7-2019

Evaluating Changes in Error-Monitoring Electrocortcial Responses as an Outcome of Attention Bias Modification Training

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EVALUATING CHANGES IN ERROR-MONITORING ELECTROCORTICAL RESPONSES AS AN OUTCOME OF ATTENTION BIAS MODIFICATION TRAINING

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THESIS

Submitted to

Northern Michigan University

In partial fulfillment of the requirements

For the degree of

MASTERS OF SCIENCE IN PSYCHOLOGICAL SCIENCE

Office of Graduate Education and Research

July 2019

SIGNATURE APPROVAL FORM

Evaluating changes in error-monitoring electrocortical responses as an outcome of attention bias modification training

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ABSTRACT

EVALUATING CHANGES IN ERROR-MONITORING ELECTROCORTICAL RESPONSES AS AN OUTCOME OF ATTENTION BIAS MODIFICATION TRAINING

By

Jeremy A. Andrzejewski

Anxiety disorders are among one of the most debilitating and prevalent mental disorders. Maladaptive anxiety has been associated with enhanced attention bias to threat as well as heightened error-monitoring following an erroneous response. In an effort to reduce an anxious individual's attention bias to threat, an attention training paradigm known as attention bias modification (ABM) was developed. While ABM training has demonstrated the ability to reduce attention bias and anxiety symptoms, there are inconsistencies in the magnitude of symptom reduction and there is a lack of neuroimaging support in regards to ABM outcome. Therefore, this study evaluated the outcome of ABM training using error-related negativity (ERN) an event-related potential (ERP) that is associated with an error-monitoring response after an individual commits an error. To elicit an erroneous response a modified flanker task paradigm was used. The ERN has the potential to be used as a measure of ABM outcome due to the common neural structures that both processes recruit – in particular, the anterior cingulate cortex (ACC). The results demonstrate no reduction in anxiety following ABM, but reductions in attention bias in both the ABM and control groups. There were also no significant relationships between ERN and ABM outcome, suggesting that ERN is not an effective measure of functional outcome. Limitations and future directions involving multi-session ABM and functional outcomes are discussed.

DEDICATION

This thesis is dedicated to my parents, Ben and Rebecca Andrzejewski, as well as my grandparents Norma Jean and Robert Molnar, and Theodore and Julia Pliske. Their emphasis on the primacy of a good education, as well as their support and encouragement in my pursuit of higher education has helped shape me into the person, researcher, and aspiring academic that I am today.

Additionally, this thesis is also dedicated to those who have experienced anxiety disorders at some point in their lifetime or who currently suffer from anxiety disorders or heightened levels of anxiety. It is the hope that this thesis can contribute in some way to the understanding of anxiety.

ACKNOWLEDGEMENTS

The author wishes to thank his graduate advisor and mentor, Dr. Joshua M. Carlson who provided guidance and insight throughout this project and many other aspects of my graduate schooling; his undergraduate mentor Dr. Lucy J. Troup who first sparked his interest in research and sitting on my thesis committee; Dr. Adam J. Prus for sitting on my thesis committee; Dr. Lin Fang, who was instrumental in helping make aspects of this thesis a reality and provided great feedback and assistance throughout this project; and the research assistants of the Cognitive x Affective Behavior & Integrated Neuroscience lab for their help collecting data, recruiting participants, and monitoring participant progress in this long study. Additionally, the author would like to thank the National Institute of Mental Health, as this thesis was part of a larger project (R15MH1109051) funded by this organization in an grant awarded to Dr. Carlson – without this funding this thesis would have not been possible.

This thesis follows the format prescribed by the Publication manual of the American Psychological Association, 6th edition and the Department of Psychological Science.

TABLE OF CONTENTS

LIST OF FIGURES

INTRODUCTION

Anxiety disorders are one of the most prevalent types of psychological disorder within the United States and Europe: large population-based surveys suggest that 33.7% of individuals will be diagnosed with an anxiety disorder at some point in their life (Bandelow & Michaelis, 2015). These disorders are known to lead to significant negative societal and economic impact: a 2010 global analysis of anxiety disorders ranked anxiety disorders as the sixth leading cause of disability (Baxter et al., 2014) and in 1990 the cost of anxiety disorders was estimated to be $42.3 billion in the United States (Hoffman, 2008). Currently the most utilized treatments of anxiety disorders include psychotherapy, cognitive behavioral therapy, pharmacological intervention, as well as lifestyle and dietary changes (National Institute of Mental Health – Anxiety Disorders, 2016). This current treatment profile is not without its tradeoffs in cost, efficacy, and negative side effects, which can lead to individuals avoiding treatment (Baxter et al., 2014). Therefore, there is a need for a more effective, less invasive, and more economical treatment for anxiety disorders.

A newer treatment for anxiety disorders, attention bias modification (ABM), has shown some promise, as it trains individuals to focus on non-threatening stimuli (Bar-Haim, 2010). ABM reduces treatment cost by utilizing a computer-based attention training paradigm that modifies the attention bias towards threatening stimuli; a trait shown to be linked to anxiolytic symptom generation via maladaptive threat processing (Fox, Oler, Tromp, Fudge, & Kalin, 2015). ABM has been demonstrated to be a promising treatment (Kuckertz & Amir, 2015), has been tested in placebo-controlled studies (Eldar & Bar-Haim, 2010), and has even demonstrated changes in brain structure following training in a small-sample pilot study (Aday & Carlson,

2017). Finally, this treatment has shown to be cost-effective and accessible as well, with recent ABM treatments being administered off-site via a cell phone application (Aday & Carlson, 2017; Enock, Hofmann, & McNally, 2014). However, while ABM training has promise at being effective and noninvasive, current methods of evaluating treatment effectiveness have been mostly limited to expensive magnetic resonance imaging (MRI) scans for changes in neuroplasticity as well as measuring changes within the attention bias task performance framework. Therefore, this proposal aims to reduce the cost of outcome measurement following ABM treatment by utilizing the electroencephalography (EEG) event-related potentials (ERP) technique to investigate changes in error monitoring of task performance by looking at amplitudes of Error-related Negativity (ERN). Increased ERN amplitude is also associated with attention-related maladaptation present in anxiety disorders (Weinberg, Dieterich, & Riesel, 2015), and can serve as a separate measure of ABM efficacy outside of attention bias to threatening stimuli performance and MRI brain connectivity changes.

While some initial studies have demonstrated reductions in ERN amplitude following ABM (Nelson, Jackson, Amir, & Hajcak, 2015; Nelson, Jackson, Amir, & Hajcak, 2017) one of the limitations of these studies is that they only feature single-session ABM, which has been shown to be less externally and ecologically valid in long-term anxiety reduction (MacLeod & Clarke, 2015). Therefore, the purpose of this study is to replicate and extend the previous work on ERN amplitude changes following ABM by measuring ERN amplitudes before and after a six week multi-session ABM training protocol.

Overall Research Question:

- Will ABM training lead to a reduction of error-related neural activity as measured by ERP in individuals with high levels of self-reported anxiety?

Hypotheses:

- The hypotheses are that (1) individuals with high levels of self-reported trait anxiety will demonstrate enhanced ERN amplitudes, (2) there will be sex differences in the relationship between ERN amplitude and self-reported trait anxiety with a stronger relationship being demonstrated in females opposed to males, (3) six weeks of ABM training will reduce self-reported anxiety as well as attentional bias measures and (4) ABM (relative to control) training will reduce hyperactive error-monitoring as measured by the ERN.

Literature Review

Anxiety Disorders. Anxiety disorder symptomatology has been associated with hyperactive threat processing and subsequent fear response (Etkin & Wager, 2007; Fox et al., 2015; Lang, Mcteague, & Bradley, 2016; Shin & Liberzon, 2010), maladaptive emotion regulation and processing (Etkin & Wagar, 2007; Martin, Ressler, Binder, & Nemeroff, 2009; Shin & Liberzon, 2010), fear generalization (Cha et al., 2014; Lissek et al., 2008; Mineka & Zinbarg, 2006), hyperactive physiological and neural activity when anticipating aversive stimuli (Grupe & Nitschke, 2013; Heitmann et al., 2014; Paulus & Stein, 2006; Spielberg et al., 2014; Staube, Mentzel, & Miltner, 2007; Williams et al., 2015), and hyperactive neural activity in response to errors and conflict that results in maladaptive cognitive control (Cavanagh, Meyer, & Hajcak, 2017; Hajcak, McDonald, & Simons, 2003; Larson, Clayson, & Clawson, 2014; Meyer, 2017; Moser, Moran, Schroder, Donnellan, & Yeung, 2013; Olvet & Hajcak, 2008; Weinberg, Dieterich, & Riesel, 2015).

Hyperactivity in regards to the processing of both threats and errors are of particular interest in regards to anxiety disorder symptomatology due to research suggesting that these perturbed emotional and cognitive mechanisms contribute to the development and maintenance of maladaptive anxiety (Cavanagh & Shackman, 2015; Cisler & Koster, 2010; Eldar, Yankelevitch, Lamy, & Bar-Haim, 2010; Larson et al., 2014; MacLeod & Mathews, 1986; Mathews & MacLeod, 2005; Olvet & Hajcak, 2008; Pergamin-Hight, Naim, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2015; Weinberg et al., 2015).

Attention to Threat. As mentioned above, hyperactive threat attention and subsequent attention bias to threat has been associated with the development and maintenance of anxiety in a subset of individuals who have anxiety disorders (Cisler & Koster, 2010; Eldar et al., 2010; Mathews & MacLeod, 2005; Pergamin-Hight et al., 2015). Attention to threat is not in itself a maladaptive processes – the ability of an organism to search, attend to, and respond accordingly to a threat within the environment is essential to survival. This ability to effectively detect and evade threatening and negative stimuli along with the associated physiological and cognitive processes is considered adaptive anxiety and involves an interplay between the neural mechanisms involving sensation, perception, emotion, cognition, and memory (Bishop, 2008; Bishop, Duncan, Brett, & Lawrence, 2004; Fox et al., 2015).

Considering the importance of threat detection in regards to survival, threatening stimuli engage both top-down and bottom-up attention mechanisms. Bottom-up attention is a attentional concept that has become associated with aspects of attention more closely connected with the sensation and subsequent perception of an stimulus' features, saliency, and how it is perceived relative to the environment that it is occurring in. Bottom-up attention activity is commonly associated with neural activity within the retina, lateral geniculate nuclei, early visual cortices,

and subsequent activity in the ventral and dorsal visual pathways in the case of visual stimuli (Bishop, 2008; Buschman & Miller, 2007; Sarter, Givens, & Bruno, 2001). Top-down attention is a concept that refers to aspects of attention that are more governed by experience, the demands of the task, or the desired goal(s) of the organism; this concept has been associated with neurological activity within the prefrontal cortex, posterior parietal cortices, amygdala, and the anterior cingulate cortex (Bishop, 2008; Bishop et al., 2004; Buschman & Miller, 2007; Sarter et al., 2001; Vuilleumier, 2005).

Investigations into emotional attention have helped conceptualize the interaction between top-down and bottom-up attention mechanisms and have resulted in the creation of selective attention models (Bishop, 2008; Vuilleumier, 2005) and sustained attention models (Sarter et al., 2001). An important aspect regarding both of these attentional models is that top-down and bottom-up attention do not occur in temporal or spatial isolation; instead there is an constant interplay between these two concepts in order for the organism to employ attention in a manner effective for survival (Bishop, 2008 ; Sarter et al., 2001; Vuilleumier, 2005).

The ability for an organism to selectively attend to stimuli related to threat involves the bottom-up attentional mechanisms that are more sensitive to the salience of the stimulus – stimuli that have an emotional component capture attention more readily than neutral stimuli (Bishop, 2008; Vuilleumier, 2005). In humans, these emotionally-laden stimuli can consist of faces, words, scenes, or conditioned stimuli to evoke a fear response, such as a shock or loud tone (Vuilleumier, 2005). However, the detection of a salient threat stimulus is not enough for an organism to respond appropriately; top-down mechanisms of attention (such as cognitive control) are needed to provide appropriate environmental, temporal and historical context for the

organism in order to select the most appropriate defensive behavior (Fox et a., 2015; Oler et al., 2012).

Neuroanatomical research in rodents, non-human primates, and humans has helped elucidate the cortical and subcortical regions implicated in top-down and bottom-up attention mechanisms in the context of threat detection and subsequent regulation (Bishop, 2008; Bishop et al., 2004; Fox et al., 2015; Mujica-Parodi, Cha, & Gao, 2017; Oler et al., 2012; Pederson et al., 2017; Pederson, Muftuler, & Larson, 2017. Threat attention studies have demonstrated activations within the amygdala and bed nucleus of the stria terminalis (BNST; Fox et al., 2015; Ray & Zald, 2012), the anterior cingulate cortex (ACC), the medial and superior prefrontal cortex (Etkin, Egner, & Kalisch, 2011; Ray & Zald, 2012), the sensory cortex, lateral occipital gyrus, and superior colliculus (Vuilleumier, Armony, Driver, & Dolan, 2002). Importantly, not only are these areas functionally active when attending to a threat, but there are anatomical connections between the sensory cortices, the medial and orbitofrontal cortex, the amygdala, and the thalamus (Ray & Zald, 2012); connection also exist between the BNST and the amygdala (Fox et al., 2011) as well as ACC and the amygdala (Carlson, Cha, & Mujica-Parodi, 2013; Etkin et al., 2011). Considering the roles of the amygdala, the BNST, the prefrontal cortex, and the ACC in the processing of threat, these regions have become to be referred to as the extended amygdala network (Aday & Carlson, 2017; Fox et al., 2015).

Attention bias to threat and anxiety. As mentioned above, attention to threat and the bias that organisms provide towards threatening stimuli is not itself maladaptive; it is the hyperactivity in threat attention that is associated with anxiety disorder symptomatology (MacLeod, Mathews, & Tata, 1986). In particular, research has demonstrated a bias towards threat in both emotionally-laden word stimuli (MacLeod et al., 1986; Aday & Carlson, 2018) as

well as with faces depicting fearful and angry emotional expressions (Bradley, Mogg, White, Groom, & de Bono, 1999; Carlson et al., 2012; Carlson et al., 2013; Gibb, McGeary, Beevers, 2016; Helfinstein, White, Bar-Haim, & Fox, 2008; Wang et al., 2017).

When using both word and facial stimuli, a common behavioral paradigm used to measure an individual's attention bias to threat is the dot-probe task (MacLeod et al., 1986). The dot-probe paradigm begins with a fixation point that is followed by the simultaneous presentation of two emotional stimuli – in the context of attention bias to threat literature one stimulus is typically neutral, and one is negative (MacLeod et al., 1986). Following the presentation of the stimuli, a dot probe is subsequently presented behind one of the stimuli – the probe's position is considered either congruent (the probe is presented behind the fearful stimulus) or incongruent (the probe is presented behind the neutral stimulus); attention bias is calculated by taking the average reaction time for the incongruent trials and subtracting it from the average congruent trial reaction time (MacLeod et al., 1986). This difference in task performance between incongruent and congruent trial types is considered the standard measure of attention bias and is thought to be caused by alterations in the attention mechanisms known as orienting and disengagement (Koster, Crombez, Verschuere, & De Houwer, 2004; Price et al., 2014; Torrence, Wylie, & Carlson, 2017). However, while both changes in orientation and disengagement are considered to contribute to the development and maintenance of attention bias to threat, the difficulties in disengaging from a threatening stimulus due to hyperactive attention to threat is more associated with subclinical and clinical anxiety (Koster et al., 2004; Price et al., 2014).

The dot-probe task has faced some criticisms in both the reliability of the task itself as a measure of attention bias to threat and in the paradigm's ability to correlate with anxiety

measures (Kappenman, Farrens, Luck, & Proudfit, 2014; Price et al., 2015; Schmuckle, 2005; Staugaard 2009; Waechter, Nelson, Wright, Hyatt, & Oakman, 2014). The paradigm has been criticized for having low internal reliability as well as having inconsistent test-retest measures when looking at reaction time measures of attention bias (Kappenman et al., 2014; Schmuckle, 2005; Price et al., 2015), and has been criticized for having little association with self-reported trait measures of anxiety (Kappenman et al., 2014; Waechter et al., 2014). These methodological concerns have led to some researchers cautioning against using the dot-probe task as an individual measure of attention bias to threat (Chapman, Devue, Grimshaw, 2019; Kappenman et al., 2014; Price et al., 2015 Schmuckle, 2005 Staugaard, 2009; Waechter et al., 2014). However, there is a body of research that is in support of the paradigm, particularly when measures of attention bias as measured by reaction time are combined with physiological measures, such as event-related potentials or eye-tracking (Bantin, Stevens, Gerlach, & Hermann, 2016; Gibb et al., 2016; Kappenman et al., 2014; Waechter et al., 2014). While the dot-probe task may not be reliable for measuring individual differences, it has been suggested that attention bias measurements via this task are more reliable in a group design, and can therefore be used with more confidence in between-group experimental designs (Staugaard, 2009). Additionally, it has also been suggested that multiple sessions of the dot-probe paradigm improve reliability, validity, and the correlation with state and trait anxiety measures (Aday & Carlson, 2018).

Attention Bias Modification. As mentioned above, the dot-probe task is a commonly utilized paradigm to measure attention bias to threat (MacLeod et al., 1986). Given the continued support within the literature of attention bias to threat and its relationship to anxiety (see *Attention bias to threat and anxiety* section above), questions began to be raised by the creators of the dot-probe paradigm if this paradigm could be utilized to not only measure attention bias to

threat, but to also alter attention bias (MacLeod, 1995). These questions first had experimental support in a conference presentation, in which MacLeod (1995) suggested that not only could the dot-probe paradigm be used to alter attention bias, but these alterations would result in subsequent alterations of state anxiety. In this experiment, MacLeod (1995) had two groups of participants: one group had their attention trained towards an emotionally negative word, while the other group had their attention trained away from the emotionally negative word. These preliminary results demonstrated that non-anxious participants who had their attention trained away from the negative word stimulus had less of an increase in state anxiety when the training was followed with a stress induction task (MacLeod, 1995).

