAT Heart Rate

N =37
Group 1= Stress= 17
Group 2 = Control= 20
B**etween factor:** Stress group, Control group
Within factor: Post_BAT heart rate, 3mfu_BATheart rate
Covariate: Pre_BAT heart rate Age, Gender
Exclusions: none
Outcome: No sig difference between groups.

Descriptive Statistics

	Mean Grooup	Mean	Std. Deviation	N
HR_avg_postBAT	1.00	80.712975	9.1586585	17
	2.00	81.521381	6.1186945	20
	Total	81.149951	7.5634937	37
HR_avg_3mfuBAT	1.00	76.958425	4.3925955	17
	2.00	77.293773	6.4170150	20

Total	77.139694	5.5079117	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.150	5.661[b]	1.000	32.000	.023	.150
	Wilks' Lambda	.850	5.661[b]	1.000	32.000	.023	.150
	Hotelling's Trace	.177	5.661[b]	1.000	32.000	.023	.150
	Roy's Largest Root	.177	5.661[b]	1.000	32.000	.023	.150
factor1 * Age	Pillai's Trace	.120	4.365[b]	1.000	32.000	.045	.120
	Wilks' Lambda	.880	4.365[b]	1.000	32.000	.045	.120
	Hotelling's Trace	.136	4.365[b]	1.000	32.000	.045	.120
	Roy's Largest Root	.136	4.365[b]	1.000	32.000	.045	.120
factor1 * Gender	Pillai's Trace	.001	.045[b]	1.000	32.000	.834	.001
	Wilks' Lambda	.999	.045[b]	1.000	32.000	.834	.001
	Hotelling's Trace	.001	.045[b]	1.000	32.000	.834	.001
	Roy's Largest Root	.001	.045[b]	1.000	32.000	.834	.001
factor1 * HR_avg_preBAT	Pillai's Trace	.151	5.684[b]	1.000	32.000	.023	.151
	Wilks' Lambda	.849	5.684[b]	1.000	32.000	.023	.151
	Hotelling's Trace	.178	5.684[b]	1.000	32.000	.023	.151
	Roy's Largest Root	.178	5.684[b]	1.000	32.000	.023	.151
factor1 * Grooup	Pillai's Trace	.000	.001[b]	1.000	32.000	.981	.000
	Wilks' Lambda	1.000	.001[b]	1.000	32.000	.981	.000
	Hotelling's Trace	.000	.001[b]	1.000	32.000	.981	.000
	Roy's Largest Root	.000	.001[b]	1.000	32.000	.981	.000

a. Design: Intercept + Age + Gender + HR_avg_preBAT + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	168.207	1	168.207	5.661	.023	.150
	Greenhouse-Geisser	168.207	1.000	168.207	5.661	.023	.150
	Huynh-Feldt	168.207	1.000	168.207	5.661	.023	.150
	Lower-bound	168.207	1.000	168.207	5.661	.023	.150
factor1 * Age	Sphericity Assumed	129.710	1	129.710	4.365	.045	.120
	Greenhouse-Geisser	129.710	1.000	129.710	4.365	.045	.120
	Huynh-Feldt	129.710	1.000	129.710	4.365	.045	.120
	Lower-bound	129.710	1.000	129.710	4.365	.045	.120
factor1 * Gender	Sphericity Assumed	1.330	1	1.330	.045	.834	.001
	Greenhouse-Geisser	1.330	1.000	1.330	.045	.834	.001
	Huynh-Feldt	1.330	1.000	1.330	.045	.834	.001
	Lower-bound	1.330	1.000	1.330	.045	.834	.001
factor1 * HR_avg_preBAT	Sphericity Assumed	168.907	1	168.907	5.684	.023	.151
	Greenhouse-Geisser	168.907	1.000	168.907	5.684	.023	.151
	Huynh-Feldt	168.907	1.000	168.907	5.684	.023	.151
	Lower-bound	168.907	1.000	168.907	5.684	.023	.151
factor1 * Grooup	Sphericity Assumed	.016	1	.016	.001	.981	.000
	Greenhouse-Geisser	.016	1.000	.016	.001	.981	.000
	Huynh-Feldt	.016	1.000	.016	.001	.981	.000
	Lower-bound	.016	1.000	.016	.001	.981	.000
Error(factor1)	Sphericity Assumed	950.872	32	29.715			
	Greenhouse-Geisser	950.872	32.000	29.715			
	Huynh-Feldt	950.872	32.000	29.715			
	Lower-bound	950.872	32.000	29.715			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	4989.274	1	4989.274	84.266	.000	.725
Age	.374	1	.374	.006	.937	.000
Gender	37.277	1	37.277	.630	.433	.019
HR_avg_preBAT	2.373	1	2.373	.040	.843	.001
Grooup	2.785	1	2.785	.047	.830	.001
Error	1894.670	32	59.208			

Effects of Stress on Renewal (Post-Treatment)

ANCOVA: BAT Kitchen vs Garden BAT score
Post-Treatment

N =37
Group 1= Stress= 17
Group 2 = Control= 20
Between factor: Stress group, Control group
Within factor: Post_ BATscore_Kitchen, Post_ BAT_Garden score
Covariate: age, gender
Exclusions: none

Descriptive Statistics

	Mean Grooup	Mean	Std. Deviation	N
BAT_post_K_score	1.00	5.1176	.33211	17
	2.00	5.1500	.67082	20
	Total	5.1351	.53552	37
BAT_post_G_score	1.00	4.8824	.48507	17
	2.00	4.6000	.94032	20
	Total	4.7297	.76915	37

Multivariate Tests[a]

Effect	Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared

factor1	Pillai's Trace	.190	7.717[b]	1.000	33.000	.009	.190
	Wilks' Lambda	.810	7.717[b]	1.000	33.000	.009	.190
	Hotelling's Trace	.234	7.717[b]	1.000	33.000	.009	.190
	Roy's Largest Root	.234	7.717[b]	1.000	33.000	.009	.190
factor1 * Age	Pillai's Trace	.084	3.044[b]	1.000	33.000	.090	.084
	Wilks' Lambda	.916	3.044[b]	1.000	33.000	.090	.084
	Hotelling's Trace	.092	3.044[b]	1.000	33.000	.090	.084
	Roy's Largest Root	.092	3.044[b]	1.000	33.000	.090	.084
factor1 * Gender	Pillai's Trace	.076	2.723[b]	1.000	33.000	.108	.076
	Wilks' Lambda	.924	2.723[b]	1.000	33.000	.108	.076
	Hotelling's Trace	.083	2.723[b]	1.000	33.000	.108	.076
	Roy's Largest Root	.083	2.723[b]	1.000	33.000	.108	.076
factor1 * Grooup	Pillai's Trace	.067	2.372[b]	1.000	33.000	.133	.067
	Wilks' Lambda	.933	2.372[b]	1.000	33.000	.133	.067
	Hotelling's Trace	.072	2.372[b]	1.000	33.000	.133	.067
	Roy's Largest Root	.072	2.372[b]	1.000	33.000	.133	.067

a. Design: Intercept + Age + Gender + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	2.457	1	2.457	7.717	.009	.190
	Greenhouse-Geisser	2.457	1.000	2.457	7.717	.009	.190
	Huynh-Feldt	2.457	1.000	2.457	7.717	.009	.190
	Lower-bound	2.457	1.000	2.457	7.717	.009	.190
factor1 * Age	Sphericity Assumed	.969	1	.969	3.044	.090	.084

	Greenhouse-Geisser	.969	1.000	.969	3.044	.090	.084
	Huynh-Feldt	.969	1.000	.969	3.044	.090	.084
	Lower-bound	.969	1.000	.969	3.044	.090	.084
factor1 * Gender	Sphericity Assumed	.867	1	.867	2.723	.108	.076
	Greenhouse-Geisser	.867	1.000	.867	2.723	.108	.076
	Huynh-Feldt	.867	1.000	.867	2.723	.108	.076
	Lower-bound	.867	1.000	.867	2.723	.108	.076
factor1 * Grooup	Sphericity Assumed	.755	1	.755	2.372	.133	.067
	Greenhouse-Geisser	.755	1.000	.755	2.372	.133	.067
	Huynh-Feldt	.755	1.000	.755	2.372	.133	.067
	Lower-bound	.755	1.000	.755	2.372	.133	.067
Error(factor1)	Sphericity Assumed	10.507	33	.318			
	Greenhouse-Geisser	10.507	33.000	.318			
	Huynh-Feldt	10.507	33.000	.318			
	Lower-bound	10.507	33.000	.318			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	86.336	1	86.336	165.693	.000	.834
Age	1.676	1	1.676	3.217	.082	.089
Gender	.054	1	.054	.103	.750	.003
Grooup	.466	1	.466	.895	.351	.026
Error	17.195	33	.521			

ANCOVA: BAT Kitchen vs Garden Heart Rate
Post-Treatment

N =37

Group 1= Stress= 17
Group 2 = Control= 20
Between factor: Stress group, Control group
Within factor: Post_ BAT avg heart rate Kitchen , Post BAT avg heart rate Garden
Covariate: age, gender
Exclusions: none
Outcome: No significant main effect of group or group x interaction. Sig main effect of context (higher avg HR in Garden, relative to Kitchen context, across groups).