Harris and Menzies (1998) used a similar methodology to MacLeod (1995) in which non-anxious participants were divided into an increase condition (attention trained to spider-related words) and a decrease condition (attention trained away from spider-related words). In order to check reduction of anxiety pre- and post-training a spider-phobia questionnaire was used, and to see if these training effects would generalize to other aspects of attention bias an emotional Stroop task was also included. The results from Harris and Menzies (1998) demonstrated alterations in attention bias in both the increase and decrease conditions (with participants responding quicker to the words that they were trained towards); however, these changes in attention bias did not result in any changes in self-reported anxiety, and the change in attention did not generalize to the emotional Stroop task.

While the first published empirical study to investigate the relationship between attentional training and self-reported anxiety was inconclusive (Harris & Menzies, 1998) compared to MacLeod's first proposal (MacLeod, 1995), subsequent studies not long after the work of Harris and Menzies (1998) would provide support for what became known as attention

training and subsequent alterations in self-reported anxiety (Eldar, Ricon, & Bar-Haim, 2008; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). Both of these studies featured two groups that either trained their attention away or towards emotionally negative stimuli, and both studies also featured pre- and post- training measures of performance that could be used to validate the efficacy of the attentional training (Eldar et al., 2008; MacLeod et al., 2002). Where the studies differ is one study involved non-anxious children and facial stimuli (Eldar et al., 2008), whilst the other involved non-anxious adults and word stimuli (MacLeod et al., 2002). Even though these studies look at different samples with different stimuli, both studies had similar outcomes with Eldar and colleagues (2008) demonstrated training effects in the towards-threat condition that resulted in enhanced attention bias and subsequent increases in self-reported anxiety; MacLeod and colleagues (2002) also saw an enhanced attention bias in the towards-threat condition in both of their experiments within this study, and this enhanced bias resulted in detrimental performance in a subsequent stress-induction task compared to the away-threat training condition.

Given these initial proof-of-concept results regarding attentional training (Eldar et al., 2008; MacLeod et al., 2002), ethical concerns began to get raised about the utility of increasing attention bias and the impacts it had on anxiety and emotional vulnerability (MacLeod et al., 2002). Instead of training an individual's attention towards a threat, MacLeod and colleagues (2002) suggested that these dot-probe variants should instead be utilized to train an individual's attention away from threat instead of towards it in an effort to reduce attention bias.

The potential of using modified dot-probe paradigms in an effort to train an individual's attention away from threat instead of towards it as a potential therapeutic mechanism for subclinical anxiety/anxiety disorders led to increase in such studies in the early 21st century in a

procedure that became known as Attention Bias Modification (ABM); these experiments were evaluated in a meta-analysis (Hakamata et al., 2010) and a qualitative review (Bar-Haim, 2010) in 2010 to investigate this clinical potential. Even though only the number of studies included in both of these papers was small (15 for Bar-Haim (2010) and 10 for Hakamata et al., (2010)), the authors argue that ABM had thus far been delivering on its clinical promise (Bar-Haim, 2010; Hakamata et al., 2010). While the changes to attention bias and self-reported anxiety did occur in clinical, subclinical, and healthy individuals in these reviews, both papers noted variability in the magnitude of the results (Bar-Haim, 2010; Hakamata et al., 2010).

Bar-Haim (2010) suggested that these differences in results were due to non-specific threat stimuli, the varieties of attention training contingencies, and varieties in the amount of training trials and sessions. In order to address these discrepancies, Bar-Haim (2010) outlines a need for more systematic manipulation of these characteristics in order to delineate the most effective ABM training protocol. While Hakamata and colleagues (2010) also agree that variability of ABM training protocols contribute to variations in effect size between studies, they also provided some additional elaborations and explanations. A larger effect size was found for ABM with word stimuli compared emotional facial stimuli, a larger effect size was found for studies that included anxious (clinical and sub-clinical) participant's compared to controls, and finally the largest effect size was found when patients were performing ABM in conjunction with cognitive behavioral therapy (CBT) and/or selective serotonin reuptake inhibitor (SSRI) use (Hakamata et al., 2010). In an effort to address these discrepancies, the Hakamata and colleagues (2010) suggest that research should be conducted to further tease out the efficacy of conjunctive ABM and CBT/SSRI treatment packages in randomized clinical trials (RCTs) for both subclinical and clinical populations separate from any conjunctive treatments. Additionally, it

was suggested that ABM should be combined with neuroimaging techniques to connect outcomes to biological mechanisms (Hakamata et al., 2010). Importantly, both reviews suggest a need to take into account a participant's level of attention bias to threat prior to ABM, as well as comparing and contrasting efficiency between administering ABM either in clinical, laboratory, or remote environments (Bar-Haim, 2010; Hakamata et al., 2010).

Subsequent studies into ABM have made attempts to address some of the concerns mentioned above and have led to developments into ABM training protocols. In terms of ABM as a conjunctive treatment, one study with Post-Traumatic Stress Disorder (PTSD) demonstrated that ABM was more effective when administered to individuals with PTSD that were already seeking other psychological treatment (Kuckertz et al., 2014). Additionally, Kuckertz and colleagues (2014) noted that the greater an individual's attention bias was pre-treatment, the greater the subsequent reduction in attention bias and PTSD symptoms.

In regards to the concerns raised about the variability in the amount of trials and sessions and the subsequent results in ABM efficacy, researchers began to ask whether single session ABM training or ABM training spaced out over multiple sessions would be more effective (Bar-Haim, 2010; Hakamata et al., 2010). In an effort to address these concerns, MacLeod and Clarke (2015) published a review that compared and contrasted single session and multi-session ABM studies. The authors came to the conclusions that in the studies they looked at for single session ABM, only two out of 14 studies (14.29%) failed to manipulate participant's attention bias and four out of 14 (28.57%) studies failed to alter anxiety symptoms (MacLeod & Clarke, 2015). On the other hand, multi-session ABM had less-consistent results, with 10 out of 22 (45.45%) studies reporting a modification in attention bias, and 10 out of 22 (45.45%) studies reporting changes in anxiety symptoms (MacLeod & Clarke, 2015).

Even given these discrepancies in results between session numbers, MacLeod and Clarke (2015) still argue that multi-session ABM is more externally valid and more clinically appropriate for the following reasons: 1) that single session ABM has commonly used a laboratory stress-induction task to measure subsequent change in anxiety has high internal validity, and is not representative of the emotional stressors that anxious individuals face in the natural environments, 2) that when multi-session ABM study does demonstrate a change in attention bias, there has also always been a reported change in anxiety symptoms, and 3) lack of results in other multi-session ABM studies are mostly likely due to failures in the protocol to effectively train attention, too many sessions reduced participant engagement, or there was a failure to account for pre-training attention bias in treatment outcome.

This emphasis on multi-session ABM has been supported by other studies within the ABM literature, as well as an additional meta-analysis (Beard, Sawyer, & Hofmann, 2012). The aforementioned PTSD ABM study mentioned a limitation that ABM on its own was likely not effective due to them having fewer than 14 sessions (Kuckertz et al., 2014). More importantly, in the same year as the MacLeod and Clarke (2015) review, two other studies were critical of single-session ABM, either for not being able to account for individual variability in attention bias in a single session (Heeren, Philippot, & Koster, 2015) or by failing to replicate alterations in ABM demonstrated in previous single-session ABM in three separate experiments (Everaert, Mogoaşe, David, & Koster, 2015).

While multi-session ABM is suggested to be more clinically valid and has demonstrated that it can manipulate attention bias and reduce anxiety symptoms (MacLeod & Clarke, 2015), logistical and financial concerns have been raised about feasibility of multi-session ABM (Bar-Haim, 2010). These logistical and financial concerns led to researchers wondering if ABM could

be administered in the field, considering the simplicity of the ABM paradigm (MacLeod, Soong, Rutherford, & Campbell, 2007). These remote administrations of ABM have taken a couple of forms: either the experiment is performed online via a participant's home computer (Boettcher, Berger, Renneberg, 2012; Carlbring et al., 2012; Kuckertz et al., 2014; Neubauer et al., 2013; See, MacLeod, & Bridle, 2009) or ABM is administered on the participant's cell phone via an application (Aday & Carlson, 2017; Enock et al., 2014). While caution has been raised over using ABM in a field environment due to lack of experimental control and enforcement of participant engagement (Mogoaşe, David, & Koster, 2014; Kuckertz & Amir, 2015; MacLeod & Clarke, 2015) and some remote ABM studies have not demonstrated training effects (Boettcher et al., 2012; Carlbring et al., 2012; Enock et al., 2014; Neubauer et al., 2013), some field ABM studies have shown training effects and reductions in anxiety symptoms (Kuckertz et al., 2014; See et al., 2009). Consistent with previous insights into ABM efficacy discrepancies previously mentioned, researchers believe that these discrepancies between results have more to do with failures in manipulating attention, maintaining participant interest though many sessions, and the lack of tasks outside of remote ABM used to assess attention bias and anxiety symptom changes (Mogoaşe, David, & Koster, 2014; Kuckertz & Amir, 2015; MacLeod & Clarke, 2015). More importantly, a renewed desire for the utilization functional and structural neuroimaging techniques in an attempt to more fully understand the possible mechanisms of ABM training and efficacy was mentioned (Aday & Carlson, 2017; Kuckertz & Amir, 2015; Hakamata et al., 2010).

Neural Correlates of Attention Bias Modification. Investigations regarding ABM provides structural neural changes following treatment are for the most part unknown; currently only pilot data exists demonstrating the potential of ABM efficacy being measured via changes

in gray matter volume in the extended amygdala network, with decreases in gray matter volume occurring in the extended amygdala/basal forebrain, and the medial prefrontal cortex and gray matter volume increases occurring in the ventrolateral and dorsolateral prefrontal cortex (Aday & Carlson, 2017). However, functional neuroimaging studies have investigated ABM utility by utilizing both event-related potential (ERP) and functional magnetic resonance imaging (fMRI) techniques (Britton et al., 2014; Browning, Holmes, Murphy, Goodwin, & Harmer, 2010; Eldar & Bar-Haim, 2010; Nelson et al., 2015; Nelson et al., 2017; O'Toole & Dennis, 2012; Suway et al., 2013; Taylor et al., 2014).

fMRI research into ABM has suggested that ABM training modifies neural activity in the amygdala (Britton et al., 2014; Taylor et al., 2014), anterior cingulate cortex (ACC), insula (Taylor et al., 2014), lateral prefrontal cortex (lPFC; Browning et al., 2010), ventromedial prefrontal cortex (vmPFC), and orbitofrontal cortex (OFC; Taylor et al., 2014). However, the results between fMRI studies feature some inconsistencies: one study demonstrating increased amygdala activation following training (Britton et al., 2014), while another displayed decreased amygdala activation following training (Taylor et al., 2014), and one study did not find any change in amygdala activation at all (Browning et al., 2010). Outside of the amygdala, activations of lPFC was demonstrated when attention was directed away from treat, and lPFC deactivations were demonstrated when attention was directed towards threat (Browning et al., 2015). When contrasting pre- and post-training fMRI activations, Taylor and colleagues (2014) demonstrated increased activity in the bilateral amygdala, bilateral insula, and subgenual ACC before training, following training there were significant differences in activation within the vmPFC as well as the OFC; these significant changes suggest that attentional training engages pre-frontal regions associated with cognitive control and emotional regulation.

Outside of fMRI, other functional neuroimaging studies via the ERP technique have been done to look at changes in neurological function in regards to ABM training. These studies have investigated electrocortical changes in both stimulus-locked (i.e. P1, N170, P2, N1, N2, visual mismatch negativity (vMMN), and P3; Arad, Abend, Pine, & Bar-Haim, 2018; Eldar & Bar-Haim, 2010; Osinsky, Wilisz, Kim, Karl , & Hewig, 2014; O'Toole & Dennis, 2012) and response-locked (i.e. ERN) ERP components (Nelson et al., 2015; Nelson et al., 2017). In regards to stimulus-locked ERPs, electrocortical alterations associated with attentional mechanisms have been demonstrated following ABM training via altered ERP component amplitudes in the P1 (O'Toole & Dennis, 2012), P2 (Eldar & Bar-Haim, 2010; O'Toole & Dennis, 2012), N2 (Eldar & Bar-Haim, 2010), P3 (Eldar & Bar-Haim, 2010), and vMMN (Arad et al., 2018); no training-related differences in N1 (Eldar & Bar-Haim, 2010) or N170 (O'Toole & Dennis, 2012) were found. However, these outcomes have not been necessarily consistent: other studies have demonstrated no ABM training effects in P1 (Eldar & Bar-Haim, 2010), N2 (Osinsky, et al., 2014; O'Toole & Dennis, 2012), or P3 amplitudes (O'Toole & Dennis, 2012). In the two studies that reported training effects in the P2 component, there were differences in the amplitude change with one study finding a reduction in P2 amplitude in the ABM group with an increase in P2 amplitude in the control group (Eldar & Bar-Haim, 2010), while the other found increases in P2 amplitude following ABM (O'Toole & Dennis, 2012). Even the changes in vMMN need to be interpreted with caution in the context of ABM, as the study did not include a control (i.e. absence of training) condition (Arad et al., 2018). These inconsistencies in stimulus-locked ERP amplitude changes following ABM training might be explained by differences in the training paradigms itself, as manipulations of stimulus presentations within training did not replicate differences in N2 or P3 (O'Toole & Dennis, 2012) that were found in another study

(Eldar & Bar-Haim, 2010). Additionally, variability in training outcome as measured by ERP might be confounded by the variability of the dot-probe task itself even outside ABM training, as a recent review has suggested that task variability drives differences in stimulus-locked ERP component amplitude differences (Torrence & Troup, 2017).

More promise has been seen in using the response-locked ERN ERP as a measure of ABM outcome, even though only a couple of studies currently exist (Nelson et al., 2015; Nelson et al., 2017). In both of these studies, the relationship between ERN amplitude, attention bias, and self-reported anxious, depressing, and stress-related symptomologies and featured either ABM followed by an flanker task (Nelson et al., 2015) or a pre- and post-ABM flanker tasks in an effort to see if the ERN could serve as a measure of ABM outcome (Nelson et al., 2017). While the first study had some methodological limitations such as not having a control group for comparison and having an absence of any within-subjects pre- and post-training ERN amplitude comparisons (Nelson et al., 2015) the subsequent replication and extension addressed these limitations and still demonstrated the potential of the ERN as an index of ABM training efficacy, with individuals in the ABT treatment group seeing a post-training reduction in ERN amplitude compared to controls (Nelson et al., 2017). Investigations into changes in ERN amplitude following ABM also have the added benefit of not using the dot-probe task in pre- and post-training assessments, but still utilize mechanisms involving cognitive control and emotion that are featured within the dot-probe (Nelson et al., 2015; Nelson et al., 2017).

Error-Monitoring and Anxiety. As mentioned above (see the Anxiety disorders section) hyperactive neural and physiological activity regarding error-monitoring has been associated with anxiety disorders and anxious symptomatology (Cavanagh et al., 2017; Hajcak et al., 2003; Larson et al., 2014; Meyer, 2017; Meyer & Gawlowska, 2017; Moser et al., 2013; Olvet &

Hajcak, 2008; Weinberg et al., 2015). From an evolutionary perspective, it is important for an organism to be able to monitor its behavioral responses and adapt to any errors it commits in an effort to become more efficient in goal-directed behavior repertoires. Similar to attention bias to threat, aspects of error monitoring becomes maladaptive when hyper-arousal limits effective learning and adaptation following an erroneous response (Moser et al., 2013; Olvet & Hajcak, 2008; Weinberg et al., 2015).

Error monitoring, like attention to threat, involves recruitment of both top-down and bottom-up attentional mechanisms –some prominent models that attempt to explain this interplay are the cognitive control theory (see Larson et al., 2014 for a review), the mismatch theory, the reinforcement and learning-based theory, the conflict monitoring theory, and the motivational significance theory (see Olvet & Hajcak 2008 for a review). While there is some disagreement in the actual functions of response error monitoring across these theories, what they all have in common is that this monitoring is an essential process that an organism engages in in order to balance environmental availability with internally motivated demands, and failed attempts at this balance will result in enhanced error monitoring and subsequent correction (Larson et al., 2014; Moser et al., 2013; Olvet & Hajcak, 2008; Weinberg et al., 2015).

Research into the underlying structural and functional mechanisms of error-monitoring, suggests there is a strong association with error-monitoring processes and the caudal and rostral areas of the ACC, which has been demonstrated in multiple methodologies including voxel-based morphometry MRI, human lesion case studies, fMRI, and concurrent EEG-fMRI (Best et al., 2008; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Iannaccone et al., 2015; Kiehl, Liddle, & Hopfinger, 2000; Liu, Hanna, Carrasco, Gehring, & Fitzgerald, 2014; Mathalon, Whitfield, & Ford, 2003; Moser et al., 2013; Olvet & Hajcak, 2008; Swick & Turken, 2002; van

Veen & Carter, 2002; Weinberg et al., 2015). This association of error-monitoring and the ACC is of particular importance in the context of anxiety, given that the ACC is part of the extended amygdala network, which has been associated with both attention to threat and emotion/motivation mechanisms (Cardinal, Parkinson, Hall, Everitt, 2002; Fox et al., 2015). Additionally, electrophysiological measures of error-monitoring and attention bias to threat are within the Negative Valence Systems Domain within the Research Domain Criteria framework and are thus considered to have similar mechanisms of action and psychopathological associations (Gibb, McGeary, & Beevers, 2016; Weinberg et al., 2015).