Descriptive Statistics

	Grooup	Mean	Std. Deviation	N
HR_avg_postBAT	1.00	80.712975	9.1586585	17
	2.00	81.521381	6.1186945	20
	Total	81.149951	7.5634937	37
HR_avg_postGBAT	1.00	84.150326	8.6064624	17
	2.00	84.667500	9.0286364	20
	Total	84.429879	8.7184449	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.170	6.750[b]	1.000	33.000	.014	.170
	Wilks' Lambda	.830	6.750[b]	1.000	33.000	.014	.170
	Hotelling's Trace	.205	6.750[b]	1.000	33.000	.014	.170
	Roy's Largest Root	.205	6.750[b]	1.000	33.000	.014	.170
factor1 * Age	Pillai's Trace	.177	7.113[b]	1.000	33.000	.012	.177
	Wilks' Lambda	.823	7.113[b]	1.000	33.000	.012	.177
	Hotelling's Trace	.216	7.113[b]	1.000	33.000	.012	.177
	Roy's Largest Root	.216	7.113[b]	1.000	33.000	.012	.177
factor1 * Gender	Pillai's Trace	.001	.022[b]	1.000	33.000	.882	.001
	Wilks' Lambda	.999	.022[b]	1.000	33.000	.882	.001
	Hotelling's Trace	.001	.022[b]	1.000	33.000	.882	.001
	Roy's Largest Root	.001	.022[b]	1.000	33.000	.882	.001
factor1 * Grooup	Pillai's Trace	.001	.025[b]	1.000	33.000	.877	.001
	Wilks' Lambda	.999	.025[b]	1.000	33.000	.877	.001
	Hotelling's Trace	.001	.025[b]	1.000	33.000	.877	.001

	Roy's Largest Root	.001	.025[b]	1.000	33.000	.877	.001

a. Design: Intercept + Age + Gender + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	313.090	1	313.090	6.750	.014	.170
	Greenhouse-Geisser	313.090	1.000	313.090	6.750	.014	.170
	Huynh-Feldt	313.090	1.000	313.090	6.750	.014	.170
	Lower-bound	313.090	1.000	313.090	6.750	.014	.170
factor1 * Age	Sphericity Assumed	329.907	1	329.907	7.113	.012	.177
	Greenhouse-Geisser	329.907	1.000	329.907	7.113	.012	.177
	Huynh-Feldt	329.907	1.000	329.907	7.113	.012	.177
	Lower-bound	329.907	1.000	329.907	7.113	.012	.177
factor1 * Gender	Sphericity Assumed	1.038	1	1.038	.022	.882	.001
	Greenhouse-Geisser	1.038	1.000	1.038	.022	.882	.001
	Huynh-Feldt	1.038	1.000	1.038	.022	.882	.001
	Lower-bound	1.038	1.000	1.038	.022	.882	.001
factor1 * Grooup	Sphericity Assumed	1.137	1	1.137	.025	.877	.001
	Greenhouse-Geisser	1.137	1.000	1.137	.025	.877	.001
	Huynh-Feldt	1.137	1.000	1.137	.025	.877	.001
	Lower-bound	1.137	1.000	1.137	.025	.877	.001
Error(factor1)	Sphericity Assumed	1530.600	33	46.382			
	Greenhouse-Geisser	1530.600	33.000	46.382			

	Huynh-Feldt	1530.600	33.000	46.382			
	Lower-bound	1530.600	33.000	46.382			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	32116.697	1	32116.697	385.463	.000	.921
Age	75.264	1	75.264	.903	.349	.027
Gender	41.120	1	41.120	.494	.487	.015
Grooup	8.567	1	8.567	.103	.750	.003
Error	2749.551	33	83.320			

ANCOVA: BAT Kitchen vs Garden Speed
Post-Treatment

N =37
Group 1= Stress= 17
Group 2 = Control= 20
Between factor: Stress group, Control group
Within factor: Post_ BAT speed Kitchen , Post BAT speed Garden
Covariate: age, gender
Exclusions: none
Outcome: No significant main effect of group or group x interaction,

Descriptive Statistics

	Mean Grooup	Mean	Std. Deviation	N
BAT_Post_Speed	1.00	.010923343142369	.004028525573105	17
	2.00	.009005874777772	.003138602203456	20
	Total	.009886873756100	.003653824853392	37
BAT_Post_G_Speed	1.00	.007466701990429	.003634907798433	17
	2.00	.008084902264309	.003275002408204	20
	Total	.007800864300634	.003410359613205	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.001	.021[b]	1.000	33.000	.887	.001
	Wilks' Lambda	.999	.021[b]	1.000	33.000	.887	.001
	Hotelling's Trace	.001	.021[b]	1.000	33.000	.887	.001
	Roy's Largest Root	.001	.021[b]	1.000	33.000	.887	.001
factor1 * Age	Pillai's Trace	.016	.535[b]	1.000	33.000	.470	.016
	Wilks' Lambda	.984	.535[b]	1.000	33.000	.470	.016
	Hotelling's Trace	.016	.535[b]	1.000	33.000	.470	.016
	Roy's Largest Root	.016	.535[b]	1.000	33.000	.470	.016
factor1 * Gender	Pillai's Trace	.021	.696[b]	1.000	33.000	.410	.021
	Wilks' Lambda	.979	.696[b]	1.000	33.000	.410	.021
	Hotelling's Trace	.021	.696[b]	1.000	33.000	.410	.021
	Roy's Largest Root	.021	.696[b]	1.000	33.000	.410	.021
factor1 * Grooup	Pillai's Trace	.103	3.802[b]	1.000	33.000	.060	.103
	Wilks' Lambda	.897	3.802[b]	1.000	33.000	.060	.103
	Hotelling's Trace	.115	3.802[b]	1.000	33.000	.060	.103
	Roy's Largest Root	.115	3.802[b]	1.000	33.000	.060	.103

a. Design: Intercept + Age + Gender + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	1.859E-7	1	1.859E-7	.021	.887	.001
	Greenhouse-Geisser	1.859E-7	1.000	1.859E-7	.021	.887	.001
	Huynh-Feldt	1.859E-7	1.000	1.859E-7	.021	.887	.001
	Lower-bound	1.859E-7	1.000	1.859E-7	.021	.887	.001
factor1 * Age	Sphericity Assumed	4.836E-6	1	4.836E-6	.535	.470	.016
	Greenhouse-Geisser	4.836E-6	1.000	4.836E-6	.535	.470	.016
	Huynh-Feldt	4.836E-6	1.000	4.836E-6	.535	.470	.016
	Lower-bound	4.836E-6	1.000	4.836E-6	.535	.470	.016
factor1 * Gender	Sphericity Assumed	6.290E-6	1	6.290E-6	.696	.410	.021
	Greenhouse-Geisser	6.290E-6	1.000	6.290E-6	.696	.410	.021
	Huynh-Feldt	6.290E-6	1.000	6.290E-6	.696	.410	.021
	Lower-bound	6.290E-6	1.000	6.290E-6	.696	.410	.021
factor1 * Grooup	Sphericity Assumed	3.437E-5	1	3.437E-5	3.802	.060	.103
	Greenhouse-Geisser	3.437E-5	1.000	3.437E-5	3.802	.060	.103
	Huynh-Feldt	3.437E-5	1.000	3.437E-5	3.802	.060	.103
	Lower-bound	3.437E-5	1.000	3.437E-5	3.802	.060	.103
Error(factor1)	Sphericity Assumed	.000	33	9.040E-6			
	Greenhouse-Geisser	.000	33.000	9.040E-6			
	Huynh-Feldt	.000	33.000	9.040E-6			
	Lower-bound	.000	33.000	9.040E-6			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	.000	1	.000	21.997	.000	.400
Age	1.337E-7	1	1.337E-7	.008	.929	.000
Gender	3.491E-6	1	3.491E-6	.209	.650	.006
Grooup	6.596E-6	1	6.596E-6	.395	.534	.012
Error	.001	33	1.668E-5			

Effects of Stress during Exposure Therapy

Two-way Repeated Measures ANCOVA Analysis: US-expectancy ratings

N =37
Group 1= Stress= 17
Group 2 = Control=20
Between factor: Stress group, Control group
Within factor: Start expectancy, end expectancy
Covariate: Age, Gender
Exclusions: none
Outcome: Main effect of time and group approaching significance. Post-hoc tests reveal sig, high exp ratings at the start of exposure in stress group relative to control group

Descriptive Statistics

	Grooup	Mean	Std. Deviation	N
T1_1st_Exp_Start	1.00	4.4837	2.53082	17
	2.00	2.6792	2.42358	20
	Total	3.5083	2.60342	37
T1_1st_Exp_End	1.00	2.1301	1.32843	17
	2.00	1.5431	1.23846	20
	Total	1.8128	1.29683	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.002	.051[b]	1.000	33.000	.823	.002

	Wilks' Lambda	.998	.051[b]	1.000	33.000	.823	.002
	Hotelling's Trace	.002	.051[b]	1.000	33.000	.823	.002
	Roy's Largest Root	.002	.051[b]	1.000	33.000	.823	.002
factor1 * Age	Pillai's Trace	.005	.169[b]	1.000	33.000	.683	.005
	Wilks' Lambda	.995	.169[b]	1.000	33.000	.683	.005
	Hotelling's Trace	.005	.169[b]	1.000	33.000	.683	.005
	Roy's Largest Root	.005	.169[b]	1.000	33.000	.683	.005
factor1 * Gender	Pillai's Trace	.084	3.010[b]	1.000	33.000	.092	.084
	Wilks' Lambda	.916	3.010[b]	1.000	33.000	.092	.084
	Hotelling's Trace	.091	3.010[b]	1.000	33.000	.092	.084
	Roy's Largest Root	.091	3.010[b]	1.000	33.000	.092	.084
factor1 * Grooup	Pillai's Trace	.104	3.824[b]	1.000	33.000	.059	.104
	Wilks' Lambda	.896	3.824[b]	1.000	33.000	.059	.104
	Hotelling's Trace	.116	3.824[b]	1.000	33.000	.059	.104
	Roy's Largest Root	.116	3.824[b]	1.000	33.000	.059	.104

a. Design: Intercept + Age + Gender + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	.114	1	.114	.051	.823	.002
	Greenhouse-Geisser	.114	1.000	.114	.051	.823	.002
	Huynh-Feldt	.114	1.000	.114	.051	.823	.002
	Lower-bound	.114	1.000	.114	.051	.823	.002
factor1 * Age	Sphericity Assumed	.380	1	.380	.169	.683	.005
	Greenhouse-Geisser	.380	1.000	.380	.169	.683	.005