Error-Related Negativity. While the underlying neuroanatomy associated with error-monitoring mechanisms has been well established using multiple research methodologies (see Error-monitoring and anxiety section), concerns have been raised at using solely structural or fMRI techniques, given their limited temporal resolution, especially when considering the rapid behavioral responses that result from successful error-monitoring and subsequent correction (Iannaccone et al., 2015; Mathalon et al., 2003; van Veen & Carter, 2002). In attempts to more fully understand the mechanisms of this rapid process, a shift towards utilizing electroencephalography (and in particular, event-related potential) methodologies has been undertaken due to their high temporal resolution (Iannaccone et al., 2015; Mathalon et al., 2003; van Veen & Carter, 2002). One of the most prominent and robust ERPs associated with error-monitoring is the error-related negativity, or ERN (Hajcak, Moser, Yeung, & Simons, 2005; Larson et al., 2014; Meyer, 2017; Moser et al., 2013; Olvet & Hajcak, 2008; Riesel, Weinberg, Endrass, Meyer, & Hajcak, 2013; Weinberg et al., 2015).

The ERN was first discovered independently around the same time period in two different laboratories in the United States (Gehring, Coles, Meyer, & Donchin, 1990) and

Germany (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991). As the name of the component suggests, the ERN features a sharp negative amplitude peak that occurs approximately 100ms after an erroneous task-related response and is seen maximally in frontocentral electrodes on the scalp (Gehring et al., 1990; Falkenstein et al., 1991). This location is understandable given that it is the approximate to the location of the ACC and has been confirmed with subsequent simultaneous fMRI-EEG studies (Iannaccone et al., 2015; Mathalon et al., 2003; van Veen & Carter, 2002). The ERN (see Figure 1 for an exemplar ERN waveform) is associated specifically with an erroneous response and not simply a motor response in general due to the stark difference in amplitude between correct and incorrect responses (Gehring et al., 1990; Falkenstein et al., 1991).

While the ERN was originally demonstrated in healthy individuals (Gehring et al., 1990; Falkenstein et al., 1991; Hajcak et al., 2005), interest has grown for using the ERN as a biomarker for hyperactive error monitoring, which as previously mentioned is another aspect of anxiety disorders (Cavanagh et al., 2017; Olvet & Hajcak, 2008; Weinberg et al., 2015). Additionally, enhancements in ERN amplitude when compared to controls have also been demonstrated in individuals with anxious symptomatology, including trait self-report measures of anxiety, worry, and phobias (Hajcak et al., 2003; Schroder, Glazer, Bennett, Moran, & Moser, 2017; Moser et al., 2013).

Additionally, a recent meta-analysis that investigated sex differences in ERN and anxiety suggests a moderation effect, with females having not only larger ERN amplitudes, but there also being a more significant relationship between ERN and anxiety in women (Moser, Moran, Kniep, Schroder, & Larson, 2016). This meta-analysis utilized random effects models with Cohen's *d* to investigate the relationship between ERN amplitude and obsessive compulsive

symptoms and anxiety symptoms in men and women, and demonstrated a moderate negative relationship between anxiety and ERN in women compared to men who demonstrated no significant relationship; this suggests that ERN amplitude might be a more reliable correlate of anxiety for women (Moser et al., 2016).

Considering that the ERN can be used to investigate both clinical and preclinical anxiety, it is important to consider the developmental stability of the ERN, the task paradigms that most reliability elicit the ERN, and the amount of EEG trials needed to average a robust ERN waveform. Developmentally, research has suggested that the ERN is a stable biomarker across development (see Meyer, 2017 for a review). In terms of the behavioral task paradigm, three tasks are commonly used: the emotional Stroop task, the go/no-go task, and the flanker task (Moser et al., 2013; Riesel et al., 2013; Weinberg et al., 2015). When these tasks were compared directly by Riesel and colleagues (2013), the flanker task was demonstrated to have the strongest reliability in eliciting the ERN, and is stabilized with less trials than either the emotional Stroop or go/no-go paradigms.

In ERN research, the flanker task that is commonly used is a modified version of the Eriksen flanker task (Eriksen & Eriksen, 1974) in which instead of responding to letters, the participant attempts to respond as quickly and as accurately as possible to indicate the direction that a center arrow facing during a compatible (e.g. > > > > >) or incompatible (e.g. > > < > >) trial; these similarities in stimulus presentation and the task demands for rapid responses lead to ERN generation following an incorrect response. Methodology investigations have demonstrated that in order to effectively stabilize the ERN component in order to make effective comparisons across developmental and anxiety/control groups, 6-8 trials are needed (Larson, Baldwin, Good, & Fair, 2010; Olvet & Hajcak, 2009; Pontifex et al., 2010). Given the stability, reliability, and

neural generator of the ERN, it makes it a good biomarker to investigate efficacy of treatment in both ABM (Nelson et al., 2015; Nelson et al., 2017) and other therapeutic contexts related to anxiety disorders (e.g. Schroder, Moran, & Moser, 2018).

Rationale

Anxiety disorders and anxiety disorder symptomatology have been associated with both maladaptive attention bias to threat as well as enhanced error-monitoring. While ABM has shown some promise in alleviating anxiety symptoms, there has been some inconsistencies in the magnitude and consistency of results. To address these inconsistencies, it has been suggested that not only should ABM training be extended from a single session to multiple sessions, but neuroimaging techniques should be introduced in order to more effectively measure the outcome of ABM training.

Therefore, this thesis aims to address these suggestions by including a pre- and post-ABM flanker task to elicit ERN ERPs. While the ERN is associated with error-monitoring, its neural generator is the ACC, which is a structure that is also involved in attention bias to threat. If electrocortical activity as demonstrated by the ERN can serve as a measure of ABM outcome. Not only will individuals with high levels of self-reported anxiety demonstrate enhanced ERN amplitudes, but this relationship between ERN and self-reported anxiety will be more significant in females opposed to males. It is also hypothesized that six weeks of ABM training will reduce self-reported anxiety and attention bias measures, and that effective administration of ABM will reduce hyperactive error-monitoring as measured by the ERN.

Methods

Participants

Sixty-five individuals (male = 24, female = 41) between the ages of 18-38 (*M* = 22.77, *SD* = 5.47) were recruited through an associated project from NMU and the surrounding community. This sample size is based off of previous studies that have used the ERN to measure ABM efficacy (Nelson et al., 2015; Nelson et al., 2017).

Participants for this experiment were recruited as part of a larger research project (NIMH R15MH1109051) and were therefore be subject to the same recruitment procedure. Inclusionary criteria include: possession of a smartphone device in order to access the ABM training application, participants must be between 18-42 years of age, possess normal and/or corrected-to-normal vision, and must be right-handed (via self-report). Participants must also have a trait anxiety score of at least 40 at the time of screening (as measured by the STAI – see below), and an attention bias score of at least 7 ms (as measured by congruent trial reaction time subtracted form incongruent reaction time in the dot-probe task – see below). Exclusionary criteria include: MRI contraindications, history of recent concussive and other head injury, known neurological disorder, and if the participant is taking psychoactive medication or currently participating in mental health counseling/therapy at the start of the procedure. Recruitment will involve both individuals from Northern Michigan University (NMU) as well as the surrounding community. Advertisement for recruitment will feature on-campus and community flyer postings, mass emails to NMU mailing lists, Facebook advertising, media engagements, as well as word of mouth. All advertisements mention that participants can earn up to $65 for meeting the study requirements and completing the study.

After initial recruitment, the participant completed a two-step screening procedure. The first step consisted of an online survey (via Qualtrics) in which the participant was assessed on their inclusionary/exclusionary criteria via the inclusion/exclusion checklist (see appendix); the participant's trait anxiety score was also assessed online with the Speilberger state-trait anxiety inventory (STAI). If the participant's responses were sufficient for study inclusion, they were then asked to come into the CABIN laboratory for additional screening. At this additional screening, the participant first signed an informed consent form, and had the opportunity to inquire more into the expectations of the study and its time course. After providing informed consent, the participant completed the screening procedure, which consisted of a dot-probe task in order to measure attentional bias and a re-administration of the STAI in order to confirm their online score. Participants whose scores feature required levels of attentional bias and trait anxiety while fulfilling all other inclusionary criteria described above by the NIMH grant were then asked to participate in the study. If the participant decided to continue with the study, they were then asked to return to the university at a later date for their initial pre-training session, and all of their pertinent demographic information (age, biological sex, race, ethnicity, etc.) was collected. Participants were also be reminded that they can contact the NMU counseling office if needed or if any concerns arise while participating in this experiment, and that they can refuse to continue participation at any time and receive $10 compensation.

Of the 65 participants recruited for this study, 13 participants opted to drop out of the study before completion, one participant had hair that was incompatible with EEG recording, and 19 participants had an insufficient number of ERP segment counts in their pre and/or post training flanker task EEG data (described below in EEG Processing and ERP Data Analysis) resulting in 32 total participants included in these thesis analyses (male = 12, female = 20)

between the ages of 18 and 38 (*M* = 22.54, *SD* = 5.74). The Attention Bias Modification group consisted of 15 participants (male = 5, female = 10) ages 18-36 (*M* = 21.73, *SD* = 4.67), while the control group consisted of 17 participants (male = 7, female = 10) ages 18-38 (*M* = 23.29, *SD* = 6.59).

Self-report Measures

Measures of self-reported anxiety. To measure a participant's level of self-reported anxiety, the Speilberger state-trait anxiety inventory (STAI) was used (Speilberger, Gorsuch, & Lushene, 1970). The STAI is broken up into two dimensions that measure both transient (i.e. state) and persistent (i.e. trait) levels of anxiety, and has been previously shown to have good validly, reliability, and discriminative ability between these two dimensions (Metzger, 1976). There are 40 items within the STAI, 20 items for both state and trait anxiety. The participant ranks each item on a 4-point Likert scale (1 = almost never, 4 = almost always) on how much it applies to them in a general sense (trait scale) or for how much it applies to them at the moment of administration (state scale). The 20 items for each scale consist of either direct-scored (e.g. "I feel that difficulties are piling up so that I cannot overcome them", "I feel nervous") or reverse-scored (e.g. "I make decisions easily", "I feel self-confident") items that are calculated to find a participants state and trait anxiety levels, with higher values indicating higher levels of state and/or trait anxiety.

Inclusion and exclusion checklist. In order to make sure participants meet all of the inclusion/exclusion criteria for the NIMH study, they were required to fill out the inclusion and exclusion checklist online via Qualtrics. This nine item checklist consists of personal history questions (e.g. age, corrected vision, neurological disorder, head injury) as well as items that pertain to their MRI eligibility (e.g. permanent metal in body, claustrophobia); how the

participant responds was a factor in whether they were included or excluded from the study (See appendix for full checklist and criteria).

Positive and negative affective measures. To measure a participant's self-reported affect, the short-form Positive and Negative Affect Schedule (PANAS) was used (Thompson, 2007) which is an adaptation of the original PANAS (Watson, Clark, & Tellegen, 1988). The short-form PANAS consists of two five-item scales for both positive and negative affect in which the participant indicates on a five-point Likert scale (1 indicating "not at all" to 5 indicating "extremely") how much the current feeling applies to them. The short-form PANAS has demonstrated good internal consistency and high discriminative validity between the two mood scales, and has comparable validity and reliability to the original PANAS (Thompson, 2007; Watson et al., 1988).

Procedure

The entire experimental protocol occurred in three stages: (1) pre-training anxiety measures, (2) off-site ABM training for six weeks, and (3) post-training anxiety measures. The pre- and post-training anxiety measures are identical, with the only experimental group distinctions occurring within the ABM training itself. The anxiety measurement sessions consisted of a dot-probe task, a modified flanker task ERP paradigm, and an MRI scanning session at UPHS – Marquette. All of the pre- and post-training measures occurred within one week of the start and finish of ABM training, respectively.

Dot-probe task. The dot-probe task was performed on a Dell 570L computer within the CABIN laboratory. The task was presented to the participant with EPrime 2.0 (Psychology Software Tools, Sharpsburg, PA) presentation software, and their responses were recorded via

button press on a Chronos (Psychology Software Tools, Sharpsburg, PA) response box. The task consisted of facial stimuli pairs that feature both neutral and fearful facial expressions. 10 pairs of stimuli for a total of 20 stimuli were used (50% female); all faces are cropped to remove hair and presented in gray scale for stimulus consistency. Twelve stimuli were retrieved from the Karolinska Directed Emotional Faces (KDEF) database (Lundqvist, Flykt, & Öhman, 1998), and eight stimuli were retrieved from the 3D Facial Emotional Stimuli database (Gur et al., 2002).

The dot-probe paradigm has five blocks of 90 trials each, for a total of 450 trials. Within each block, there were three equally presented stimulus types: incongruent trials (in which the dot always appeared behind the neutral stimulus in a neutral-fearful stimulus pairing), congruent trials (dot appears behind fearful stimulus in a neutral-fearful stimulus pairing) and neutral-same trials (dot appears behind neutral stimulus in a neutral-neutral stimulus pairing). Each trial consisted of a 1000ms fixation cue, which is immediately followed by one of the three stimulus pairings (described above) presented horizontally to the fixation cue for 200ms. This stimulus presentation is then replaced by a dot (position determined by trial type) that will remain on the screen until a participant makes a response. The participant is required to respond which side of the screen the dot is on, and after their response there is an inter-trial interval of 1000ms. To perform the task, the participant will be seated 59cm from the monitor (ViewSonic VG1930wm) and read instructions (See appendix for protocol).

After the participant completes the dot probe task, an attention bias score was automatically calculated, and an attention bias score (measured by taking the average reaction time for congruent trials and subtracting it from the average reaction time for incongruent trials) was reported to ensure the participant was able to continue participation in the study.

Flanker task. A modified version of the flanker task was administered within the NIRS/EEG lab on a computer (HP Compaq Elite 8300 CMT) with EPrime 3.0 presentation software. The participants' responses were recorded via button press on a Chronos response box. The participant was seated 59cm from the computer monitor (HP Compaq LA2306x) so that the stimuli presented occupied 2˚ vertically and 10 ˚ horizontally of their visual field. For each trial (see Figure 2), five white, centered, and horizontally aligned arrowheads were presented for 200ms after a 1000ms fixation cue. The stimuli presented were either be classified as a compatible trial (e.g. < < < < < or > > > > >) or an incompatible trial (e.g. < < > < < or > > < > >) and each of the four trial types had an equal probability of occurring, with half of the overall trials being compatible. Arrow stimuli were utilized because these stimuli have been shown to have the strongest convergent validity for ERN elicitation (Riesel et al., 2013). After stimulus presentation, there was an inter-trial interval from 1000-1500 seconds in which the participant provided their response, which consisted of indicating which direction the center arrow was facing (either left or right). The task began with a practice block of 20 trials, and then consisted of seven subsequent blocks of 60 trials each (15 trials of each stimulus type) for a total of 420 trials. The experiment was performed according to a protocol, which consisted of collecting participant demographic information, fitting the EEG cap to the participant, running the task, and subsequent cleaning of the EEG cap (See Flanker Protocol in Appendix).

In terms of behavioral task performance, verbal emphasis was given in regards to both speed and accuracy, and was provided to the participant in order to help meet the requirements to elicit a valid error-related negativity event-related potential; the participant had to maintain an accuracy level between 75%-90% for each block (Larson et al., 2010; Olvet & Hajcak, 2009; Pontifex et al., 2010). To do this, at the end of each block within the task, a screen was displayed

detailing the participant's accuracy for that block. Based on their performance for the block, the experimenter provided one of three types of feedback: the participant was instructed to respond faster in the attempt to have them commit more errors (if their accuracy was above 90%), they were be instructed to respond slower (accuracy below 75%), or they were told that they have responded appropriately in a balance between speed and accuracy (accuracy between 75-90%; see Flanker Protocol in Appendix).

Attention bias modification training. The ABM task was administered via smart phone in a task similar to an ABM training previously hypothesized and piloted (Aday & Carlson, 2017). However, some modifications have been made from the Aday and Carlson's (2017) application: while the training was still six weeks in duration, it featured both face and word stimuli and increased in difficulty as the training progressed. The facial stimuli were the same set of facial stimuli utilized in the dot-probe task (mentioned above). The word stimuli consisted of 60 stimuli taken from the Affective Norms for English words (ANEW) dataset (Bradley & Lang, 1999). Words from the ANEW dataset were categorized by their valence and arousal into neutral and fearful stimuli, and subsequently matched into neutral and fearful word pairs (for a total of 30 pairs) based on length and frequency in a manner consistent with previous ANEW categorizations (Bradley & Lang, 1999; Stevenson, Mikels, & James, 2007).

Each participant used their own personal smart phone device for training; therefore the application was designed to perform on both Apple iPhones and Android devices. Before beginning the training, participants read a brief set of instructions and rationale regarding the training, and were asked if they had questions regarding the procedure (See at the beginning of ABM: Instructions provided to participants in the appendix). The training lasted six weeks, during which the participant will complete six sessions a week for a total of 36 sessions. While

the participant was encouraged to do no more than one session a day in order to space out their training, they had the ability to perform up to three sessions in a day. If the participant fell behind in their sessions by more than a week, this was considered non-compliance to the training procedure and the participant was excluded from further participation and was provided with $10 of compensation. Each session that the participant performed followed the following procedure, which is detailed below.

First, a 'Prepare for Trial' screen appeared that instructed the participant to 1) Set phone to 'Do Not Disturb', 2) Turn brightness to highest level, and 3) Find a quiet distraction-free environment to complete the session. After the participant advances the screen, they were then presented with ten PANAS items in which they were asked to 'Indicate to what extend you CURRENTLY feel this way' on a scale ranging from 1 ('Not at all') to 5 ('Extremely'). Following their PANAs ratings for the session, the participant saw the following prompt: "please try your best to concentrate on the task. Your performance may be compared anonymously with other participant's performance at a later time". By tapping 'next' the participant subsequently saw the following prompt: "Focus your gaze on the cross. You will briefly see two stimuli. Tap the half of the screen where the dot appears next as promptly as you can!". Once the participant tapped next they began the training session, which consisted of 240 trials per session. After the participant responds for a given trial, they received two types of feedback: one was governed by the accuracy of the participant's response (correct vs. incorrect) while the other was governed by the participant's response time, with the options being 'fast' (RT under 300ms), 'OK' (RT between 300-1000 ms), and 'Too Slow' (RT above 1000 ms).