	Huynh-Feldt	.380	1.000	.380	.169	.683	.005
	Lower-bound	.380	1.000	.380	.169	.683	.005
factor1 * Gender	Sphericity Assumed	6.763	1	6.763	3.010	.092	.084
	Greenhouse-Geisser	6.763	1.000	6.763	3.010	.092	.084
	Huynh-Feldt	6.763	1.000	6.763	3.010	.092	.084
	Lower-bound	6.763	1.000	6.763	3.010	.092	.084
factor1 * Grooup	Sphericity Assumed	8.592	1	8.592	3.824	.059	.104
	Greenhouse-Geisser	8.592	1.000	8.592	3.824	.059	.104
	Huynh-Feldt	8.592	1.000	8.592	3.824	.059	.104
	Lower-bound	8.592	1.000	8.592	3.824	.059	.104
Error(factor1)	Sphericity Assumed	74.140	33	2.247			
	Greenhouse-Geisser	74.140	33.000	2.247			
	Huynh-Feldt	74.140	33.000	2.247			
	Lower-bound	74.140	33.000	2.247			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	67.519	1	67.519	12.127	.001	.269
Age	6.447	1	6.447	1.158	.290	.034
Gender	1.379	1	1.379	.248	.622	.007
Grooup	21.790	1	21.790	3.914	.056	.106
Error	183.732	33	5.568			

Two-way Repeated Measures ANCOVA Analysis: SUDs

N =37
Group 1= Stress= 17
Group 2 = Control=20
Between factor: Stress group, Control group
Within factor: Start SUDs, end SUDs
Covariate: Age, Gender
Exclusions: none

Outcome: Main effect of time (higher SUDs ratings at the start relative to the end, across groups). No differences between groups.

Descriptive Statistics

	Grooup	Mean	Std. Deviation	N
T1_1st_SUDs_Start	1.00	5.8263	1.68739	17
	2.00	5.4746	1.22938	20
	Total	5.6362	1.44731	37
T1_1st_SUDs_End	1.00	3.5289	.94819	17
	2.00	2.9379	.92952	20
	Total	3.2094	.97198	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.133	5.055[b]	1.000	33.000	.031	.133
	Wilks' Lambda	.867	5.055[b]	1.000	33.000	.031	.133
	Hotelling's Trace	.153	5.055[b]	1.000	33.000	.031	.133
	Roy's Largest Root	.153	5.055[b]	1.000	33.000	.031	.133
factor1 * Age	Pillai's Trace	.001	.020[b]	1.000	33.000	.888	.001
	Wilks' Lambda	.999	.020[b]	1.000	33.000	.888	.001
	Hotelling's Trace	.001	.020[b]	1.000	33.000	.888	.001
	Roy's Largest Root	.001	.020[b]	1.000	33.000	.888	.001
factor1 * Gender	Pillai's Trace	.031	1.059[b]	1.000	33.000	.311	.031
	Wilks' Lambda	.969	1.059[b]	1.000	33.000	.311	.031
	Hotelling's Trace	.032	1.059[b]	1.000	33.000	.311	.031
	Roy's Largest Root	.032	1.059[b]	1.000	33.000	.311	.031
factor1 * Grooup	Pillai's Trace	.005	.159[b]	1.000	33.000	.693	.005
	Wilks' Lambda	.995	.159[b]	1.000	33.000	.693	.005
	Hotelling's Trace	.005	.159[b]	1.000	33.000	.693	.005
	Roy's Largest Root	.005	.159[b]	1.000	33.000	.693	.005

a. Design: Intercept + Age + Gender + Grooup
Within Subjects Design: factor1
b. Exact statistic

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	5.127	1	5.127	5.055	.031	.133
	Greenhouse-Geisser	5.127	1.000	5.127	5.055	.031	.133
	Huynh-Feldt	5.127	1.000	5.127	5.055	.031	.133
	Lower-bound	5.127	1.000	5.127	5.055	.031	.133
factor1 * Age	Sphericity Assumed	.020	1	.020	.020	.888	.001
	Greenhouse-Geisser	.020	1.000	.020	.020	.888	.001
	Huynh-Feldt	.020	1.000	.020	.020	.888	.001
	Lower-bound	.020	1.000	.020	.020	.888	.001
factor1 * Gender	Sphericity Assumed	1.074	1	1.074	1.059	.311	.031
	Greenhouse-Geisser	1.074	1.000	1.074	1.059	.311	.031
	Huynh-Feldt	1.074	1.000	1.074	1.059	.311	.031
	Lower-bound	1.074	1.000	1.074	1.059	.311	.031
factor1 * Grooup	Sphericity Assumed	.161	1	.161	.159	.693	.005
	Greenhouse-Geisser	.161	1.000	.161	.159	.693	.005
	Huynh-Feldt	.161	1.000	.161	.159	.693	.005
	Lower-bound	.161	1.000	.161	.159	.693	.005
Error(factor1)	Sphericity Assumed	33.471	33	1.014			
	Greenhouse-Geisser	33.471	33.000	1.014			
	Huynh-Feldt	33.471	33.000	1.014			
	Lower-bound	33.471	33.000	1.014			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	105.711	1	105.711	51.205	.000	.608
Age	1.735	1	1.735	.840	.366	.025
Gender	.160	1	.160	.078	.782	.002
Grooup	3.639	1	3.639	1.762	.193	.051
Error	68.127	33	2.064			

Two-way Repeated Measures ANCOVA Analysis: Heart Rate

N =37
Group 1= Stress= 17
Group 2 = Control=20
Between factor: Stress group, Control group
Within factor: Start avg heart rate (1st trial), end avg heart rate (last trial)
Covariate: Age, Gender
Exclusions: none
Outcome: No Main effect of time, group or interaction effect.

Descriptive Statistics

	Grooup	Mean	Std. Deviation	N
HR_start_Task1_T1	1.00	77.215158	11.3449170	17
	2.00	75.660933	8.9722430	20
	Total	76.375037	10.0153127	37
HR_end_Task1_T1	1.00	77.970520	2.6440481	17
	2.00	82.567869	7.9046923	20
	Total	80.455573	6.4404841	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.026	.878[b]	1.000	33.000	.356	.026
	Wilks' Lambda	.974	.878[b]	1.000	33.000	.356	.026
	Hotelling's Trace	.027	.878[b]	1.000	33.000	.356	.026
	Roy's Largest Root	.027	.878[b]	1.000	33.000	.356	.026

factor1 * Age	Pillai's Trace	.013	.431[b]	1.000	33.000	.516	.013
	Wilks' Lambda	.987	.431[b]	1.000	33.000	.516	.013
	Hotelling's Trace	.013	.431[b]	1.000	33.000	.516	.013
	Roy's Largest Root	.013	.431[b]	1.000	33.000	.516	.013
factor1 * Gender	Pillai's Trace	.001	.022[b]	1.000	33.000	.882	.001
	Wilks' Lambda	.999	.022[b]	1.000	33.000	.882	.001
	Hotelling's Trace	.001	.022[b]	1.000	33.000	.882	.001
	Roy's Largest Root	.001	.022[b]	1.000	33.000	.882	.001
factor1 * Grooup	Pillai's Trace	.068	2.400[b]	1.000	33.000	.131	.068
	Wilks' Lambda	.932	2.400[b]	1.000	33.000	.131	.068
	Hotelling's Trace	.073	2.400[b]	1.000	33.000	.131	.068
	Roy's Largest Root	.073	2.400[b]	1.000	33.000	.131	.068

a. Design: Intercept + Age + Gender + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
factor1	Sphericity Assumed	65.839	1	65.839	.878	.356	.026
	Greenhouse-Geisser	65.839	1.000	65.839	.878	.356	.026
	Huynh-Feldt	65.839	1.000	65.839	.878	.356	.026
	Lower-bound	65.839	1.000	65.839	.878	.356	.026
factor1 * Age	Sphericity Assumed	32.281	1	32.281	.431	.516	.013
	Greenhouse-Geisser	32.281	1.000	32.281	.431	.516	.013

	Huynh-Feldt	32.281	1.000	32.281	.431	.516	.013
	Lower-bound	32.281	1.000	32.281	.431	.516	.013
factor1 * Gender	Sphericity Assumed	1.673	1	1.673	.022	.882	.001
	Greenhouse-Geisser	1.673	1.000	1.673	.022	.882	.001
	Huynh-Feldt	1.673	1.000	1.673	.022	.882	.001
	Lower-bound	1.673	1.000	1.673	.022	.882	.001
factor1 * Grooup	Sphericity Assumed	179.947	1	179.947	2.400	.131	.068
	Greenhouse-Geisser	179.947	1.000	179.947	2.400	.131	.068
	Huynh-Feldt	179.947	1.000	179.947	2.400	.131	.068
	Lower-bound	179.947	1.000	179.947	2.400	.131	.068
Error(factor1)	Sphericity Assumed	2474.306	33	74.979			
	Greenhouse-Geisser	2474.306	33.000	74.979			
	Huynh-Feldt	2474.306	33.000	74.979			
	Lower-bound	2474.306	33.000	74.979			

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	32044.526	1	32044.526	485.752	.000	.936
Age	172.908	1	172.908	2.621	.115	.074
Gender	60.792	1	60.792	.922	.344	.027
Grooup	74.378	1	74.378	1.127	.296	.033
Error	2176.972	33	65.969			

Effects of Stress on Attention

Two-way Repeated Measures ANCOVA Analysis: eye gaze across Task 1, 2,3

N =37
Group 1= Stress= 17

Group 2 = Control=20
Between factor: Stress group, Control group
Within factor: % eye gaze Task 1, Task 2, Task 3
Covariate: Age, Gender, total no. trials across 3 tasks
Exclusions: none
Outcome: No sig. effects.