While the training application utilizes a variant of the dot-probe task (described above) and appears to function identically for all participants the trial-types differed depending on

whether the participant was assigned to the ABM treatment group or the neutral control group. If the participant was in the ABM treatment group, every trial (for both face and word stimuli) consisted of an incongruent trial type (with the dot-probe always appearing behind the neutral stimulus) in an effort to train a participant's attention away from the fearful stimulus. If the participant was in the control group, their application training consisted of a standard dot-probe paradigm, in which there was an equal amount of incongruent and congruent trial types in each training session.

For each session the participant was able to monitor their progress for the session by viewing a trial counter at the top right of the cell phone app; the participant was also able to view their current accuracy (displayed as a percentage) on the top left of the application screen (See Figure 3 for an example of the presentation of a trial within the application). The participant's progress was also monitored by experimenters through the application website (www.cabinlab.net) to track participant compliance. Contact was made with the participant if their accuracy for a session was below 75% to determine if their phone was functioning properly or if they had any questions about the training procedure. Additional contact was made with the participant if they were falling behind in their session requirements for the week. If the participant had 1-2 days of non-usage the participant was sent the following message: "From the CABIN Lab: To complete the required 6 sessions per week, you will need to complete X sessions in the next Y days", with X being their remaining sessions that needed to be completed within the week and Y being the amount of days left in the week. After three days of non-usage the participant was sent the following message: "From the CABIN Lab: You are in danger of not meeting the study requirements and being excluded from further participation. To complete the required 6 sessions per week, you will need to complete X sessions in the next X days. Please

contact the CABIN lab at cabin.lab@gmail.com, if you will not be able to complete these sessions". If the participant feel behind in their sessions by more than a week (i.e. more than six training sessions behind) the participant was considered to be non-compliant and was excluded from further participation. The participant was notified of their exclusion from further participation and was compensated $10.

EEG recording. Continuous EEG was recorded during the flanker task using a 64 channel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR) with AgCl electrodes placed according to the international 10-20 system. The EEG was recorded via Net Station 4.5.4 software (Electrical Geodesics Inc., Eugene, OR) and was digitized at a sampling rate of 500 Hz. Impedances were kept below 75 kΩ before the start of the recording, and were checked again after the completion of the flanker task.

Analysis

Behavioral Data Analysis

Dot-probe behavioral data. The behavioral data was combined and averaged within E Prime 2.0 software. In order to increase the reliability of the dot-probe task, trials that had an incorrect response and/or trials that had a RT < 150 ms or > 750 ms were be excluded form analysis (Aday & Carlson, 2018); Pre- and post- training attention bias was calculated by taking the average reaction times (RT) for both incongruent and congruent trials and subtracting the mean congruent RT from the incongruent RT.

Flanker task behavioral data. The behavioral data from the flanker task was combined and averaged within E Prime 3.0 software; the accuracy for each block consisted of the average of all of the trials for that block, and the participant's overall accuracy for the task was

calculated. In line with previous literature on the flanker task, any participant who had an overall task accuracy below 75% was be excluded from further analysis – no participants were excluded due to this criteria.

EEG Processing and ERP Data Analysis

EEG preprocessing occurred within Net Station 4.5.4 software as follows: each continuous EEG file was bandpass filtered (30 Hz lowpass, 0.1 Hz hipass) and was segmented -500ms to 500ms around the participant's response within the flanker task; these segments were separated by participant response (correct or incorrect). Artifact detection consisted of eye movements with an amplitude difference greater than 55 μV for 20ms, eye blinks with an amplitude difference greater than 140 μV for 20ms. EEG channels were considered 'bad' if there was a 200 μV difference for an entire segment. Overall, a segment was considered 'bad' if any of the three following criteria were met: 1) if it contains more than 10 bad channels, 2) if it contains an eye blink, and 3) if it contains an eye movement. Bad channel replacement was performed with Net Station's bad channels replacement algorithms, and the segments were averaged. Finally, the data was re-referenced offline to a mastoid-average.

After each EEG file has been preprocessed, the files were combined in a manner dependent upon both the participant's experimental group (ABM vs. control) and their experimental session (pre- or post-training) for a total of four groups. Each of these combinations were then subjected to a -400ms to -200ms baseline correction. In order to determine whether each participant had enough valid incorrect-response trial segments to elicit a valid ERN, their segment counts for pre- and post-training were inspected to ensure that there were at least eight valid incorrect response segments; if either the pre- or post-training data file for a participant did not meet this segment count, they were be excluded from subsequent analysis. After participants

were excluded for either having unsatisfactory behavioral task performance (n = 0) or segment counts (n = 19), the remaining participant's segment averages were combined into grand average files. Each of these four grand average files (pre-training control, pre-training ABM, post-training control, post-training ABM) were then visually inspected in order to determine the frontocentral electrode that has the best represented ERN, which was the electrode FCz. The average amplitude of that electrode for both a correct and an incorrect response was statistically extracted from each grand average file in a 0-100ms post-response window for statistical analysis. This utilization of the FCz electrode is consistent with previous ERN methodology studies that have observed maximal ERN amplitudes at this electrode site (Larson et al., 2010; Olvet & Hajcak, 2009; Pontifex et al., 2010).

Statistical Analysis

In order to test the first hypothesis, a correlation analysis between the pre-ABM self-reported anxiety scores and ΔERN amplitudes was performed. Support for this hypothesis would demonstrate a significant negative correlation between self-reported anxiety and pre-ABM ΔERN amplitude (i.e. a more negative ΔERN amplitude is correlated with higher self-reported anxiety measures).

To test the second hypothesis, the correlation mentioned above was separated by biological sex. It was hypothesized that there will be a significant negative correlation between pre-ABM ΔERN amplitude and self-reported anxiety in females, but no there will be no significant relationship in male participants.

For the third hypothesis, a 2 (ABM vs Control) x 2 (pre-STAI vs post-STAI) mixed ANOVA was performed to test for changes in self-reported anxiety following training, and a 2

(ABM training vs. control training) x 2 (pre-attention bias vs post-attention bias) mixed ANOVA was conducted to test for changes in attention bias following training. Assumptions for normal distributions were checked by surveying Q-Q plots, and Levene's Test of Equality of Error Variances was used to check for homogeneity of variance. Significant main effects found in either ANOVA were followed up with pairwise post-hoc comparisons with Bonferroni alpha adjustments. With the exception of the Bonferroni alpha adjustments, significance was considered at $\alpha = .05$. If supported, significant main effects for both ANOVAs would be demonstrated, with subsequent pairwise comparisons indicating significant changes in pre- and post-attention training attention bias and self-reported anxiety in the ABM group only.

To address the fourth hypothesis (effective ABM will reduce hyperactive error-monitoring as measured by the ERN), a mixed measures analysis of covariance (ACNOVA) was used to compare ΔERN (correct response amplitude subtracted from incorrect response amplitude) amplitudes from both the pre- and post-treatment EEG sessions by treatment group (Control vs. ABM Treatment), with the change in attention bias used as a continuous covariate. A mixed measures ANCOVA was used due to their being two independent variables, with one variable being between subjects (treatment group) and one variable being a repeated measure within subjects (ERN pre and post treatment), with the dependent variable being the amplitude associated with the elicitation of the ERN. Change of attention bias will be used as a covariate due to previous research showing that the strength of an individual's attention bias can influence their ERN amplitude (Nelson et al., 2017).

In order to check the parametric assumptions required to run a mixed repeated measures ANCOVA the following steps were taken: Q-Q plots were surveyed to check for normal distributions, and Levene's Test of Equality of Error Variances was used to check for

homogeneity of variance. Significant main effects found in the ANOVA were subsequently followed up with post-hoc pairwise comparisons with Bonferroni alpha adjustments. With the exception of Bonferroni alpha adjustments, all other statistical tests will be considered at $\alpha = .05$.

Support for the fourth hypothesis will be demonstrated if a significant main effect between time (pre vs. post), group (treatment vs. control), and ΔERN is demonstrated. Subsequent pair-wise comparisons that demonstrate a greater reduction in ΔERN following training in the training group opposed to the control group will provide further support for this hypothesis.

Results

Hypothesis one: individuals with high levels of self-reported trait anxiety will demonstrate enhanced ERN amplitudes

There was not a statistically significant correlation between pre-training STAI-T (M = 54, SD = 6.84) and pre-training ΔERN amplitudes (M = -3.33 μV, SD = 4.58 μV), $r(30) = -.073$, $p = .691$, $R^2 = 0.005$ (Figure 4).

Hypothesis two: there will be sex differences in the relationship between ERN amplitude and self-reported trait anxiety with a stronger relationship being demonstrated in females opposed to males

There was not a statistically significant correlation in men between pre-training STAI-T (M = 53, SD = 5.59) and pre-training ΔERN amplitudes (M = -5.73 μV, SD = 5.05 μV), $r(10) = .47$, $p = .12$, $R^2 = 0.22$ (Figure 5). On the other hand, there was a statistically significant correlation in women between pre-training STAI-T (M = 54.6, SD = 7.57) and pre-training

ΔERN amplitudes (M = -1.89 μV, SD = 3.71 μV), $r(18) = -.50$, $p = .026$, $R^2 = 0.25$ (Figure 6). Fisher's z score indicates a significant difference between the correlations, $Z = 2.56$, $p = .011$.

Hypothesis three: six weeks of ABM training will reduce self-reported anxiety as well as attentional bias measures

There was not a statistically significant reduction self-reported anxiety as measured by the STAI-T; pre-training (M = 54.00, SD = 6.84) and post-training (M = 54.28, SD = 7.45) meaning that levels of STAI-T did not change following training, $F(1,30) = 0.061$, $p = .806$, $\eta_p^2 = .002$ (Figure 7). The interaction between session and experimental group was also insignificant, $F(1,30) = 0.087$, $p = .77$, $\eta_p^2 = .003$.

For attention bias, there was an overall main effect of session on attention bias with pre-training attention bias (M = 15.66, SD = 7.43) being higher than post-training attention bias (M = 8.31, SD = 9.65), $F(1,30) = 11.87$, $p = .002$, $\eta_p^2 = .28$ (Figure 8). There was not a significant interaction effect between session and experimental group on attention bias, $F(1, 30) = 1.61$, $p = .214$, $\eta_p^2 = .051$.

Hypothesis four: effective ABM (relative to control) will reduce hyperactive error-monitoring as measured by the ERN

There was a significant difference between pre-training flanker task accuracy (M = 87.71, SD = 3.31) and post-training flanker task accuracy (M = 85.21, SD = 3.94), $t(31) = 2.93$, $p = .006$. There was a significant difference in pre-training ERP amplitudes following a correct response (M = 5.25 μV, SD = 5.55 μV) compared to an incorrect response (M = 1.92 μV, SD = 1.91 μV), $t(31) = 4.11$, $p = .000268$. There was also a significant difference in post-training ERP amplitudes following a correct response (M = 5.03 μV, SD = 7.51 μV) compared to an incorrect

response (M = 0.41 μV, SD = 5.64 μV), $t(31) = 5.33$, $p = .000008$. See Figures 9 and 10 for ERP waveforms for incorrect and correct response for the control and ABM groups, respectively.

There was not a significant effect of the covariate ΔAB on ΔERN amplitudes, $F(1, 29) = 0.022$, $p = .883$, $\eta_p^2 = .001$. There was no significant main effect of ΔERN, with pre-training ΔERN amplitudes (M = -3.33 μV, SD = 4.58 μV) not statistically differing from post-training ΔERN amplitudes (M = -4.62 μV, SD = 4.9 μV), $F(1, 29) = 0.69$, $p = .412$, $\eta_p^2 = .023$. There was no significant interaction effect between ΔERN and ΔAB, $F(1, 29) = 1.21$, $p = .281$, $\eta_p^2 = .04$. There was also no significant interaction effect between ΔERN and experimental group, $F(1, 29) = 0.02$, $p = .882$, $\eta_p^2 = .001$. See figure 10 for pre- and post-training ΔERN waveforms for each group.

Considering the lack of significant influence that the covariate ΔAB had on ΔERN amplitudes, and additional 2 (pre-training vs. post-training) x 2 (ABM vs. control) group ANOVA was performed on ΔERN. There was not a significant main effect for ΔERN, with pre-training ΔERN amplitudes (M = -3.33, SD = 4.58) not statistically differing from post-training ΔERN amplitudes (M = -4.61, SD = 4.9), $F(1, 30) = 2.78$, $p = .106$, $\eta_p^2 = .085$. There was also not a significant interaction between ΔERN and experimental group, $F(1, 30) = 0.01$, $p = .92$, $\eta_p^2 < .001$.

Discussion

This study provides insight into multiple aspects of using changes in error-monitoring ERPs as a measure of ABM outcome. In regards to the relationship between ΔERN amplitudes and levels of self-reported anxiety, there were was not a significant relationship irrespective of the participant's sex; however, there was a significant relationship between these two variables in

women but not in men. There were also no significant changes in self-reported anxiety levels following the training in either experimental group, suggesting that ABM did not result in a reduction in self-reported anxiety measures. There was, however, a decrease in attention bias following training, but this reduction was irrespective of experimental group. These changes in attention bias were not reflected with a change in error monitoring, as there was not an overall (i.e. irrespective of experimental group) reduction in ΔERN amplitudes following training, and there was not a specific reduction in ΔERN amplitudes in the ABM group.

Self-reported anxiety and ERN amplitudes

There was no support for the first hypothesis, with there being no significant correlation between pre-training STAI-T scores and pre-training ΔERN amplitudes overall (i.e. irrespective of experimental group; Figure 4). The second hypothesis was supported – while there was a significant moderate negative relationship between pre-training STAI-T scores and pre-training ΔERN amplitudes being demonstrated in female participants (Figure 6), there was no significant relationship between these variables in male participants (Figure 5).

The lack of an overall correlation between self-reported trait measures of anxious symptomatology is not consistent with some previous studies that have investigated this relationship (e.g. Hajcak et al., 2003; Schroder et al., 2017). This discrepancy may be due to the specific questionnaire used to measure self-reported levels of persistent anxiety: Schroder and colleagues (2017) and Hajcak and colleagues (2003) both used the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovek, 1990). Additionally, a previous meta-analysis called into question the overall reliability of high STAI-T scores and enhanced ERN amplitudes (Moser et al., 2013) which may be due to the trait scale of the STAI having

items that have been associated with depressive as well as anxious symptomatology (Bieling, Antony, Swinson, 1998; Moser et al., 2013). Therefore, it is possible that the overall relationship between ERN amplitude and self-reported levels of anxiety might be more specific, relating more to aspects of persistent anxiety that are more associated with apprehension and worry opposed to a more generalized or aggregate concept of anxiety.

Overall relationships between anxiety levels and ERN amplitudes aside, the significant relationship between these two variables in the female participants is in line with a recent meta-analysis performed on ERN and sex differences that suggested that the ERN is a more reliable neural correlate of anxiety in women (Moser et al., 2016). This study demonstrates a negative relationship in females between ERN and anxiety, where an increase in self-reported persistent anxiety as measured by the trait scale of the STAI results in a more enhanced (i.e. more negative) ERN amplitude. Considering the significance of this relationship when compared to males or the overall sample, the anxious severity of symptoms reported via the STAI-T might be a reliable correlate in women only. It is also important to note that 30% (4 out of 13 of the anxiety datasets in the meta-analysis by Moser and colleagues (2016) utilized the STAI-T as an anxiety measure, compared to 23% (3 out of 13) of the anxiety datasets that used the PSWQ. This suggests that further research into relationships between self-reported trait anxiety measures and ERN amplitude enhancements when considering biological sex is needed to help reconcile these discrepancies. While these results seem to support previous work by Moser and colleagues (2016), it should be noted that the sex differences noted in this study should be interpreted with caution given the small sample size for both sexes.

Pre- and post-training measures of anxiety and attention bias

There were no significant changes in self-reported levels of trait anxiety following training both overall and between groups. Interestingly, there was a minute change in the average score from pre (M = 54) to post (M = 54.28) at all (Figure 7), which suggests on the surface level that ABM lead to no reduction in self-reported anxiety. However, some considerations need to be taken into account. While there is research that supports the validity and the reliability of the STAI-T and its ability to discriminate from the state/transient scale of anxiety (Metzger, 1976), the STAI and in particular the STAI-T is not without critics. Specifically, criticisms have been raised that the trait scale of the STAI contains items that are more related to depressive symptoms opposed to anxiety symptoms (Beck, Brown, Epstein, & Steer, 1988; Bieling, Antony, & Swinson, 1998). Bieling and colleagues (1998) used factor analysis to suggest that of the twenty items on the STAI-T scale, all twenty relate more to negative affect generally than to anxiety per se (e.g. “I wish I could be as happy as others seem to be”, “I feel that difficulties are piling up so that I can’t overcome them”), seven items relate more to depression opposed to anxiety (e.g. “I lack self-confidence”, “I feel like a failure”), and only four of the twenty items were more specific to persistent levels of anxiety opposed to depression.(E.g. “I worry too much over something that doesn’t really matter”, “I have disturbing thoughts”). Considering this, an additional analysis investigating changes in self-reported anxiety pre- and post-training was performed with just these four items, but did not reveal any significant results (See supplementary analyses in the appendix). Additionally, the STAI was originally developed in a normal undergraduate population (Speilberger et al., 1970) and has been considered more effective at distinguishing between anxious and non-anxious samples in undergraduate

populations more so than measuring changes due to interventions in highly anxious subclinical or clinical samples (Beck et al., 1988; Bieling et al., 1998).

Although there were no changes in self-reported anxiety following training, there was an overall effect of attention bias (Figure 8), with a reduction in attention bias being demonstrated as measured by the post-training dot-probe paradigm. Contrary to what was hypothesized, attention bias reduction occurred in both groups, instead of just the ABM group.

This overall reduction in attention bias might be the result of a few factors. First, it has been suggested reductions in attention bias can occur in both control and ABM conditions when the differences in contingencies are unclear to the participant (Kuckertz & Amir, 2015; Kuckertz, Schofield, Clerkin, & Primack, 2019; Mogg & Bradley 2016; 2018). When aspects of the training are not as clear (by explaining the differences between groups or trial types and that participants might be assigned to a control condition) it is argued that the training consists more solely of bottom-up or stimulus-driven attention (i.e. the emotionally-laden word and face stimuli) and less so about a balance between top-down goal-directed attentional processes and bottom-up processes, which are both considered important for ABM-specific changes and subsequent anxiety reduction (Mogg & Bradley, 2016; 2018; MacLeod & Grafton, 2016). This is important to consider in this study; while instructions were provided to participants about their at-home app training (See At the beginning of the ABM: Instructions provided to participants in the appendix), this was an addition that was not implemented until about a third of the participants in this sample were recruited and thus may have limited influence on goal-directed attention mechanisms in this sample. Second, reductions in attention bias in both the control and ABM groups can also occur when the training has similar cognitive loads (Britton et al., 2015;

Kuckertz et al., 2014) which leads to similar implicit learning changes in the absence of explicit learning goals (Kuckertz et al., 2014, Mogg & Bradley, 2016).

These concepts demonstrate that attention training still occurs in both tasks in the absence of more explicit goal-directed attention, and can still lead to beneficial reductions of attention bias (Britton et al., 2015; Kuckertz et al., 2014), which was also demonstrated in this study's sample. This suggests that certain neural mechanisms associated with bottom-up/stimulus-driven attention to threat (Bishop, 2008) can be modified in both ABM and control trainings in the absence of any modification regions implicated top-down attention, such as the prefrontal cortex (Bishop et al., 2004).

However, it is important for control and ABM groups to have similar cognitive loads. Otherwise, changes in attention bias and symptom reduction cannot be fully attributed to attentional training in the context of attention bias and can be can considered as a study limitation (Nelson et al., 2017); this adds support to the notion that future ABM studies should include more explicit instructions in order to facilitate more goal-directed (i.e. top-down) attention mechanisms. Finally, previous research has suggested that difficulties might arise in effectively measuring a change in attention bias when the paradigm and/or stimuli used to measure pre- and post- attention bias is similar to the training paradigm itself (Kuckertz & Amir, 2015; Mogg & Bradley, 2016; Mogoaşe et al., 2014), due to the notion that implicit learning and associations can occur when performing a task, and any subsequent measure of change could be more specific to the paradigm itself, opposed to a change in attention bias.

Overall, while a change in attention bias across groups without a reduction in self-reported anxiety might be contrary to previously meta-analysis that have shown that reductions

in attention bias for at-home are usually accompanied by reductions in anxious symptoms (MacLeod & Clarke, 2015) the above considerations make it difficult to draw conclusions.

One additional note of importance in regards to this disconnect between anxiety and attention bias is that this sample is a subclinical sample – other research into ABM suggests that measuring changes in anxiety symptoms in subclinical samples is more difficult due to their symptoms being less severe than clinical samples and as such it is more difficult to measure comparatively smaller changes in symptoms when compared to outcomes severe clinical anxiety (Kuckertz & Amir, 2015; Mogoaşe et al., 2014). While increases in STAI scores are considered to reflect increasing severity in anxiety (Speilberger et al., 1970), it is considered a continuum which could contribute to the difficulties in measuring any changes in symptoms or anxiety reduction.

Future studies into measuring changes of self-reported anxiety and attention bias following ABM should therefore utilize multiple forms of self-report that encapsulate more specific anxiety symptoms, such as the PSWQ (Meyer, Miller, Metzger, & Borkovek, 1990). Another option could be to include a more diverse scale that captures both anxiety and depression symptoms so distinctions between anxiety and depression can be made if necessary, such as the Depression Anxiety Stress Scale (DASS; Lovibond & Lovibond, 1993) or the Inventory of Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012). Outside changes to self-report questionnaires, future studies could also benefit from a passive control group, to further elucidate differences in training effects between experimental groups and investigate the possibility that both ABM and attention control training might both be effective at reducing attention bias. This inclusion of a passive control group could also provide additional insight into the reductions of attention bias in both the ABM and attention control training group

due to the possibility that reductions of attention bias might be more attributed to an regression to the mean effect, considering that participants were explicitly recruited for high attention bias, which has been previously demonstrated to be an important predictor of ABM outcome (Fox, Zougkou, Ashwin, & Cahill, 2015; Heeren, Philippot, & Koster, 2015). However, this effect could be considered unlikely due to the inclusion criteria for this study also required high levels of self-reported anxiety.

Error-related Negativity and Attention Bias

The results suggest that there was no significant reduction in ΔERN amplitudes following ABM. Not only were there no amplitude reductions in ΔERN in the ABM group, but there was no significant change in ΔERN pre- to post-training overall. Additionally, there was no significant effect of the covariate ΔAB, which suggests either that the difference measure of attention bias is not as effective of a measure of change in attention bias as previously proposed (Nelson et al., 2017), that the ΔERN is not an effective neural correlate for ABM outcome, or that the ΔERN might be a more specific measure of ABM outcome (i.e. top-down attention) not demonstrated in this study. Visual inspection of the ΔERN waveforms specifically it appears that ERN amplitudes increased following training, opposed to the decrease that was hypothesized (Figure 11), however this interpretation lacks statistical support. Additional analyses were also performed to see if there was any relationship between ERN amplitudes and correct response (CR) amplitudes and ABM outcome which has been done previously (Nelson et al., 2017), but these analyses were not significant (see supplementary analyses in appendix for ERN and correct-response amplitude analyses).

The behavioral results from the flanker task could also provide insight into these results. Even though every participant's accuracy was within the established range (75-90%), there was a significant reduction in accuracy pre- and post- training, which was contrary to the results demonstrated by Nelson and colleagues (2017) in which there was no difference. While other ERN reliability research suggests that differences in ERN amplitudes following errors are pretty stable after 8 valid trials (Olvet & Hajcak. 2009; Pontifex et al., 2010), this is a concern worth considering in terms the context of test-retest reliability, where it is suggested that at least 14 valid error trials for each testing session are needed to make more reliable conclusions between two time points (Larson et al., 2010). While this study has less to do with ERN reliability, this could be an important consideration for future studies in order to draw more effective conclusions. Unfortunately, in this study there were sizable amount of participants in the sample (n = 12) that would not have met this criteria in either the pre- or post- flanker task experimental session.

Sex differences could also be a factor in resulting ERN amplitudes, while (as previously mentioned) ERN amplitudes are more associated with anxiety in females, some studies have demonstrated higher ERN amplitudes in males compared to females even though there is less of an association with anxiety (Moser et al., 2016); these relationships were also demonstrated in this sample. Additionally, this discrepancy has particularly been noted in non-clinical or subclinical anxiety samples (Moser et al., 2016). Therefore, this should be taken into account when considering these results, considering that the distribution of sex in the control (male = 7, female = 10) and ABM (male = 5, female = 10) groups was not equal.

Interestingly, there has been inconsistent results regarding the change in attention bias and ERN amplitudes in two similar studies (Nelson et al., 2017; Nelson et al., 2017). While there

was change in ΔERN amplitudes following changes in attention bias to threat in one study (Nelson et al., 2015), this change was not demonstrated in the subsequent study (Nelson et al., 2017). Instead, Nelson and colleagues (2017) suggest that changes in ΔERN amplitude might be more driven by additional attention modifications towards positive stimuli, which was also part of their ABM training protocol. While Nelson and colleagues (2017) suggested that a difference score in change of attention bias might improve the reliability opposed to their regression-based approach, using ΔAB here did not provide any insight to the relationship between ABM outcome and ΔERN amplitudes.

These discrepancies between single-session ABM results (Nelson et al., 2017) and multi-session ABM results from this study warrant further a couple of possibilities. First, it might mean that functional neuroanatomical changes in error-monitoring as measured by the ERN might be more transient and only observed after a single session, which could have more to do with attentional training more generally than ABM specifically, which has been considered a limitation of single-session ABM (MacLeod & Clarke, 2015). In contrast, multi-session ABM might lead to more structural differences that might be more accurately measured by either investigating specific structural differences in the extended amygdala network (Aday & Carlson, 2017) or the neuroanatomical correlates associated with error-monitoring outside of the ACC, such as the prefrontal cortex or insula (Iannaccone et al., 2015). However, direct comparisons between single-session and multi-session the relationship of the ERN and ABM outcome are limited due to the limited sample size of the study.

General Limitations

The main limitation for this study is its lack of statistical power. While the desired amount of participants were recruited for this study (n = 65) attrition (n = 13) and removal of subjects due to insufficient EEG data (n =19) resulted in a significant reduction of final participants available for analysis (n = 32). While attrition in multisession ABM studies is not uncommon (e.g. Enock and colleagues (2014) attrition rate for a cell-phone based ABM training was 23% or 75 out of 326 participants), especially when administered remotely (Beard & Weisberg, 2012; Enock et al., 2014; MacLeod & Clarke, 2015), attrition within this study had an amplified effect in that there was less ERP data, which is reliant on having larger sample sizes in order to improve signal-to-noise ratios and provide more reliable data.

Attrition during ABM training aside, the amount of participants that were excluded from either their pre- or post-training sessions for not having enough valid incorrect response trials also greatly reduced the number of participants available for analysis. While participants being excluded for having improper EEG data is not uncommon and was present in previous studies on the relationship between ERN and ABM (Nelson et al., 2015; Nelson et al., 2017), conducting ERN data pre-and post-multi session training increased the likelihood of having insufficient data in either session, resulting in data exclusion for the participant overall.

Future Directions

Other than some of the more specific future directions mentioned in the above sections concerning self-reported anxiety measures, attention bias measurement procedures, and passive control groups, an additional future direction would be to take steps in an effort to reduce participant attrition during attention training. While the rates of attrition here were lower than the

other multi-session ABM study that utilized participant's cellphones (Enock et al., 2014), these attrition rates are higher than some other multi-session ABM studies (Eldar et al., 2012; Hazen, Vasey, & Schmidt, 2009; Kuckertz et al., 2014; See et al., 2009). Previous qualitative and quantitative research into ABM participant perceptions and attitudes has taken some steps in identifying possible reasons why they would not find ABM research worthwhile and result in opting out of a study or falling behind in their sessions (Beard et al., 2012; Kuckertz et al., 2019).

In particular, these researchers have noted that while participants can be optimistic and curious about this training and the possibilities of what it can do at the beginning, this optimism can quickly subside when they begin the training (Beard et al., 2012; Kuckertz et al., 2019). In particular, the repetitious presentation of stimuli in a dot-probe paradigm can be perceived as boring or repetitive and the participant can lose interest, or the lack of clarity in what the training is designed to do can further exacerbate boredom and result in lack of engagement with the training (Beard et al., 2012). These aspects of boredom or confusion as to the task design have been demonstrated to impact behavioral performance, which can in turn influence ABM efficacy (Kuckertz et al., 2019).

One possible way to mitigate these perceptions and increase participant engagement with ABM include providing more detailed descriptions of the rationale and why the presentation of the training occurs the way it does as well as explaining some aspects of the paradigm in order to facilitate goal-directed attention (Beard et al., 2012; Kuckertz & Amir, 2015; Kuckertz et al., 2019; Mogg & Bradley, 2016; Mogg & Bradley 2018). These increases in goal-directed attention could serve a dual purpose by not only reducing attrition, but could also improve reductions in attention bias specific to ABM (See pre- and post-training measures of anxiety and attention bias section above).

Another aspect of reducing ABM attrition is through a process considered ‘gamification’ where the training takes on more video-game like elements to make it more engaging (Dennis-Tiwary, Denefrio, & Gelber, 2017; Dennis-Tiwary, Egan, Babkirk, & Denefrio, 2016; Dennis & O’Toole, 2014; MacLeod & Clarke, 2015) or by making the training more adaptive by changing difficulty or presentation times dynamically based on active participant performance (Amir, Kuckertz, & Strege, 2016; Nelson et al., 2017). These additional elements could reduce perceptions that participants have previously expressed about the training seeming sterile or obscure (Beard et al., 2012). While this study did featured some gamification elements, such as ‘levels’ that the participants advanced in as they completed required sessions each week that were accompanied by a badge they could view on the results page, these elements might have not been sufficient enough to facilitate completion of six weeks of attention training.

In terms of the ERN ERP data to measure functional outcome, future studies should attempt to make improvements to the task design in an effort to improve the quality of the EEG data in order to ensure more valid error response segments occur to reduce participant exclusion from analysis. It was observed during data collection that participants would sometimes grimace or strongly blink when they provided an incorrect response, and these movements could result in that particular trial being removed from analysis due to motion artifact detection. If this occurred feedback was provided to the participant after the block reminding them to minimize their facial and eye movements, but that was after a whole block of flanker trials occurred. Another aspect of the task performance that could have limited the amount of valid error trials is that feedback on a participant’s performance was only provided at the end of each block. While every participant’s overall performance was within the range defined in the protocol, it took some participants multiple blocks to reach this desired performance. In other words, if a participant performed the

first block with 100% accuracy, a seventh of the trials within the flanker task paradigm were completed without one error trial. Future studies using the flanker paradigm should not only have shorter blocks in order to provide more feedback to the participant about facial movements and eye blinks, but should also involve more dynamic trial by trial feedback based on reaction time and accuracy to more rapidly ensure behavioral compliance in order to more reliability elicit a stable ERN.

Conclusions

While this study did not have support for most of its hypotheses, this study still offers some valuable insight and contributions to the ABM and ERN literature, even though its limitations (discussed above) limit conclusions or interpretations. To the author's knowledge, this study is the first of its kind to address some of the future directions suggested by Nelson and colleagues (2017). Namely, this study investigated the ERN as a possible measure of attention bias modification outcome in a multiple session training protocol that featured stimuli of equal valence in both the control and ABM groups. Additionally, the participants were specifically recruited with preexisting attention biases and high levels of trait anxiety opposed to a more general undergraduate sample, and the control and ABM training paradigms were matched in cognitive load and task difficulty. Even though these suggestions were implemented, the results from the study provide insight to the logistical difficulty of investigating functional changes in cognitive control following multi-session ABM training using electroencephalography and in particular response-locked event-related potentials. Given these logistical difficulties, another possible ERP called the N2 could be used to investigate functional changes in cognitive control following multi-session ABM; the N2 is a stimulus-locked opposed to a response-locked ERP that is thought to share a similar neuroanatomical source as the ERN (Iannaccone et al., 2015).

While the N2 is considered to be more related to stimulus conflict opposed to error-monitoring (Iannaccone et al., 2105; Larson et al., 2014), a comparison between these two cognitive control ERPs in this context could be beneficial in future studies, especially since enhanced N2 amplitudes have been associated with anxiety symptomatology (Cavanagh et al., 2017).

Even in this limited sample, there is support that the ERN has a stronger association with levels of self-reported anxiety in females opposed to males, and this is an important consideration that should be taken into account for future ERN studies, even those that do not also include ABM. Aside from sex differences in the relationship between ERN and self-reported anxiety, there were no observed differences in anxiety following ABM training, and attention bias decreased in both the ABM group and the control attention training after their at-home training was completed. This change in attention bias was not reflected in the neural correlates of error-monitoring, with no reductions in ΔERN amplitudes occurring in either the ABM or control group.