Descriptive Statistics

	Grooup	Mean	Std. Deviation	N
T1_all_0.7	1.00	78.538555	14.6181693	17
	2.00	80.833996	10.0460690	20
	Total	79.779334	12.2304479	37
Task2_all_0.7	1.00	81.523949	10.6282977	17
	2.00	73.300945	23.4809615	20
	Total	77.079082	18.9329811	37
Task3_0.7	1.00	87.600392	12.7129350	17
	2.00	83.347577	14.1530867	20
	Total	85.301573	13.4968994	37

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
factor1	Pillai's Trace	.097	1.667[b]	2.000	31.000	.205	.097
	Wilks' Lambda	.903	1.667[b]	2.000	31.000	.205	.097
	Hotelling's Trace	.108	1.667[b]	2.000	31.000	.205	.097
	Roy's Largest Root	.108	1.667[b]	2.000	31.000	.205	.097
factor1 * Age	Pillai's Trace	.033	.528[b]	2.000	31.000	.595	.033
	Wilks' Lambda	.967	.528[b]	2.000	31.000	.595	.033
	Hotelling's Trace	.034	.528[b]	2.000	31.000	.595	.033
	Roy's Largest Root	.034	.528[b]	2.000	31.000	.595	.033
factor1 * Gender	Pillai's Trace	.071	1.180[b]	2.000	31.000	.321	.071
	Wilks' Lambda	.929	1.180[b]	2.000	31.000	.321	.071
	Hotelling's Trace	.076	1.180[b]	2.000	31.000	.321	.071
	Roy's Largest Root	.076	1.180[b]	2.000	31.000	.321	.071
factor1 * T123_no	Pillai's Trace	.037	.592[b]	2.000	31.000	.559	.037
	Wilks' Lambda	.963	.592[b]	2.000	31.000	.559	.037

	Hotelling's Trace	.038	.592[b]	2.000	31.000	.559	.037
	Roy's Largest Root	.038	.592[b]	2.000	31.000	.559	.037
factor1 * Grooup	Pillai's Trace	.090	1.534[b]	2.000	31.000	.232	.090
	Wilks' Lambda	.910	1.534[b]	2.000	31.000	.232	.090
	Hotelling's Trace	.099	1.534[b]	2.000	31.000	.232	.090
	Roy's Largest Root	.099	1.534[b]	2.000	31.000	.232	.090

a. Design: Intercept + Age + Gender + T123_no + Grooup
Within Subjects Design: factor1

b. Exact statistic

Tests of Between-Subjects Effects
Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	7035.400	1	7035.400	15.611	.000	.328
Age	1298.694	1	1298.694	2.882	.099	.083
Gender	1.727	1	1.727	.004	.951	.000
T123_no	722.063	1	722.063	1.602	.215	.048
Grooup	523.307	1	523.307	1.161	.289	.035
Error	14420.990	32	450.656			

Mediation Analysis 1

Tested mediators: Cortisol and NE
Short-term spontaneous recovery: Pre-Post SPQ

N=37
Y: Pre-Post SPQ
X: Group. 1=Stress, 2=Control
M1: sAA (measure of NE)
M2: Cortisol
Covariates: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****

Model : 6
Y : PrePoSPQ
X : Grooup
M1 : sAAav
M2 : cortav

Covariates:
Age Gender

Sample
Size: 37

****

OUTCOME VARIABLE:
sAAav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.0908	.0082	2380.0408	.0915	3.0000	33.0000	.9642

Model

	coeff	se	t	p	LLCI	ULCI
constant	105.8376	38.1226	2.7762	.0090	28.2751	183.4001
Grooup	-.6090	16.3240	-.0373	.9705	-33.8210	32.6030
Age	-.4734	.9219	-.5135	.6110	-2.3491	1.4023
Gender	-2.2459	18.1334	-.1239	.9022	-39.1393	34.6475

****

OUTCOME VARIABLE:
cortav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.6070	.3685	.0033	4.6677	4.0000	32.0000	.0044

Model

	coeff	se	t	p	LLCI	ULCI
constant	.2169	.0502	4.3205	.0001	.1146	.3191
Grooup	-.0766	.0194	-3.9584	.0004	-.1160	-.0372
sAAav	.0003	.0002	1.2959	.2043	-.0002	.0007
Age	.0001	.0011	.0869	.9313	-.0021	.0023

```
Gender       .0304      .0215     1.4144      .1669     -.0134      .0742

**************************************************************************
OUTCOME VARIABLE:
 PrePoSPQ

Model Summary
        R       R-sq        MSE          F        df1         df2          p
     .5056      .2556     5.6996     2.1288     5.0000    31.0000      .0882

Model
             coeff         se          t          p       LLCI       ULCI
constant   12.9132     2.6072     4.9528      .0000     7.5956    18.2308
Grooup     -2.7216      .9750    -2.7913      .0089    -4.7102     -.7330
sAAav       -.0041      .0087     -.4717      .6405     -.0219      .0137
cortav    -12.4719     7.2966    -1.7093      .0974   -27.3537     2.4099
Age         -.0526      .0453    -1.1617      .2542     -.1450      .0398
Gender       .0574      .9149      .0627      .9504    -1.8086     1.9234

****************** DIRECT AND INDIRECT EFFECTS OF X ON Y *****************

Direct effect of X on Y
    Effect         se          t          p       LLCI       ULCI
   -2.7216      .9750    -2.7913      .0089    -4.7102     -.7330

Indirect effect(s) of X on Y:
        Effect     BootSE   BootLLCI   BootULCI
TOTAL     .9600      .6575     -.0541     2.5922
Ind1      .0025      .2195     -.2655      .6445
Ind2      .9555      .6338     -.0688     2.4529
Ind3      .0020      .0892     -.2127      .1730

Indirect effect key:
Ind1 Grooup     ->   sAAav      ->   PrePoSPQ
Ind2 Grooup     ->   cortav     ->   PrePoSPQ
Ind3 Grooup     ->   sAAav      ->   cortav     ->   PrePoSPQ

********************** ANALYSIS NOTES AND ERRORS ************************

Level of confidence for all confidence intervals in output:
  95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
  5000

------ END MATRIX -----
```

Long-term spontaneous recovery: Pre-3mFU SPQ

N=37

Y: Pre-FUSPQ
X: Group. 1=Stress, 2=Control
M1: sAA (measure of NE)
M2: Cortisol
Covariates: Age, Gender

Run MATRIX procedure:

***************** PROCESS Procedure for SPSS Version 4.1 *****************

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 6
Y : PreFUSPQ
X : Grooup
M1 : sAAav
M2 : cortav

Covariates:
Age Gender

Sample
Size: 37

****
OUTCOME VARIABLE:
sAAav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.0908	.0082	2380.0408	.0915	3.0000	33.0000	.9642

Model

	coeff	se	t	p	LLCI	ULCI
constant	105.8376	38.1226	2.7762	.0090	28.2751	183.4001
Grooup	-.6090	16.3240	-.0373	.9705	-33.8210	32.6030
Age	-.4734	.9219	-.5135	.6110	-2.3491	1.4023
Gender	-2.2459	18.1334	-.1239	.9022	-39.1393	34.6475

```
**************************************************************************
OUTCOME VARIABLE:
 cortav

Model Summary
        R       R-sq        MSE          F        df1        df2          p
     .6070      .3685      .0033     4.6677     4.0000    32.0000      .0044

Model
             coeff         se          t          p       LLCI       ULCI
constant      .2169      .0502     4.3205      .0001      .1146      .3191
Grooup       -.0766      .0194    -3.9584      .0004     -.1160     -.0372
sAAav         .0003      .0002     1.2959      .2043     -.0002      .0007
Age           .0001      .0011     .0869       .9313     -.0021      .0023
Gender        .0304      .0215     1.4144      .1669     -.0134      .0742

**************************************************************************
OUTCOME VARIABLE:
 PreFUSPQ

Model Summary
        R       R-sq        MSE          F        df1        df2          p
     .6711      .4504     4.5811     5.0815     5.0000    31.0000      .0016

Model
             coeff         se          t          p       LLCI       ULCI
constant    13.4010     2.3375     5.7331      .0000     8.6336    18.1684
Grooup      -3.2007      .8741    -3.6616      .0009    -4.9835    -1.4179
sAAav         .0014      .0078     .1738       .8632     -.0146      .0173
cortav     -22.9467     6.5416    -3.5078      .0014   -36.2886    -9.6047
Age           -.0669      .0406    -1.6472      .1096     -.1497      .0159
Gender       2.3024      .8202     2.8070      .0086      .6295     3.9754

****************** DIRECT AND INDIRECT EFFECTS OF X ON Y *****************

Direct effect of X on Y
    Effect         se          t          p       LLCI       ULCI
   -3.2007      .8741    -3.6616      .0009    -4.9835    -1.4179

Indirect effect(s) of X on Y:
        Effect    BootSE  BootLLCI  BootULCI
TOTAL     1.7609     .8136     .3257     3.4971
Ind1      -.0008     .1379    -.3330     .2547
Ind2      1.7580     .7976     .3642     3.4512
Ind3       .0037     .1300    -.2780     .2791
```

Indirect effect key:
Ind1 Grooup -> sAAav -> PreFUSPQ
Ind2 Grooup -> cortav -> PreFUSPQ
Ind3 Grooup -> sAAav -> cortav -> PreFUSPQ

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Renewal: BAT score Kitchen-Garden SPQ

N=37
Y: Kitchen-Garden
X: Group. 1=Stress, 2=Control
M1: sAA (measure of NE)
M2: Cortisol
Covariates: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 6
Y : BATpoKG
X : Grooup
M1 : sAAav
M2 : cortav

Covariates:
Age Gender

Sample
Size: 37

****

OUTCOME VARIABLE:
sAAav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.0908	.0082	2380.0408	.0915	3.0000	33.0000	.9642

Model

	coeff	se	t	p	LLCI	ULCI
constant	105.8376	38.1226	2.7762	.0090	28.2751	183.4001
Grooup	-.6090	16.3240	-.0373	.9705	-33.8210	32.6030
Age	-.4734	.9219	-.5135	.6110	-2.3491	1.4023
Gender	-2.2459	18.1334	-.1239	.9022	-39.1393	34.6475

****
OUTCOME VARIABLE:
cortav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.6070	.3685	.0033	4.6677	4.0000	32.0000	.0044

Model

	coeff	se	t	p	LLCI	ULCI
constant	.2169	.0502	4.3205	.0001	.1146	.3191
Grooup	-.0766	.0194	-3.9584	.0004	-.1160	-.0372
sAAav	.0003	.0002	1.2959	.2043	-.0002	.0007
Age	.0001	.0011	.0869	.9313	-.0021	.0023
Gender	.0304	.0215	1.4144	.1669	-.0134	.0742

****
OUTCOME VARIABLE:
BATpoKG

Model Summary

R	R-sq	MSE	F	df1	df2	p
.5461	.2983	.5641	2.6353	5.0000	31.0000	.0425

Model

	coeff	se	t	p	LLCI	ULCI
constant	.3111	.8202	.3792	.7071	-1.3618	1.9839
Grooup	.3633	.3067	1.1843	.2453	-.2623	.9888
sAAav	.0068	.0027	2.4869	.0185	.0012	.0124
cortav	-.6789	2.2954	-.2958	.7694	-5.3606	4.0027
Age	-.0231	.0143	-1.6206	.1152	-.0522	.0060
Gender	-.4539	.2878	-1.5770	.1250	-1.0409	.1331

********** DIRECT AND INDIRECT EFFECTS OF X ON Y **********

Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
.3633	.3067	1.1843	.2453	-.2623	.9888

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
TOTAL	.0480	.2201	-.2729	.6128
Ind1	-.0042	.1303	-.1815	.3598
Ind2	.0520	.1633	-.2457	.4146
Ind3	.0001	.0120	-.0297	.0185

Indirect effect key:
Ind1 Grooup -> sAAav -> BATpoKG
Ind2 Grooup -> cortav -> BATpoKG
Ind3 Grooup -> sAAav -> cortav -> BATpoKG

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Short-term spontaneous recovery: Pre-Post FSQ

N=37
Y: Pre-Post FSQ
X: Group. 1=Stress, 2=Control
M1: sAA (measure of NE)
M2: Cortisol
Covariates: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****

Model : 6
Y : PrePoFSQ
X : Grooup
M1 : sAAav
M2 : cortav

Covariates:
Age Gender

Sample
Size: 37

****

OUTCOME VARIABLE:
sAAav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.0908	.0082	2380.0408	.0915	3.0000	33.0000	.9642

Model

	coeff	se	t	p	LLCI	ULCI
constant	105.8376	38.1226	2.7762	.0090	28.2751	183.4001
Grooup	-.6090	16.3240	-.0373	.9705	-33.8210	32.6030
Age	-.4734	.9219	-.5135	.6110	-2.3491	1.4023
Gender	-2.2459	18.1334	-.1239	.9022	-39.1393	34.6475

****

OUTCOME VARIABLE:
cortav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.6070	.3685	.0033	4.6677	4.0000	32.0000	.0044

Model

	coeff	se	t	p	LLCI	ULCI
constant	.2169	.0502	4.3205	.0001	.1146	.3191
Grooup	-.0766	.0194	-3.9584	.0004	-.1160	-.0372
sAAav	.0003	.0002	1.2959	.2043	-.0002	.0007
Age	.0001	.0011	.0869	.9313	-.0021	.0023
Gender	.0304	.0215	1.4144	.1669	-.0134	.0742

****

OUTCOME VARIABLE:
PrePoFSQ

Model Summary

R	R-sq	MSE	F	df1	df2	p
.5633	.3173	310.9471	2.8815	5.0000	31.0000	.0300

Model

	coeff	se	t	p	LLCI	ULCI
constant	96.2342	19.2575	4.9972	.0000	56.9573	135.5110
Grooup	-17.9465	7.2016	-2.4920	.0183	-32.6346	-3.2584
sAAav	.1005	.0646	1.5574	.1295	-.0311	.2322
cortav	-77.7042	53.8938	-1.4418	.1594	-187.6238	32.2154
Age	-.6899	.3346	-2.0618	.0477	-1.3723	-.0074
Gender	-3.1056	6.7577	-.4596	.6490	-16.8883	10.6772

********** DIRECT AND INDIRECT EFFECTS OF X ON Y **********

Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
-17.9465	7.2016	-2.4920	.0183	-32.6346	-3.2584

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
TOTAL	5.9045	4.8471	-.6803	18.0335
Ind1	-.0612	2.1183	-3.1571	5.7217
Ind2	5.9530	4.1611	.2518	16.4438
Ind3	.0127	.5630	-1.3664	.9977

Indirect effect key:

Ind1 Grooup -> sAAav -> PrePoFSQ
Ind2 Grooup -> cortav -> PrePoFSQ
Ind3 Grooup -> sAAav -> cortav -> PrePoFSQ

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Long-term spontaneous recovery: Pre-3mfu FSQ

N=37
Y: Pre-3mfu FSQ

X: Group. 1=Stress, 2=Control
M1: sAA (measure of NE)
M2: Cortisol
Covariates: Age, Gender

Run MATRIX procedure:

***************** PROCESS Procedure for SPSS Version 4.1 *****************

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 6
Y : PreFUFSQ
X : Grooup
M1 : sAAav
M2 : cortav

Covariates:
Age Gender

Sample
Size: 37

****
OUTCOME VARIABLE:
sAAav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.0908	.0082	2380.0408	.0915	3.0000	33.0000	.9642

Model

	coeff	se	t	p	LLCI	ULCI
constant	105.8376	38.1226	2.7762	.0090	28.2751	183.4001
Grooup	-.6090	16.3240	-.0373	.9705	-33.8210	32.6030
Age	-.4734	.9219	-.5135	.6110	-2.3491	1.4023
Gender	-2.2459	18.1334	-.1239	.9022	-39.1393	34.6475

****
OUTCOME VARIABLE:
cortav

Model Summary

```
      R       R-sq        MSE          F        df1        df2          p
  .6070      .3685      .0033     4.6677     4.0000    32.0000      .0044

Model
            coeff         se          t          p       LLCI       ULCI
constant     .2169      .0502     4.3205      .0001      .1146      .3191
Grooup      -.0766      .0194    -3.9584      .0004     -.1160     -.0372
sAAav        .0003      .0002     1.2959      .2043     -.0002      .0007
Age          .0001      .0011     .0869       .9313     -.0021      .0023
Gender       .0304      .0215     1.4144      .1669     -.0134      .0742

**************************************************************************
OUTCOME VARIABLE:
 PreFUFSQ

Model Summary
      R       R-sq        MSE          F        df1        df2          p
  .5034      .2534   342.0909     2.1046     5.0000    31.0000      .0914

Model
            coeff         se          t          p       LLCI       ULCI
constant   89.2612    20.1989     4.4191      .0001    48.0643   130.4581
Grooup    -18.6329     7.5537    -2.4667      .0194   -34.0390    -3.2268
sAAav        .0768      .0677     1.1346      .2652     -.0613      .2149
cortav     -78.8644    56.5283    -1.3951      .1729  -194.1573    36.4285
Age         -.5004      .3510    -1.4259      .1639    -1.2162      .2154
Gender      6.3862     7.0880     .9010       .3745    -8.0703    20.8427

****************** DIRECT AND INDIRECT EFFECTS OF X ON Y *****************

Direct effect of X on Y
    Effect         se          t          p       LLCI       ULCI
  -18.6329     7.5537    -2.4667      .0194   -34.0390    -3.2268

Indirect effect(s) of X on Y:
        Effect    BootSE  BootLLCI  BootULCI
TOTAL   6.0080    4.7074   -1.5266   17.1971
Ind1    -.0468    1.6965   -2.9503    4.4632
Ind2    6.0419    4.3970   -1.0160   16.2283
Ind3     .0128     .5476   -1.2671    1.0757

Indirect effect key:
Ind1 Grooup    ->   sAAav      ->   PreFUFSQ
Ind2 Grooup    ->   cortav     ->   PreFUFSQ
Ind3 Grooup    ->   sAAav      ->   cortav     ->   PreFUFSQ
```

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
 95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
 5000

------ END MATRIX -----

Short-term spontaneous recovery: Pre-post BAT

N=37
Y: Pre-post BAT
X: Group. 1=Stress, 2=Control
M1: sAA (measure of NE)
M2: Cortisol
Covariates: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 6
Y : BATprpo
X : Grooup
M1 : sAAav
M2 : cortav

Covariates:
Age Gender

Sample
Size: 37

****
OUTCOME VARIABLE:
sAAav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.0908	.0082	2380.0408	.0915	3.0000	33.0000	.9642

Model

	coeff	se	t	p	LLCI	ULCI
constant	105.8376	38.1226	2.7762	.0090	28.2751	183.4001
Grooup	-.6090	16.3240	-.0373	.9705	-33.8210	32.6030
Age	-.4734	.9219	-.5135	.6110	-2.3491	1.4023
Gender	-2.2459	18.1334	-.1239	.9022	-39.1393	34.6475

****

OUTCOME VARIABLE:
cortav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.6070	.3685	.0033	4.6677	4.0000	32.0000	.0044

Model

	coeff	se	t	p	LLCI	ULCI
constant	.2169	.0502	4.3205	.0001	.1146	.3191
Grooup	-.0766	.0194	-3.9584	.0004	-.1160	-.0372
sAAav	.0003	.0002	1.2959	.2043	-.0002	.0007
Age	.0001	.0011	.0869	.9313	-.0021	.0023
Gender	.0304	.0215	1.4144	.1669	-.0134	.0742