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Appendix

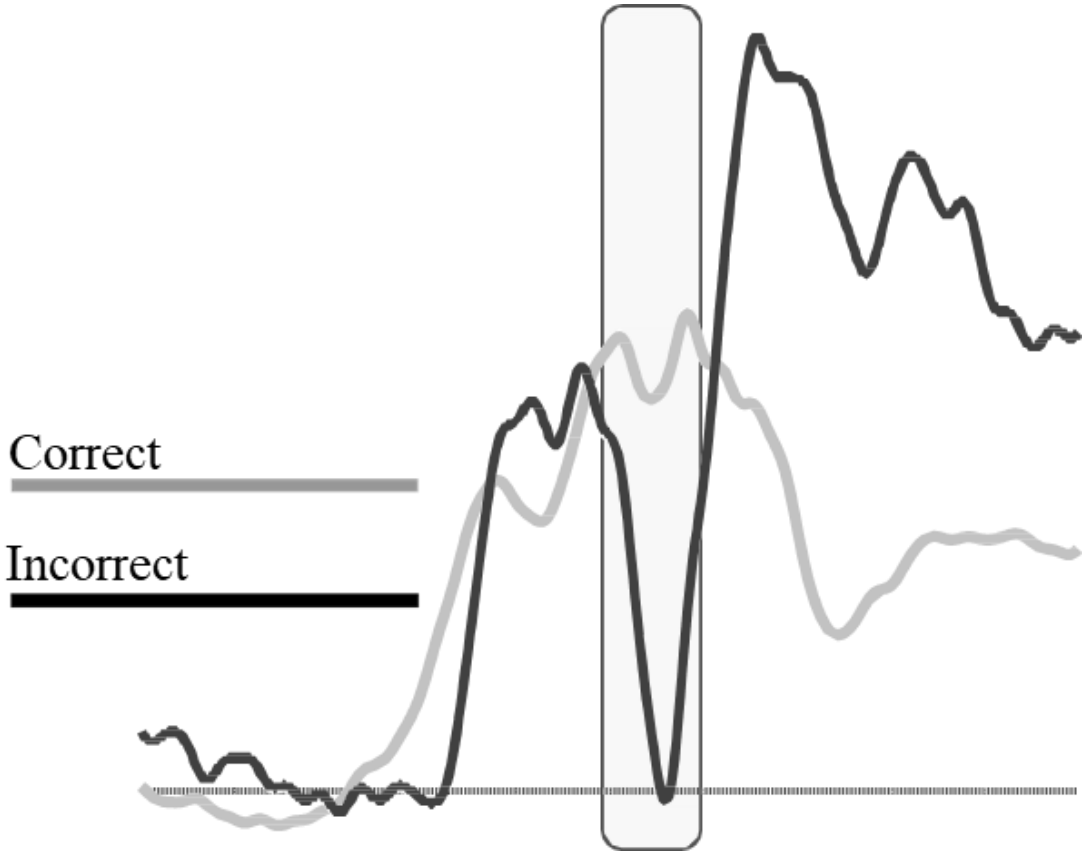

Figure 1. An example of an error-related negativity waveform for both an incorrect and a correct response

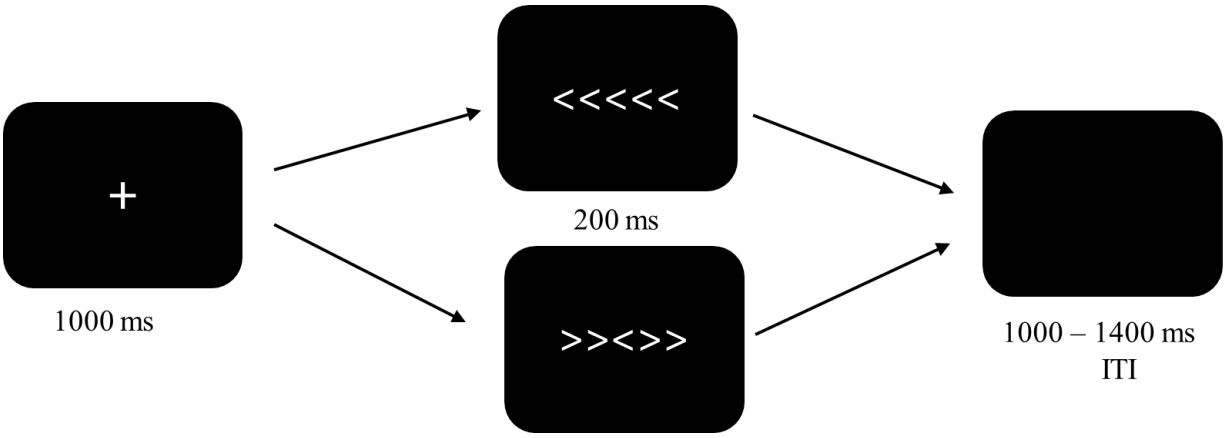

Figure 2. The modified flanker task paradigm

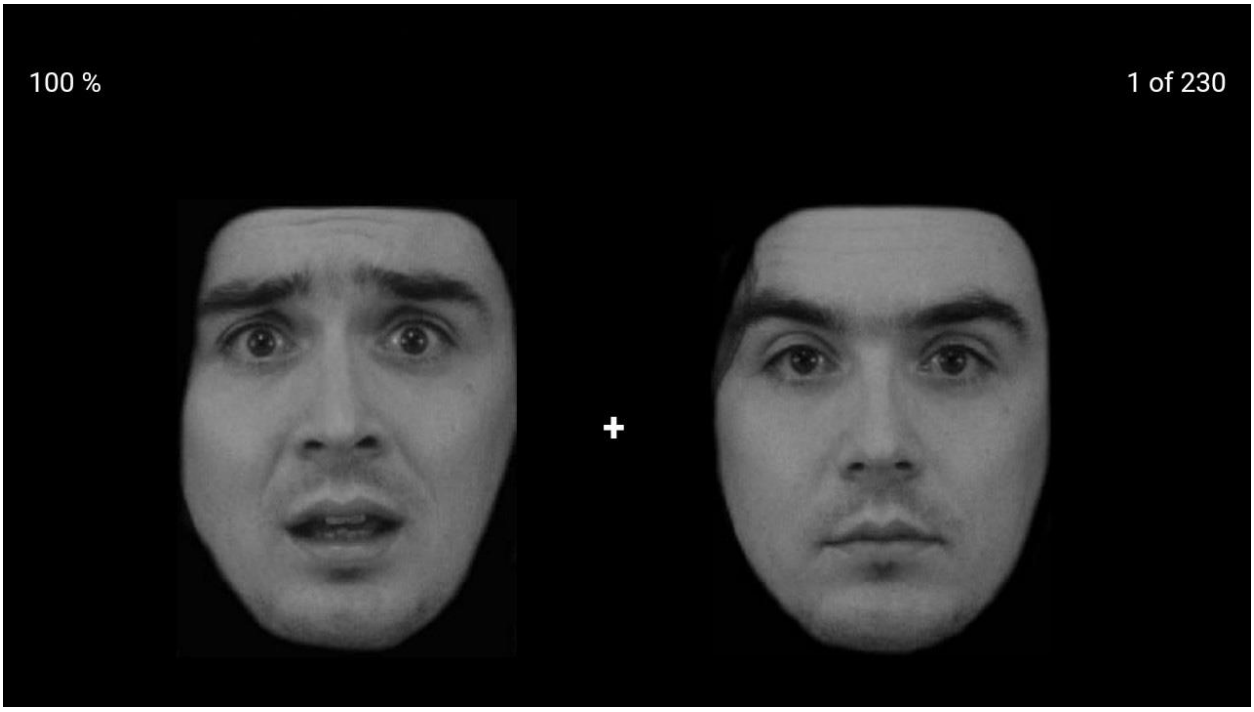

Figure 3. An example of the ABM training application. The participant's current accuracy is displayed top-left, and their session progress is displayed top-right

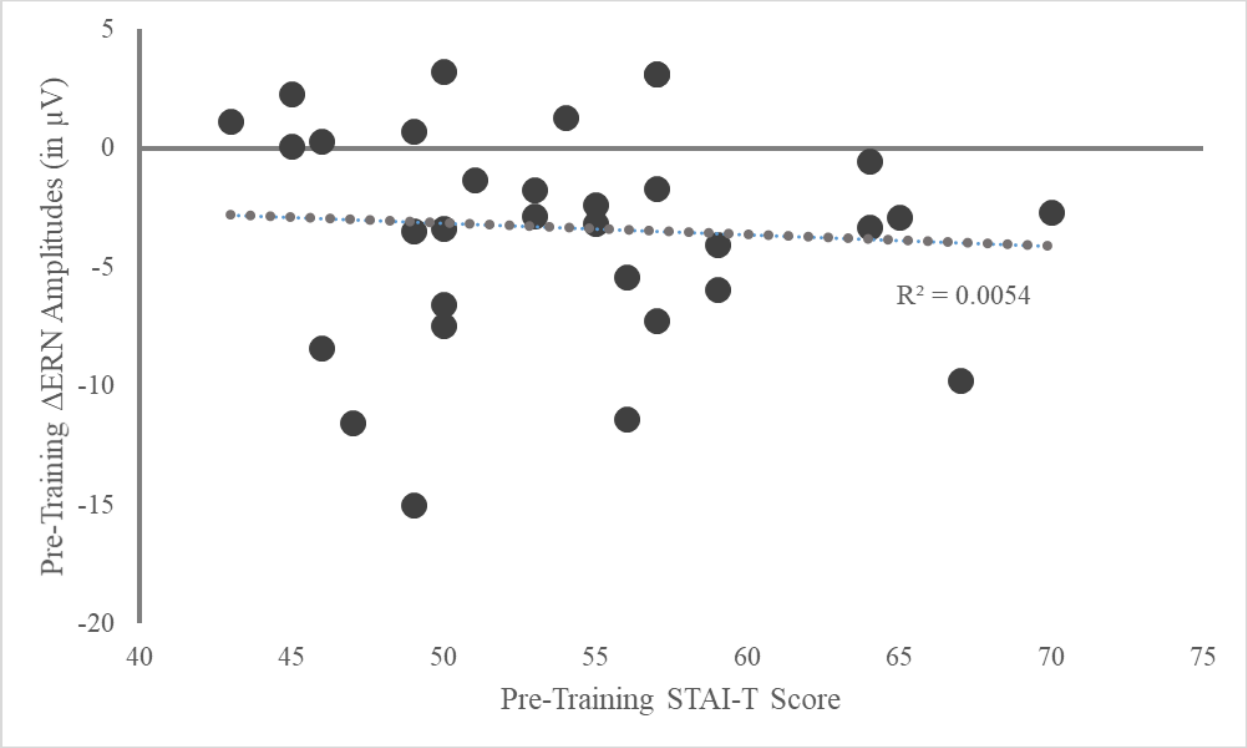

Figure 4. The correlation between pre-training STAI-T score and pre-training ΔERN pre-training amplitudes (in μV) across all participants

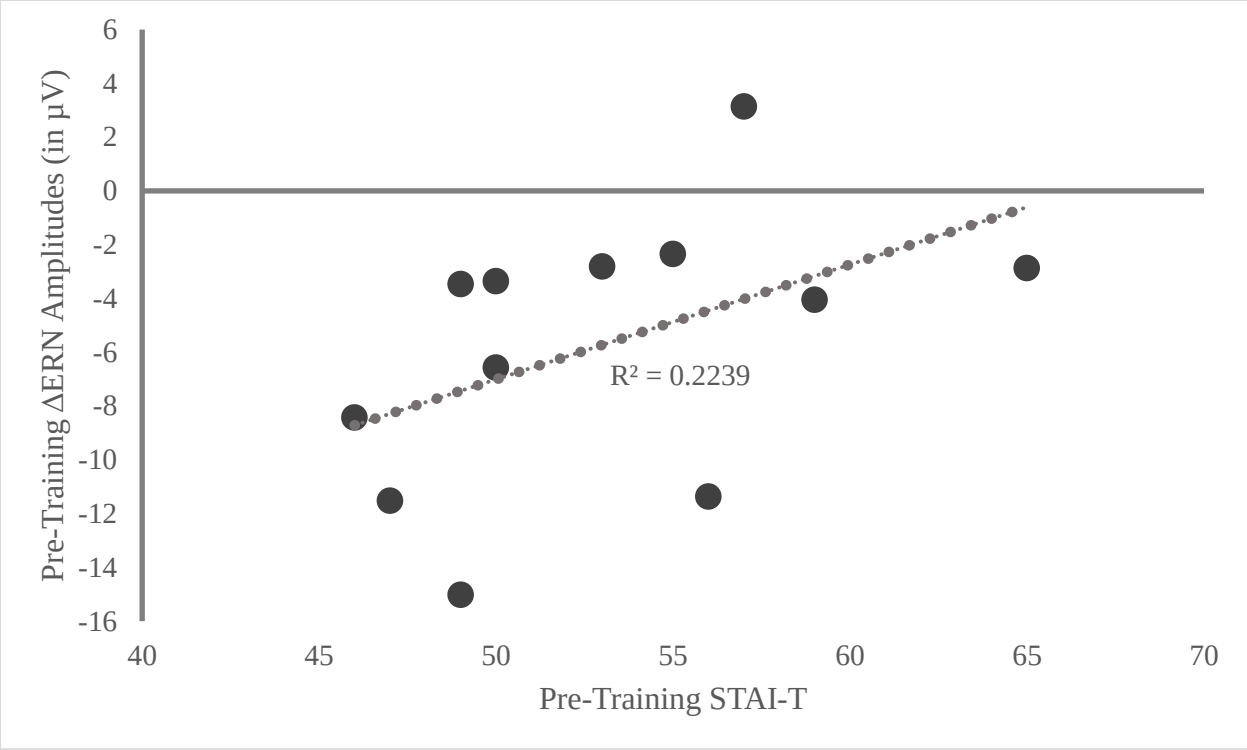

Figure 5. The correlation between pre-training STAI-T score and pre-training ΔERN pre-training amplitudes (in μV) in male participants

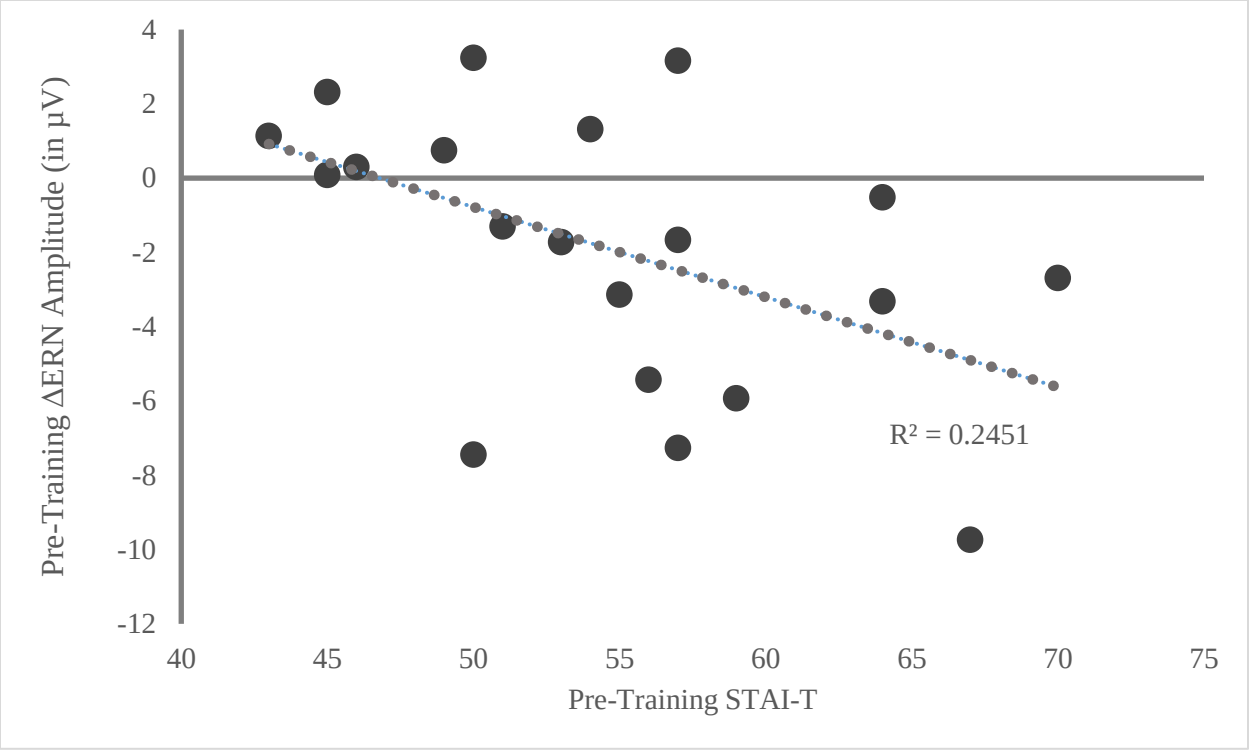

Figure 6. The correlation between pre-training STAI-T score and pre-training ΔERN pre-training amplitudes (in μV) in female participants

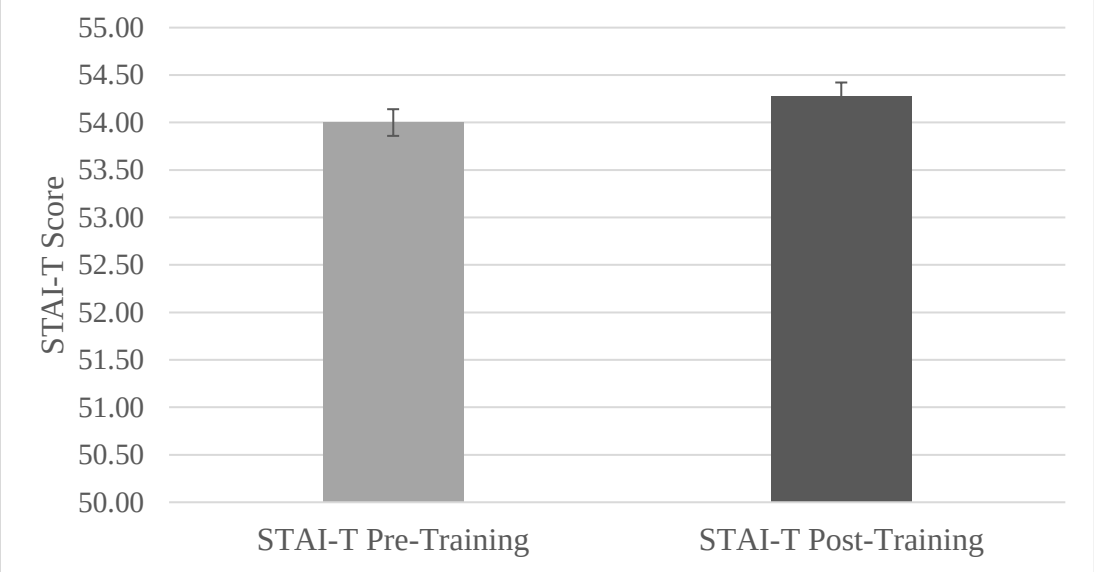

Figure 7. Overall STAI-T scores pre-and post-training.

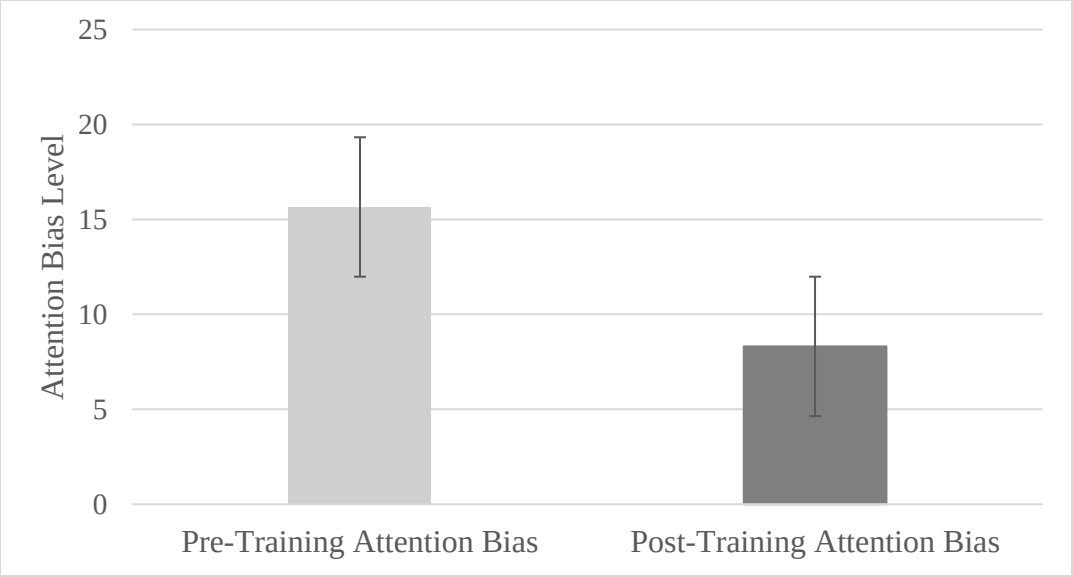

Figure 8. Overall levels of attention bias pre- and post-training.