****

OUTCOME VARIABLE:
BATprpo

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3770	.1422	.7659	1.0274	5.0000	31.0000	.4188

Model

	coeff	se	t	p	LLCI	ULCI
constant	1.1868	.9557	1.2418	.2236	-.7624	3.1361
Grooup	.1420	.3574	.3974	.6938	-.5869	.8710
sAAav	.0049	.0032	1.5248	.1375	-.0016	.0114
cortav	1.3416	2.6747	.5016	.6195	-4.1136	6.7967
Age	.0256	.0166	1.5411	.1334	-.0083	.0595
Gender	.0536	.3354	.1600	.8740	-.6304	.7377

********** DIRECT AND INDIRECT EFFECTS OF X ON Y **********

Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
.1420	.3574	.3974	.6938	-.5869	.8710

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
TOTAL	-.1060	.2692	-.5880	.5047
Ind1	-.0030	.1237	-.1604	.3629
Ind2	-.1028	.2154	-.5476	.3070
Ind3	-.0002	.0150	-.0376	.0244

Indirect effect key:
Ind1 Grooup -> sAAav -> BATprpo
Ind2 Grooup -> cortav -> BATprpo
Ind3 Grooup -> sAAav -> cortav -> BATprpo

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Long-term spontaneous recovery: Pre-post BAT

N=37
Y: Pre-3mfu BAT
X: Group. 1=Stress, 2=Control
M1: sAA (measure of NE)
M2: Cortisol
Covariates: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 6
Y : BATpre3m
X : Grooup
M1 : sAAav
M2 : cortav

Covariates:
Age Gender

Sample
Size: 37

****

OUTCOME VARIABLE:
sAAav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.0908	.0082	2380.0408	.0915	3.0000	33.0000	.9642

Model

	coeff	se	t	p	LLCI	ULCI
constant	105.8376	38.1226	2.7762	.0090	28.2751	183.4001
Grooup	-.6090	16.3240	-.0373	.9705	-33.8210	32.6030
Age	-.4734	.9219	-.5135	.6110	-2.3491	1.4023
Gender	-2.2459	18.1334	-.1239	.9022	-39.1393	34.6475

****

OUTCOME VARIABLE:
cortav

Model Summary

R	R-sq	MSE	F	df1	df2	p
.6070	.3685	.0033	4.6677	4.0000	32.0000	.0044

Model

	coeff	se	t	p	LLCI	ULCI
constant	.2169	.0502	4.3205	.0001	.1146	.3191
Grooup	-.0766	.0194	-3.9584	.0004	-.1160	-.0372
sAAav	.0003	.0002	1.2959	.2043	-.0002	.0007
Age	.0001	.0011	.0869	.9313	-.0021	.0023
Gender	.0304	.0215	1.4144	.1669	-.0134	.0742

****

OUTCOME VARIABLE:
BATpre3m

Model Summary

R	R-sq	MSE	F	df1	df2	p
.2279	.0519	.8695	.3397	5.0000	31.0000	.8849

Model

	coeff	se	t	p	LLCI	ULCI
constant	1.7325	1.0184	1.7012	.0989	-.3445	3.8095
Grooup	.2114	.3808	.5551	.5828	-.5653	.9881
sAAav	-.0005	.0034	-.1520	.8802	-.0075	.0064
cortav	.4156	2.8500	.1458	.8850	-5.3970	6.2283
Age	.0186	.0177	1.0535	.3003	-.0174	.0547
Gender	.0612	.3574	.1712	.8652	-.6677	.7900

********** DIRECT AND INDIRECT EFFECTS OF X ON Y **********

Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
.2114	.3808	.5551	.5828	-.5653	.9881

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
TOTAL	-.0316	.2540	-.4512	.5772
Ind1	.0003	.1185	-.0981	.3844
Ind2	-.0318	.2272	-.4815	.4250
Ind3	-.0001	.0155	-.0404	.0213

Indirect effect key:
Ind1 Grooup -> sAAav -> BATpre3m
Ind2 Grooup -> cortav -> BATpre3m
Ind3 Grooup -> sAAav -> cortav -> BATpre3m

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Mediation Analysis 2

Tested mediators: Eyegaze and Expectancy of Harm

Short-term spontaneous recovery: Pre-Post SPQ

N=37
Y: Pre-Post SPQ
X: Group. 1=Stress, 2=Control
Mediators: Exp harm, eyegaze

Covariates: Age, Gender

Run MATRIX procedure:

***************** PROCESS Procedure for SPSS Version 4.1 *****************

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 4
Y : PrePoSPQ
X : Grooup
M1 : expdif1
M2 : eye.7all

Covariates:
Age Gender

Sample
Size: 37

****
OUTCOME VARIABLE:
expdif1

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3934	.1547	4.4933	2.0139	3.0000	33.0000	.1311

Model

	coeff	se	t	p	LLCI	ULCI
constant	2.4003	1.6564	1.4491	.1567	-.9698	5.7704
Grooup	-1.3870	.7093	-1.9556	.0590	-2.8301	.0560
Age	.0165	.0401	.4115	.6834	-.0650	.0980
Gender	1.3670	.7879	1.7350	.0921	-.2360	2.9701

****
OUTCOME VARIABLE:
eye.7all

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3172	.1006	152.9601	1.2303	3.0000	33.0000	.3143

Model

	coeff	se	t	p	LLCI	ULCI
constant	76.1613	9.6645	7.8805	.0000	56.4983	95.8242
Grooup	-4.2614	4.1383	-1.0298	.3106	-12.6810	4.1582
Age	.3892	.2337	1.6654	.1053	-.0863	.8648
Gender	.0161	4.5970	.0035	.9972	-9.3368	9.3690

****

OUTCOME VARIABLE:
PrePoSPQ

Model Summary

R	R-sq	MSE	F	df1	df2	p
.4771	.2276	5.9140	1.8270	5.0000	31.0000	.1366

Model

	coeff	se	t	p	LLCI	ULCI
constant	12.4907	3.2466	3.8473	.0006	5.8690	19.1124
Grooup	-1.7175	.8699	-1.9743	.0573	-3.4918	.0568
expdif1	.1724	.1999	.8622	.3952	-.2354	.5801
eye.7all	-.0458	.0343	-1.3357	.1914	-.1156	.0241
Age	-.0353	.0479	-.7369	.4668	-.1331	.0624
Gender	-.5401	.9443	-.5719	.5715	-2.4661	1.3859

********** DIRECT AND INDIRECT EFFECTS OF X ON Y **********

Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
-1.7175	.8699	-1.9743	.0573	-3.4918	.0568

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
TOTAL	-.0440	.4044	-.8856	.7794
expdif1	-.2391	.3123	-.9754	.3058
eye.7all	.1950	.2417	-.2353	.7422

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Long-term spontaneous recovery: Pre-3mfu SPQ

N=37
Y: Pre-3mfu SPQ
X: Group. 1=Stress, 2=Control
Mediators: Exp harm, eyegaze
Covariates: Age, Gender

Run MATRIX procedure:

***************** PROCESS Procedure for SPSS Version 4.1 *****************

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 4
Y : PreFUFSQ
X : Grooup
M1 : expdif1
M2 : eye.7all

Covariates:
Age Gender

Sample
Size: 37

****
OUTCOME VARIABLE:
expdif1

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3934	.1547	4.4933	2.0139	3.0000	33.0000	.1311

Model

	coeff	se	t	p	LLCI	ULCI
constant	2.4003	1.6564	1.4491	.1567	-.9698	5.7704
Grooup	-1.3870	.7093	-1.9556	.0590	-2.8301	.0560
Age	.0165	.0401	.4115	.6834	-.0650	.0980
Gender	1.3670	.7879	1.7350	.0921	-.2360	2.9701

****
OUTCOME VARIABLE:
eye.7all

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3172	.1006	152.9601	1.2303	3.0000	33.0000	.3143

Model

	coeff	se	t	p	LLCI	ULCI
constant	76.1613	9.6645	7.8805	.0000	56.4983	95.8242
Grooup	-4.2614	4.1383	-1.0298	.3106	-12.6810	4.1582
Age	.3892	.2337	1.6654	.1053	-.0863	.8648
Gender	.0161	4.5970	.0035	.9972	-9.3368	9.3690

****

OUTCOME VARIABLE:
PreFUFSQ

Model Summary

R	R-sq	MSE	F	df1	df2	p
.4510	.2034	365.0136	1.5831	5.0000	31.0000	.1940

Model

	coeff	se	t	p	LLCI	ULCI
constant	93.1397	25.5062	3.6516	.0010	41.1182	145.1611
Grooup	-13.8947	6.8343	-2.0331	.0507	-27.8337	.0444
expdif1	-.3398	1.5705	-.2164	.8301	-3.5429	2.8633
eye.7all	-.1874	.2692	-.6961	.4916	-.7363	.3616
Age	-.4558	.3765	-1.2106	.2352	-1.2237	.3121
Gender	4.3299	7.4187	.5836	.5637	-10.8011	19.4608

********** DIRECT AND INDIRECT EFFECTS OF X ON Y **********

Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
-13.8947	6.8343	-2.0331	.0507	-27.8337	.0444

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
TOTAL	1.2697	2.5458	-4.4807	6.1530
expdif1	.4713	2.2256	-4.7262	4.4866
eye.7all	.7984	1.3570	-1.3188	4.1814

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Renewal: Kitchen-Garden BAT score

N=37
Y: Kitchen-Garden BAT
X: Group. 1=Stress, 2=Control
Mediators: Exp harm, eyegaze
Covariates: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 4
Y : BATpoKG
X : Grooup
M1 : expdif1
M2 : eye.7all

Covariates:
Age Gender

Sample
Size: 37

****
OUTCOME VARIABLE:
expdif1

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3934	.1547	4.4933	2.0139	3.0000	33.0000	.1311

Model

	coeff	se	t	p	LLCI	ULCI
constant	2.4003	1.6564	1.4491	.1567	-.9698	5.7704

```
Grooup      -1.3870      .7093    -1.9556      .0590    -2.8301      .0560
Age          .0165      .0401      .4115      .6834     -.0650      .0980
Gender      1.3670      .7879     1.7350      .0921     -.2360     2.9701

**************************************************************************
OUTCOME VARIABLE:
 eye.7all

Model Summary
        R       R-sq        MSE          F        df1        df2          p
     .3172      .1006   152.9601     1.2303     3.0000    33.0000      .3143

Model
             coeff         se          t          p       LLCI       ULCI
constant   76.1613     9.6645     7.8805      .0000    56.4983    95.8242
Grooup      -4.2614     4.1383    -1.0298      .3106   -12.6810     4.1582
Age          .3892      .2337     1.6654      .1053     -.0863      .8648
Gender       .0161     4.5970      .0035      .9972    -9.3368     9.3690

**************************************************************************
OUTCOME VARIABLE:
 BATpoKG

Model Summary
        R       R-sq        MSE          F        df1        df2          p
     .4476      .2004      .6428     1.5537     5.0000    31.0000      .2023

Model
             coeff         se          t          p       LLCI       ULCI
constant     .1971     1.0703      .1842      .8551    -1.9859     2.3801
Grooup       .5432      .2868     1.8942      .0676     -.0417     1.1282
expdif1      .0754      .0659     1.1444      .2612     -.0590      .2098
eye.7all     .0064      .0113      .5697      .5730     -.0166      .0295
Age         -.0301      .0158    -1.9025      .0664     -.0623      .0022
Gender       -.5927      .3113    -1.9038      .0663    -1.2276      .0423

****************** DIRECT AND INDIRECT EFFECTS OF X ON Y *****************

Direct effect of X on Y
    Effect         se          t          p       LLCI       ULCI
     .5432      .2868     1.8942      .0676     -.0417     1.1282

Indirect effect(s) of X on Y:
            Effect    BootSE  BootLLCI  BootULCI
TOTAL       -.1320      .1300     -.4285      .0845
expdif1     -.1046      .1134     -.3848      .0663
```

eye.7all -.0274 .0643 -.1620 .1005

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Short-term spontaneous recovery: Pre-Post FSQ

N=37
Y: Pre-Post FSQ
X: Group. 1=Stress, 2=Control
Mediators: Exp harm, eyegaze
Covariates: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 4
Y : PrePoFSQ
X : Grooup
M1 : expdif1
M2 : eye.7all

Covariates:
Age Gender

Sample
Size: 37

****
OUTCOME VARIABLE:
expdif1

Model Summary
R R-sq MSE F df1 df2 p

```
    .3934     .1547     4.4933     2.0139     3.0000    33.0000      .1311

Model
            coeff         se          t          p       LLCI       ULCI
constant    2.4003     1.6564     1.4491      .1567     -.9698     5.7704
Grooup     -1.3870      .7093    -1.9556      .0590    -2.8301      .0560
Age          .0165      .0401      .4115      .6834     -.0650      .0980
Gender      1.3670      .7879     1.7350      .0921     -.2360     2.9701

**************************************************************************
OUTCOME VARIABLE:
 eye.7all

Model Summary
        R       R-sq        MSE          F        df1        df2          p
    .3172      .1006   152.9601     1.2303     3.0000    33.0000      .3143

Model
            coeff         se          t          p       LLCI       ULCI
constant   76.1613     9.6645     7.8805      .0000    56.4983    95.8242
Grooup     -4.2614     4.1383    -1.0298      .3106   -12.6810     4.1582
Age          .3892      .2337     1.6654      .1053     -.0863      .8648
Gender       .0161     4.5970      .0035      .9972    -9.3368     9.3690

**************************************************************************
OUTCOME VARIABLE:
 PrePoFSQ

Model Summary
        R       R-sq        MSE          F        df1        df2          p
    .5059      .2560   338.8732     2.1331     5.0000    31.0000      .0877

Model
            coeff         se          t          p       LLCI       ULCI
constant  101.6869    24.5759     4.1377      .0002    51.5628   151.8109
Grooup    -11.9016     6.5851    -1.8074      .0804   -25.3322     1.5291
expdif1     .7314     1.5132      .4833      .6322    -2.3549     3.8177
eye.7all   -.2051      .2594     -.7908      .4351     -.7341      .3239
Age        -.6673      .3628    -1.8393      .0755    -1.4072      .0727
Gender     -6.6447     7.1482     -.9296      .3598   -21.2237     7.9344

****************** DIRECT AND INDIRECT EFFECTS OF X ON Y *****************

Direct effect of X on Y
   Effect         se          t          p       LLCI       ULCI
 -11.9016     6.5851    -1.8074      .0804   -25.3322     1.5291
```

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
TOTAL	-.1405	2.5328	-6.1504	4.2397
expdif1	-1.0145	2.1171	-6.3213	2.3134
eye.7all	.8740	1.3574	-1.8729	3.7747

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Long-term spontaneous recovery: Pre-3mfu FSQ

N=37
Y: Pre-3mfu FSQ
X: Group. 1=Stress, 2=Control
Mediators: Exp harm, eyegaze
Covariates: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 4
Y : PreFUFSQ
X : Grooup
M1 : expdif1
M2 : eye.7all

Covariates:
Age Gender

Sample
Size: 37

****

OUTCOME VARIABLE:
expdif1

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3934	.1547	4.4933	2.0139	3.0000	33.0000	.1311

Model

	coeff	se	t	p	LLCI	ULCI
constant	2.4003	1.6564	1.4491	.1567	-.9698	5.7704
Grooup	-1.3870	.7093	-1.9556	.0590	-2.8301	.0560
Age	.0165	.0401	.4115	.6834	-.0650	.0980
Gender	1.3670	.7879	1.7350	.0921	-.2360	2.9701

****
OUTCOME VARIABLE:
eye.7all

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3172	.1006	152.9601	1.2303	3.0000	33.0000	.3143

Model

	coeff	se	t	p	LLCI	ULCI
constant	76.1613	9.6645	7.8805	.0000	56.4983	95.8242
Grooup	-4.2614	4.1383	-1.0298	.3106	-12.6810	4.1582
Age	.3892	.2337	1.6654	.1053	-.0863	.8648
Gender	.0161	4.5970	.0035	.9972	-9.3368	9.3690

****
OUTCOME VARIABLE:
PreFUFSQ

Model Summary

R	R-sq	MSE	F	df1	df2	p
.4510	.2034	365.0136	1.5831	5.0000	31.0000	.1940

Model

	coeff	se	t	p	LLCI	ULCI
constant	93.1397	25.5062	3.6516	.0010	41.1182	145.1611
Grooup	-13.8947	6.8343	-2.0331	.0507	-27.8337	.0444
expdif1	-.3398	1.5705	-.2164	.8301	-3.5429	2.8633
eye.7all	-.1874	.2692	-.6961	.4916	-.7363	.3616
Age	-.4558	.3765	-1.2106	.2352	-1.2237	.3121
Gender	4.3299	7.4187	.5836	.5637	-10.8011	19.4608

********** DIRECT AND INDIRECT EFFECTS OF X ON Y **********

Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
-13.8947	6.8343	-2.0331	.0507	-27.8337	.0444

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
TOTAL	1.2697	2.5458	-4.4807	6.1530
expdif1	.4713	2.2256	-4.7262	4.4866
eye.7all	.7984	1.3570	-1.3188	4.1814

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Short-term spontaneous recovery: Pre-post BAT

N=37
Y: Pre-post BAT
X: Group. 1=Stress, 2=Control
Mediators: Exp harm, eyegaze
b: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 4
Y : BATprpo
X : Grooup
M1 : expdif1
M2 : eye.7all

Covariates:
Age Gender

Sample
Size: 37

****
OUTCOME VARIABLE:
expdif1

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3934	.1547	4.4933	2.0139	3.0000	33.0000	.1311

Model

	coeff	se	t	p	LLCI	ULCI
constant	2.4003	1.6564	1.4491	.1567	-.9698	5.7704
Grooup	-1.3870	.7093	-1.9556	.0590	-2.8301	.0560
Age	.0165	.0401	.4115	.6834	-.0650	.0980
Gender	1.3670	.7879	1.7350	.0921	-.2360	2.9701

****
OUTCOME VARIABLE:
eye.7all

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3172	.1006	152.9601	1.2303	3.0000	33.0000	.3143

Model

	coeff	se	t	p	LLCI	ULCI
constant	76.1613	9.6645	7.8805	.0000	56.4983	95.8242
Grooup	-4.2614	4.1383	-1.0298	.3106	-12.6810	4.1582
Age	.3892	.2337	1.6654	.1053	-.0863	.8648
Gender	.0161	4.5970	.0035	.9972	-9.3368	9.3690

****
OUTCOME VARIABLE:
BATprpo

Model Summary

R	R-sq	MSE	F	df1	df2	p
.3354	.1125	.7923	.7860	5.0000	31.0000	.5677

Model

	coeff	se	t	p	LLCI	ULCI
constant	1.4554	1.1883	1.2247	.2299	-.9683	3.8791
Grooup	.1899	.3184	.5963	.5553	-.4596	.8393

expdif1	.0970	.0732	1.3256	.1947	-.0522	.2462
eye.7all	.0045	.0125	.3607	.7208	-.0211	.0301
Age	.0199	.0175	1.1331	.2659	-.0159	.0557
Gender	-.0500	.3456	-.1446	.8859	-.7549	.6550

********** DIRECT AND INDIRECT EFFECTS OF X ON Y **********

Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
.1899	.3184	.5963	.5553	-.4596	.8393

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
TOTAL	-.1538	.1560	-.5276	.0809
expdif1	-.1345	.1438	-.5083	.0391
eye.7all	-.0193	.0611	-.1351	.1215

********** ANALYSIS NOTES AND ERRORS **********

Level of confidence for all confidence intervals in output:
95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
5000