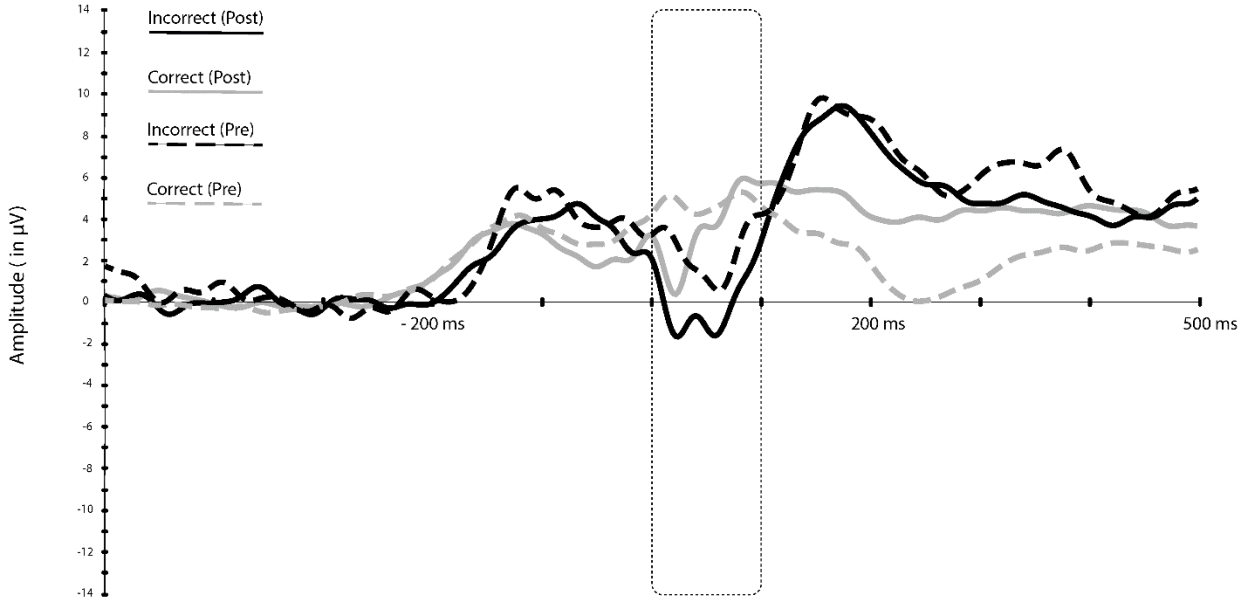

Figure 9. ERP amplitudes for correct and incorrect responses in the flanker task pre- and post-training for the control group with the dashed box outlining the ERN window from 0-100 ms

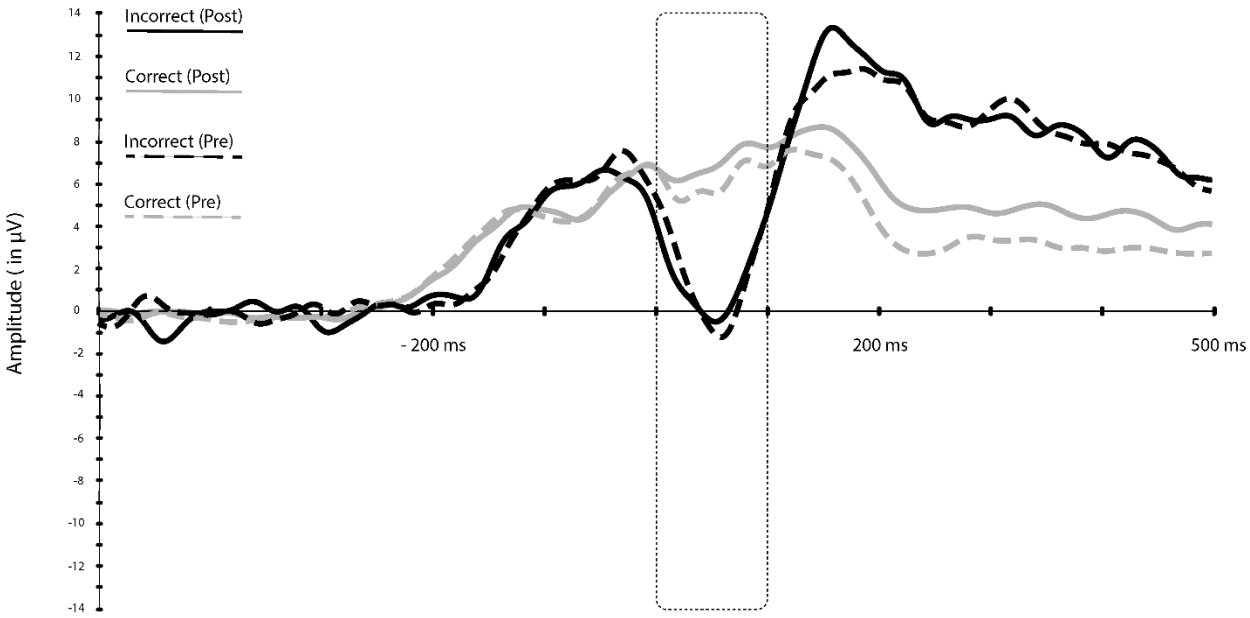

Figure 10. ERP amplitudes for correct and incorrect responses in the flanker task pre- and post-training for the ABM group with the dashed box outlining the ERN window from 0-100 ms

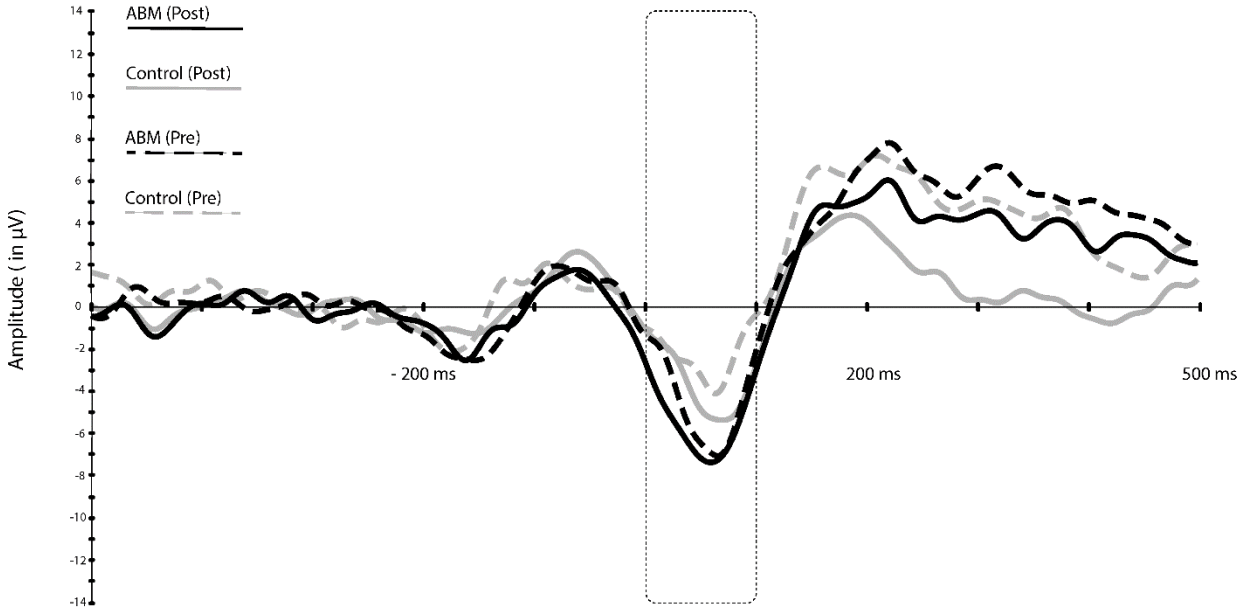

Figure 11. ΔERN amplitudes for the flanker task pre- and post-training for the ABM and control groups with the dashed box outlining the ERN window from 0-100 ms

Supplementary Analyses

Four item factor-driven STAI anxiety analyses on pre- and post-training

There was not a statistically significant reduction self-reported anxiety-factor items as measured by the STAI-T; pre-training (*M* = 11.00, *SD* = 1.88) and post-training (*M* = 10.69, *SD* = 2.13) meaning that levels of STAI-T did not change, $F(1,30) = 0.70$, $p = .408$, $\eta_p^2 = .023$. The interaction between session and experimental group was also insignificant, $F(1,30) = 0.22$, $p = .643$, $\eta_p^2 = .007$.

ERN Amplitudes and ΔAB Analysis

There was a significant effect of the covariate ΔAB on ERN amplitudes, $F(1, 29) = 5.99$, $p = .021$, $\eta_p^2 = .171$. There was no significant main effect of ERN, with pre-training ERN amplitudes (*M* = 1.92 μV, *SD* = 5.56 μV) not statistically differing from post-training ERN amplitudes (*M* = 0.41 μV, *SD* = 5.64 μV), $F(1, 29) = 0.62$, $p = .438$, $\eta_p^2 = .021$. There was no significant interaction effect between ERN and ΔAB, $F(1, 29) = 0.93$, $p = .343$, $\eta_p^2 = .031$. There was also no significant interaction effect between ERN and experimental group, $F(1, 29) = 1.22$, $p = .279$, $\eta_p^2 = .04$.

Correct response (CR) amplitudes and ΔAB Analysis

There was not a significant effect of the covariate ΔAB on CR amplitudes, $F(1, 29) = 3.43$, $p = .074$, $\eta_p^2 = .106$. There was no significant main effect of CR, with pre-training CR amplitudes (*M* = 5.25 μV, *SD* = 5.55 μV) not statistically differing from post-training CR amplitudes (*M* = 5.03 μV, *SD* = 7.51 μV), $F(1, 29) = 0.009$, $p = .925$, $\eta_p^2 = .000$. There was no significant interaction effect between CR and ΔAB, $F(1, 29) = 0.003$, $p = .956$, $\eta_p^2 = .000$. There

was also no significant interaction effect between CR and experimental group, $F(1, 29) = 1.31$, $p = .262$, $\eta_p^2 = .04$.

NORTHERN MICHIGAN UNIVERSITY

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Memorandum

TO: Joshua Carlson
Principal Investigator
Psychological Science

DATE: November 21, 2017

FROM: Robert Winn, Ph.D.
Interim Dean of Arts and Sciences/IRB Administrator

SUBJECT: **IRB Proposal** HS13-555
IRB Approval Dates: 11/12/2013 – 11/20/2018
PHS Number: 1R15 MH110951-01A1
Project title: "R15MH1109051: Neuroplasticity in an Extended Amygdala Network as a Target Mechanism for Attention Bias Modification Outcome"

The Institutional Review Board (IRB) has reviewed your proposal and has given it final approval. To maintain permission from the Federal government to use human subjects in research, certain reporting processes are required.

A. You must include the statement "Approved by IRB: Project # HS13-555" on all research materials you distribute, as well as on any correspondence concerning this project.

B. If a subject suffers an injury during research, or if there is an incident of non-compliance with IRB policies and procedures, you must take immediate action to assist the subject and notify the IRB chair (dereande@nmu.edu) and NMU's IRB administrator (rwinn@nmu.edu) within 48 hours. Additionally, you must complete an Unanticipated Problem or Adverse Event Form for Research Involving Human Subjects

C. Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding. Informed consent must continue throughout the project via a dialogue between the researcher and research participant.

D. If you find that modifications of methods or procedures are necessary, you must submit a Project Modification Form for Research Involving Human Subjects before collecting data.

E. If you complete your project within 12 months from the date of your approval notification, you must submit a Project Completion Form for Research Involving Human Subjects. If you do not complete your project within 12 months from the date of your approval notification, you must submit a Project Renewal Form for Research Involving Human Subjects. You may apply for a one-year project renewal up to four times.

NOTE: Failure to submit a Project Completion Form or Project Renewal Form within 12 months from the date of your approval notification will result in a suspension of Human Subjects Research privileges for all investigators listed on the application until the form is submitted and approved.

All forms can be found at the NMU Grants and Research website:
http://www.nmu.edu/grantsandresearch/node/102

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MEMORANDUM

TO: Joshua Carlson
Psychological Science Department

FROM: Lisa Schade Eckert LSE
Dean of Graduate Education and Research

DATE: May 30, 2019

RE: Modification to HS13-555
Original IRB Approval Date: 11/12/2013
Expiration Date: 9/14/2019
Modification Approval Date: 5/30/2019
Project Title: "R15MH1109051: Neuroplasticity in an Extended Amygdala Network as a Target Mechanism for Attention Bias Modification Outcome"

Your modifications to the project "R15MH1109051: Neuroplasticity in an Extended Amygdala Network as a Target Mechanism for Attention Bias Modification Outcome" has been approved under the administrative review process. Please include your proposal number (HS13-555) on all research materials and on any correspondence regarding this project.

Any additional changes or revisions to your approved research plan must be approved by the IRB prior to implementation. Unless specified otherwise, all previous requirements included in your original approval notice remain in effect.

If you complete your project within 12 months from the date of your approval notification, you must submit a Project Completion Form for Research Involving Human Subjects. If you do not complete your project within 12 months from the date of your approval notification, you must submit a Project Renewal Form for Research Involving Human Subjects. You may apply for a one-year project renewal up to four times.

NOTE: Failure to submit a Project Completion Form or Project Renewal Form within 12 months from the date of your approval notification will result in a suspension of Human Subjects Research privileges for all investigators listed on the application, until the form is submitted and approved.

If you have any questions, please contact the IRB at hsrr@nmu.edu.

Consent Form

NORTHERN MICHIGAN UNIVERSITY

INFORMED CONSENT STATEMENT

Title of Project: Characteristics of Attention Bias Modification

Investigators: Dr. Joshua M. Carlson (Assistant Professor, Department of Psychology, NMU)

You are invited to participate in our research study. The purpose of this study is to better understand the neural characteristics of attentional behavior. A research assistant at Northern Michigan University will be conducting the study under the advisory of Dr. Joshua M. Carlson.

INFORMATION

120 people will participate in the full study, which will consist of 2 experimental sessions at NMU lasting no longer than 2 hours each. We will also collect MRI scans of your brain during two separate sessions: 1 before and 1 after training. These sessions will occur at UP Health System – Marquette and will last 20-30min in length. You will also complete at home training sessions on your Phone over the course of 6 weeks. You will receive online survey at 3 and 6 months after the last lab session as follow-up feedback of the study.

Participants will be males or females between the ages of 18 and 42 with normal or corrected to normal vision (i.e., by wearing contacts or glasses). After reading this document and agreeing to participate in this study, we will begin the experiment.

Screening

First, you will complete an MRI screening form to determine eligibility for MRI testing. You will then complete an attentional probe task on a computer. Each trial will start with a white fixation cue (+) centered on a black background. You should always maintain fixation in this cue. Then two stimuli will be briefly presented simultaneously on the left and right side of the screen. Afterward, a target stimulus will be presented either on the left or the right side of the screen. Your goal is to identify the location of the target stimulus as quickly as possible—speed is very important in this experiment. After completing the attention task, you will fill out several brief questionnaires assessing your personality type.

We will go over the task instructions in detail prior to testing and answer any questions you might have about these instructions.

Full participation in the laboratory, MRI, and training sessions (described below) will be based on your responses to the measures obtained during the screening session. If you do not qualify for full participation you will receive partial compensation for the screening portion (see compensation section below).

Lab Session
During the laboratory sessions, brain activity will be recorded with sensors placed on your head. The sensors to be used to record your brain activity will be applied in the following manner. First, the circumference of your head will be measured in order to determine your cap size/placement. The sensor cap may be soaked in a salt solution, allowed to briefly dry, and then will be placed on your head. A computer connected to the cap will be recording your brain activity while performing an attention task. During the task, a Research Assistant will oversee the study procedures from a control room and will be able to observe you while you perform the task. If for any reason you need assistance, you can signal to the Research Assistant for assistance.

MRI Session
You will also receive an MRI of your brain during two separate sessions: 1 before and 1 after training. These sessions will occur at UP Health System – Marquette and will last 20-30min in length.
UP Health System – Marquette will be providing a contractual service to researchers from Northern Michigan University, which allows the purchase of time on the MRI scanner solely for the purposes of this study. UP Health System – Marquette is in no way involved with reviewing or examining the MRI data collected in this study for research or medical purposes. Only the researchers from Northern Michigan University lead by Dr. Carlson will have access to and analyze the MRIs obtained in this study. The researchers from Northern Michigan University are in no way qualified to make medical assessments about the MRIs collected in the study. The MRIs collected in this study will be anonymously correlated with the measures obtained in this study for research purposes. Thus, UP Health System – Marquette is not involved with the research or the MRIs collected in this study, and the procedures performed in this experiment are not medically diagnostic in nature. Nevertheless, the collection of MRI scans has the potential to detect incidental findings. That is, abnormalities identified during the analysis of the MRIs that could indicate potential health concerns for the participant that are beyond the aims of the study. For example, MRI scans could uncover possible evidence of prior stroke, tumors, or aneurysm. Most incidental findings are minor abnormalities that are common, pose no clinical risk, and require no medical referral. For example, a largescale 2009 study in the *British Medical Journal* found the overall rate of incidental findings in brain MRIs to be around 3%. However, serious incidental findings that require medical referral are much rarer (< 1%). If such an incidental finding is detected, the principal investigator will contact you to discuss what the finding possibly means. You will then be referred to your medical doctor for follow-up. You will not have access to your individual MRI results, but at the conclusion of the study, if interested, you can obtain the group-level results of the study, which will be published in an academic journal.