------ END MATRIX -----

Long-term spontaneous recovery: Pre-3mfu BAT

N=37
Y: Pre-3mfu BAT
X: Group. 1=Stress, 2=Control
Mediators: Exp harm, eyegaze
Covariates: Age, Gender

Run MATRIX procedure:

********** PROCESS Procedure for SPSS Version 4.1 **********

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2022). www.guilford.com/p/hayes3

****
Model : 4
Y : BATpre3m

```
   X  : Grooup
  M1  : expdif1
  M2  : eye.7all

Covariates:
 Age      Gender

Sample
Size:  37

**************************************************************************
OUTCOME VARIABLE:
 expdif1

Model Summary
        R       R-sq        MSE          F        df1        df2          p
     .3934      .1547     4.4933     2.0139     3.0000    33.0000      .1311

Model
            coeff         se          t          p       LLCI       ULCI
constant   2.4003     1.6564     1.4491      .1567     -.9698     5.7704
Grooup     -1.3870      .7093    -1.9556      .0590    -2.8301      .0560
Age          .0165      .0401      .4115      .6834     -.0650      .0980
Gender      1.3670      .7879     1.7350      .0921     -.2360     2.9701

**************************************************************************
OUTCOME VARIABLE:
 eye.7all

Model Summary
        R       R-sq        MSE          F        df1        df2          p
     .3172      .1006   152.9601     1.2303     3.0000    33.0000      .3143

Model
            coeff         se          t          p       LLCI       ULCI
constant  76.1613     9.6645     7.8805      .0000    56.4983    95.8242
Grooup     -4.2614     4.1383    -1.0298      .3106   -12.6810     4.1582
Age          .3892      .2337     1.6654      .1053     -.0863      .8648
Gender       .0161     4.5970      .0035      .9972    -9.3368     9.3690

**************************************************************************
OUTCOME VARIABLE:
 BATpre3m

Model Summary
        R       R-sq        MSE          F        df1        df2          p
```

```
    .2625      .0689      .8540      .4587     5.0000    31.0000      .8037

Model
             coeff         se          t          p       LLCI       ULCI
constant    1.1254     1.2337      .9122      .3687    -1.3908     3.6417
Grooup       .2643      .3306      .7996      .4300     -.4099      .9385
expdif1      .0382      .0760      .5035      .6182     -.1167      .1932
eye.7all     .0074      .0130      .5670      .5748     -.0192      .0339
Age          .0154      .0182      .8439      .4052     -.0218      .0525
Gender       .0223      .3588      .0622      .9508     -.7095      .7542

****************** DIRECT AND INDIRECT EFFECTS OF X ON Y *****************

Direct effect of X on Y
    Effect         se          t          p       LLCI       ULCI
     .2643      .3306      .7996      .4300     -.4099      .9385

Indirect effect(s) of X on Y:
            Effect     BootSE   BootLLCI   BootULCI
TOTAL       -.0845      .1356     -.4157      .1258
expdif1     -.0530      .1166     -.3529      .1117
eye.7all    -.0315      .0687     -.2015      .0857

************************ ANALYSIS NOTES AND ERRORS ************************

Level of confidence for all confidence intervals in output:
  95.0000

Number of bootstrap samples for percentile bootstrap confidence intervals:
  5000

------ END MATRIX -----
```

Corrections

1. **Address typographical errors**

Completed spell and grammar check, and proof reading. Made appropriate changes throughout thesis.

2. **Expand a bit on the behavioral procedure**

In particular, I would have liked more information about the behavioral procedures in the empirical studies, including how the different follow-up tests were actually run. (What were the participants exposed to at that time?) I appreciated the tests for both spontaneous recovery and renewal, but found the procedure for renewal testing vague (it is later revealed that the participants were exposed to the virtual therapy context and then a novel virtual context, in that order—but I didn't find this in the methods—and I was confused about whether this was addressed and corrected in the randomized-control study).

An explanation of the behavioural procedures conducted at follow-up assessments is provided on pg. 83. However, further elaborations and distinctions between renewal and spontaneous recovery procedures have been added to pg. 101 and pg. 131.

Pg 101

"*During this time, participants were exposed to the same VR spider as their pre-treatment assessment, in a clear container. However, rather than presenting the spider on the kitchen counter, it was placed on a rock in an outdoor context. Participants were asked to approach the spider and remove the lid of the container without encouragement. They were asked to say 'stop' once they could not go any further. The distance between the participant and the spider was calculated and whether they lifted the lid was coded as yes or no.*"

Pg 131

"This differed to the pilot study, which only tested participants in the unfamiliar context at post-treatment. This change and order was made to test for successful extinction retention to ensure a renewal effect was not accounted for by a failure to retain the extinction memory. "

3. **Comment on complementary work relevant to the attention measure:**

I found the eye-gaze measure of attention especially interesting and important. However, given that the results with it appear to be null, I wondered whether other research could be discussed to confirm that this particular instantiation of the eye-gaze method actually measures what it is supposed to measure.

Pg 176 Additional paragraph added to discuss limitations of the eye-gaze method and suggestion for future studies.

"Another methodological consideration for future research is the attention measure used. Whilst the proportion and average number of fixations to target stimuli within a region of interest (ROI) is a common and well-validated indicator of attentional maintenance, there are variations amongst attention studies in terms of how attentional maintenance is quantified (Yang et al., 2012). For example, studies have used durations of first fixations, average durations of fixations, and total gaze duration based on the sum of all fixation durations within an ROI. These differences in the attentional indices could explain discrepancies between studies and should be investigated further in stress studies. Moreover,

research investigating the impact of stress on attention bias to threat is primarily studied in laboratory settings using attentional paradigms (Eysenck, Derakshan, Santos & Calvo, 2007). These involve assessing participant's performance in the detection of threatening versus non-threatening stimuli (Rued, Hilmer, Strahm & Thomas, 2019), and this differs to the present study as no comparison stimulus was used. A further consideration is that the number of fixations was averaged across tasks which may have prevented the detection of stress effects at specific time points throughout exposure. Whilst this was designed to assess attentional maintenance, it did not capture initial vigilance towards threat, which may have had group differences. Therefore, future studies could: 1) define a comparison ROI to quantify attentional bias towards threatening relative to non-threatening stimuli; and 2) define different time segments to differentiate initial orienting towards phobic stimuli from attentional maintenance. Specifically, to assess the latter, researchers could calculate the proportion or length of first fixations to threat and the latency to first fixations on threat at the start of each task (Clauss, Gorday, Bardeen)."

4. **Address the minor inaccuracies in the references to learning theory.**

On p. 20, I do not believe that Rescorla (1972) (or Rescorla & Wagner, 1972) emphasized attention processes; and it seems a little inaccurate to claim here and elsewhere (e.g., p. 64) that Rescorla and Wagner say that enhanced attention can strengthen the association of the CS with the non-occurrence of the US. (They do not emphasize the latter process in their account of extinction, and their minor nod to attention is not central to the model.) The description of the Pearce-Hall model on p. 64 bottom seems to be describing "hybrid" models (e.g., Pearce & Mackintosh, 2010) rather than the P-H model itself. But the Pearce-Mackintosh model is not really a model of extinction learning (p. 110). My reactions to these things are minor, but it might be worth giving the various papers another look to get the cognitive mechanisms right.

Pg 20. Removed Rescorla (1972) citations and edited statement to correct claim in line with markers feedback. Removed statement that it strengthens the association of the CS with non-occurrence of US. "*An aspect of expectancy violation models which can affect extinction learning is attention towards the phobic object (CS) and awareness of the non-occurrence of an aversive outcome (US). This is because greater awareness of the CS-no US contingency can result in a faster rate of extinction (Craske, Treanor, Conway, Zbozinek & Vervilet, 2015). Moreover, expectancy violation models state that the salience of the CS enhances the strength of the CS-noUS contingency (Mackintosh, 1975; Pearce & Hall, 1980;) that is believed to determine the intensity of the fear response*."

Pg 64. Removed the following statement. "*Rescorla and Wagner (1972) posit that enhanced attention to the CS can strengthen the association of the CS with the non-occurrence of the US (i.e., increase extinction learning)."*

Pg 64. Corrected citation of model by removing Mackintosh (175) and Pearce and Hall (1980) and citing Pearce & Mackintosh, 2010. "*If we consider Pearce & Mackintosh's (2010) account of selective attention, it is argued that there is an initial 'automatic' selection of attention towards stimuli which have a predictive value or arousing qualities."*

Pg 110. Removed wording ' model of extinction learning' to correct statement.
"*According to the Pearce and Mackintosh (2010), this is thought to occur because narrowly*

focused attention upon a phobic object, increases its salience to maximize extinction learning and the rate of learning."

Subject: RE: Thesis Corrections and Publications
Date: Thursday, 4 May 2023 at 10:45:28 am Australian Eastern Standard Time
From: Mark Dadds
To: Elpiniki Andrew

Nice work Elpiniki. I think that is good to go.

That journal is a good choice I think.

Please note I will be in Hong Kong from Monday till 26th May but still working and on email.

Best, Mark.

From: Elpiniki Andrew <elpiniki.andrew@sydney.edu.au>
Sent: Wednesday, 3 May 2023 5:53 PM
To: Mark Dadds <mark.dadds@sydney.edu.au>
Subject: Thesis Corrections and Publications

Hi Mark,

Hope you've been well! I am finally on maternity leave and have had some time to make changes to my thesis and work on my publications. I submitted my piloit study manuscript yesterday to *Journal of Behavior Therapy and Experimental Psychiatry* as we discussed. Unfortunately, the small sample size of my pilot study was limiting which journal I selected. Once I hear back from them, I'll try get the RCT published and get your recommendations for journals.

Also, when you get a chance could you please check the corrections I have made to my thesis (word doc attached) and confirm my thesis is ready to be uploaded to the library (I've removed all signatures).

Thank you!

Elpiniki