Training
You will complete this same attention task described above during at home training sessions over the course of 6 weeks. After the at home portion of the experiment you will return to the lab on NMU and complete a final laboratory session.

Follow-up

You will receive online survey assessing your personality and emotion regulation at 3 and 6 months after the last lab session. You can answer all the items online within no more than 15 minutes.

RISKS

Risks associated with participation in this study are considered minimal. If you experience any discomfort with the neuroimaging cap, please notify the experimenter so that adjustments can be made to improve your

comfort. There is a slight risk of skin irritation due to the salt solution the cap is soaked in. If this occurs, the cap will be removed immediately, and facilities are available for the skin to be rinsed. Although it is unlikely, some of the survey questions could elicit unexpected thoughts or feelings. If you ever feel uncomfortably anxious or depressed, the NMU Counseling Center (906-227-2980) has free services for NMU students.

The following risks are related to MRI:

- The MRI scanner attracts certain metals; therefore, if you have any metal in your body (such as pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, or plates) you will be excluded from the study.
- You may feel anxious about the tight space within the MRI machine. You can stop the study at any time.
- The MRI produces a loud noise throughout the MRI session that some people find uncomfortable. We will minimize your perception of this noise by using earphones to attenuate outside noise.
- You cannot be pregnant or breastfeeding to participate in this study. MRI may not be safe during pregnancy. Therefore, if you are pregnant you will be excluded from the study.

BENEFITS

There are no direct benefits to the participants other than research experience and monetary compensation. The results of this experiment will significantly contribute to our understanding of human attentional behavior.

CONFIDENTIALITY

The data collected from participants will be stored on a computer in a secure lab using an unidentifiable subject number. This consent form with your name will be the only record of your participating in this research. There will be no link between your name and your performance data. The content form will be stored in a locked filing cabinet in a secure lab location.

COMPENSATION

You will receive $65 for fully completing this research study. If you choose not to participate in this study, there is no penalty. Participants not meeting screening criteria for full participation will receive $10 for partial participation. Participants who withdraw from the study before completion will also receive $10 for partial participation.

CONTACT

If you have questions at any time about the study or the procedures, or if you experience adverse effects as a result of participating in this study, you may contact the principal investigator, Dr. Joshua M. Carlson (joshcarl@nmu.edu and 906-227-2798) in the Department of Psychology, Northern Michigan University. This project has been reviewed and approved by the University Research Ethics Board at Northern Michigan University. If you feel you have not been treated according to the descriptions in this form, or your rights as a participant in research have been violated during the course of this project, you may contact the IRB chair Derek Anderson (dereande@nmu.edu) and NMU's IRB administrator Rob Winn (rwinn@nmu.edu).

PARTICIPATION

Your participation in this study is voluntary; you may decline to participate without penalty. If you decide to participate, you may withdraw from the study at any time without penalty and without loss of benefits to which you are otherwise entitled. If you withdraw from the study before data collection is completed your data (if part of data is collected) will be returned to you or destroyed by either Dr. Carlson or the experimenter. You have the right to omit any question(s)/procedure(s) you choose.

DATA SHARING AND PUBLICATION

De-identifiable data obtained from this study will be broadly shared on the National Institute of Mental Health (NIMH) Data Archive. Shared data will not contain your name or any other personally identifiable information. The goal of the NIMH Data Archive is to promote rapid scientific progress by making the study data available to other researchers in the field. The results of the research may be published in journal articles, and other scientific conferences and university colloquia. If you wish, the results of this study will be e-mailed to you.

CONSENT

I have read and understand the above information. I have received a copy of this form. I agree to participate in this study.

Participant's signature_____ email _____ Date _____

Age_____ Gender_____

Investigator's signature_____ Date _____

Protocols

Screening Protocol

All screening will occur in person in the lab.

Greet & Welcome the Participant – Get their information onto the sheet of paper

1. Seat and give the participant the consent form and allow them time to read it over.
    a. While they read it over, enter their data into the computer program and start up the testing computer.
    b. Once they are finished with the consent form, ask them if they have any questions and if they would like a copy of the consent form.
    c. Sign their consent form and keep the signed copy. File it away.
    d. Remind the participant that they are volunteering to participate in the study and they can leave any time without penalty.

2. Measure the participant's head circumference and note this in the spreadsheet on the google team drive.

3. Seat the participant 59 cm from the screen. ASK them to **TURN OFF** or **SILENCE** their CELL PHONES.

a. Ask if it is comfortable, and give them the following instructions:

> ***Dot-Probe Task:*** *Each trial of the experiment will start with a small '+' (plus sign) in the center of the screen. At all times keep your eyes fixated on the plus sign. After an initial period of fixation two stimuli will be briefly presented: one on each side of the screen. After these, stimuli disappear. A small dot will appear either on the left or on the right side of the screen. Your task is to locate this dot: left or right. To do this, use your right hand. Use your right index finger on the Red button on the keyboard to indicate left-sided target dots. Use your right middle finger on the Green button on the keyboard to indicate right-sided target dots. AS SOON AS YOU LOCATE THE DOT MAKE A RESPONSE. IT IS IMPORTANT THAT YOU RESPOND AS QUICKLY AND ACCURATELY AS POSSIBLE. All responses are recorded anonymously. During the testing session we will not be actively monitoring your responses. DO YOU HAVE ANY QUESTIONS?*
>
> **TO QUALIFY FOR INCLUSION IN THE REMAINDER OF THE STUDY THE PARTICIPANT MUST HAVE AN INCONGRUENT – CONGRUENT DIFFERENCE SCORE ≥ 7ms [red scores: included; white scores: excluded]. To end this experiment after you record the difference score press "q" on the keyboard**

4. After the experiment, administer the computerized **STAI-T Questionnaire**, and ask again if they have any questions?

> **TO QUALIFY FOR INCLUSION IN THE REMAINDER OF THE STUDY THE PARTICIPANT MUST HAVE A TRAIT ANXIETY SCORE ≥ 40 [if the color of the scores are red].**

5. After the STAI, administer the **DASS**: "please read the instruction very carefully". When they complete the DASS, ask participant to fill-in the **CERQ**.

6. Check to see if the app works on their phone. Enter Participant # -1 (note the negative sign) and Pin # 1941. This will allow you to access the app as an administrator.

a. Perform these checks to the participant's phone to make sure the app is compatible with the participant's phone:

i. Does the phone have the ability to provide a website link to the homescreen of the phone? (NOTE: Enter Participant # -1 and PIN from the website before adding the app to the homepage)

1. Use safari for iPhones, Chrome/Firefox for Android

ii. Once the APP is on the homepage:

1. Are you able to enter values?
2. Does it have the sensitivity to select different answers on the PANAS? (This is in the very beginning pertaining to the words that relate to how they are feeling.)
3. Are you able to provide reaction time responses that fall within the "good" range?

a. If functionality is slow, the phone might be not up to date with its current operating system. Ask the participant to update their phone.

4. Does the phone automatically rotate to landscape mode as well as take up the entirety of the screen?

b. After checking the compatibility of the participant's phone, enter cabinlab.net/#/clear into the browser. This will reset the participant number and remove administrator access. Remove icon from the participant's home screen at this time.

7. Statements regarding further participation and additional steps. Read the correct statement to the participant based on their screening results.

When they meet the inclusion criteria...

(1)**read the following statement**

"(their name) you've met the inclusion criteria! We would like to schedule your EEG and MRI sessions at this time. We also need to take a measurement of your head size to determine the appropriate EEG cap for the EEG session."

(2)**Record their head size** (Do not schedule more than 3 EEG sessions of the same cap size on the same day). Work to schedule their next session(s). Note, that it will be important to also tentatively schedule their post-training session(s). This will allow us to determine if they will be in town and if necessary, they can make arrangements to their schedule. Note that the post-training session will include the STAI, dot-probe, & EEG measures in one session (probably about 1.5-2hr as well as a separate MRI session). If the participant cannot schedule their session(s) at this time ask them:

> "Please get back to us with your availability within 24 hours (24hrs for the pre-training sessions, post-training as soon as they can)"

Also, remind the participant:

> "When we schedule your EEG session please arrive with washed hair and no makeup. This includes all types of hair gel or product and all face makeup. Thank you!"
>
> (May need to also reiterate when we send a reminder of when they are completing EEG).

(3)**Personal Data Needs to be collected and linked to the participant ID**. This should be kept in a password protected spreadsheet in the CABIN lab (Mac:). Personally identifiable information will be collected in order to create de-identified global unique identifiers (GUIDs) on the NIMH Data Archive (NDA), which allows for the linkage of data across multiple NDA datasets. Data to be collected includes:

a. Full legal name at birth (as it appears on their birth certificate)

i. i.e., first, middle, & last name are all needed

ii. no initials or nicknames/abbreviated names

b. Date of birth

c. City/municipality of birth

d. Sex (at birth)

When they do <u>NOT</u> met the inclusion criteria..

Based on our screening criteria, you do not match with some of the features we are looking for and therefore you will not be involved in further experiments. Please notice that this does not mean you had a bad performance during the screening. We thank you for your interest and participation in the study. If you have any questions or concerns please contact either Dr. Fang (lfang@nmu.edu) or Dr. Carlson (joshcarl@nmu.edu). If you feel that you have the need for counseling please contact the NMU counseling center at 906-227-2980, they have free services for students.

Flanker ERP Task Protocol

Greet & welcome participant. Get participant info: age, sex, handedness, etc.

1) Remind the participant that this EEG Study is part of the consent form that they signed during their screening procedure.

2) On the mac.
    a. Start Net Station by clicking on the icon on the bottom "Dock"
    b. Click "Session" and choose "Auditory DP" & click "Select"
    c. Identify Subject: FlankerERP + Pre or Post + the subject # (e.g., FlankerERPPre01) & click "Begin Session"
        i. IMPORTANT NOTE: obtain subject number from Google Drive Spreadsheet
    d. Click on Panels to turn on "Digital Filter Controls"
    e. Click highpass, lowpass, and notch and then click "on"
    f. Click 500 Hz sampling rate
    g. Follow steps in EGI and EEG manuals to place cap and measure impedance levels
    h. Use screen switcher to present the EEG data on the participant monitor (green)
        i. IF THE SWITCHER DOES NOT WORK
            1. Press the switcher for the desired monitor
            2. On the desired computer, detect the display
                a. Mac:
                    i. top right corner of task bar (image of monitor) – detect display
                b. Windows:
                    i. Right click on desktop – display settings – detect display

Try to lower impedance levels without electrolyte first (e.g. use the tip of a dry syringe to displace hair to improve scalp/electrode connection). If this is unsuccessful, then use the electrolyte to lightly rewet the sponges. DO NOT OVER WET THE CAP. This will bridge channels.

3) Seat participant in chair 59cm from the screen (i.e., use marked locations).
- *Ask the participant to turn off or silence their phone (no vibrate either).*
- *Make sure the control room is dark, & turn on lights in participant room.*
- *Switch the screen and audio to the experimental control computer (orange)*
- *Make sure the speakers are switched on in the participant room*

4) Note any channels in which the impedance could not get lower than the threshold, as well as any other noticed issues with the cap, the date and the protocol on the ERP cap log.

5) Before switching the screen back to the E-Prime computer, ask the participant to blink and clench their jaw. After they do so, point out those mention artifacts and mention how much

eye and facial movements influence the EEG signal, and that it is important to minimize facial and eye movements while the experiment is in progress.

6) Start the FlankerERP study using E-Run; The Icon is on the desktop. Again be sure to match the participant number to the number already assigned to them. Have the participant provide the requested demographic information. **NOTE:** For a **Pre**-ABM session, indicate **session 1** after participant number. **Post**-ABM session is **session 2** (For the resting-state EEG, enter either a "1" or "2" based on the table below when the screen prompts you with even/odd)

	Odd Participant #	Even Participant #
Pre-ABM	1	2
Post-ABM	2	1

7) The first portion of the paradigm features the flanker task

Read the following instructions: *Each trial of the experiment will start with a small '+' (plus sign) in the center of the screen. At all times keep your eyes fixated on the plus sign. After an initial period of fixation, you will be presented with a series of five arrows. Your task is to indicate which direction the center arrow is facing. Press the first button (1) on the box with your index finger to indicate the center arrow is facing left, press the second button (2) on the box with your middle finger to indicate that the center arrow is facing right. You will start first with a short practice block in order to get used to the task. At the end of each arrow presentation, you will be provided feedback on your performance. After the practice block, I will ask you if you have any questions. Then you will start the experiment, and will only receive feedback at the end of each block; I will come in and provide feedback on your performance. It is important for both the practice and subsequent blocks that you RESPOND AS QUICKILY AND AS ACCURATLY AS POSSIBLE. The IDEAL performance is a BANALANCE BETWEEN SPEED AND ACCURACY. AS SOON AS YOU SEE THE ARROWS, MAKE A RESPONSE. Do you have any questions before we begin?*

IMPORTANT!!!! Make sure you click "Record" on the mac before the participant starts!

You should wait until after the practice period to hit record. After the practice period ask the participant if they have any questions.

8) Once they begin the actual blocks, the end of each block will provide feedback on their accuracy. Based on the accuracy that is presented, provide the following feedback to the participant
    a. **If their accuracy is BELOW 75%**
        i. Instruct the participant: "Remember, it is also important to respond accuracy as well as quickly. Please respond more accurately in the next block"
    b. **If their accuracy is ABOVE 90%**

i. Instruct the participant: "Remember, it is also important to respond quickly as well as accurately. Please respond *as soon as the arrows appear on the screen*."

c. If their accuracy is between 75%-90%

i. Instruct the participant: "You're doing a great job of responding both accurately and quickly. That is the balance between speed and accuracy we are looking for. Keep it up for the next block."

NOTE: The participant *will not* be able to advance the task beyond the feedback screen. This is designed so you will have the opportunity to provide them feedback. To permit the participant to continue to the next block, press SPACE on the experimental control computer.

9) After seven blocks, the flanker task will conclude. After the task concludes, the screen will let the participant know to wait for the experimenter.

Before proceeding with the next task ***PAUSE*** the Net Station EEG recording and select "check impedances". **Note:** it is important for the next task that the following electrodes be under impedance for the next task:

- VREF
- 12
- 6
- 60
- Electrodes needed for motion artifacts (e.g. 63, 64)

10) After checking impedance levels, the resting state EEG will follow the flanker task:

Read the following instructions: *This is an EEG baseline measurement session. Each trial will start with an audio instruction. Please follow the instruction to open or close your eyes: for example, when it says "open", please keep your eyes open and looking at the fixation cross; when it says "close", please keep your eyes closed. Each trial will last for 1 minute, during which you just need to keep calm and relax. There will be 8 trials in total. Do you have any questions?*

11) After reading the script and answering any questions, test that the audio stimuli are playing appropriately:

a. When prompted, press "1" on the chronos response box to do a test of the auditory stimulus

b. Ask the participant:

i. "Is that at a volume you can hear clearly?"

c. If the stimulus is being presented clearly, press “1” to continue (otherwise press “2” to make necessary adjustments and try again)

12) After 8 minutes, the EEG resting state portion will conclude. Click “Stop” to stop and save the EEG data.
13) At the end of the session ask them if they have any questions.
14) Remove and clean the EEG net according to the EGI guide.

Inclusion/ Exclusion Check List:

1) Are you between 18 & 42 years of age?
    a. Participant responds ‘No’: Exclusion
    b. Participant responds ‘Yes’: Inclusion
2) Do you have normal or corrected (i.e., contacts or glasses) to normal vision?
    a. Participant responds ‘No’: Exclusion
    b. Participant responds ‘Yes’: Inclusion
3) Are you currently seeking psychological treatment?
    a. Participant responds ‘No’: Inclusion
    b. Participant responds ‘Yes’: Exclusion
4) Do you have any metal in your body that cannot be removed (e.g., shrapnel, pacemaker, permanent retainer)?
    a. Participant responds ‘No’: Inclusion
    b. Participant responds ‘Yes’: Exclusion
5) Do you currently have a neurological disorder?
    a. Participant responds ‘No’: Inclusion
    b. Participant responds ‘Yes’: Exclusion
6) Have you ever had a head injury or lost consciousness due to injury?

a. Participant responds ‘No’: Inclusion

b. Participant responds ‘Yes’: Exclusion

7) Are you currently on any medications? If yes, which medications?

a. Participant responds ‘No’: Inclusion

b. Participant responds ‘Yes’: The medications will be reviewed; any psychoactive medications will result in exclusion, other medications (e.g. birth control) will result in inclusion

8) Do you get anxious when in enclosed/tight spaces (i.e., are you claustrophobic)?

a. Participant responds ‘No’: Inclusion

b. Participant responds ‘Yes’: Exclusion

9) If female, are you currently pregnant?

a. Participant responds ‘No’: Inclusion

b. Participant responds ‘Yes’: Exclusion

At the beginning of the ABM: Instructions provided to participants

Attentional biases in anxiety: People with stress and anxiety tend to focus their attention on negative information and interpret situations negatively. This tendency is understandable given the life circumstances that may have caused this stress in the first place. However, this tendency to focus on the negative can also cause problems because it seems to be an automatic habit. It is very difficult to change this habit consciously by trying to focus your attention on neutral or positive information. The app training task is designed to combat this habit. The task itself is very repetitive and easy, but it may help you change the habit of focusing on negative information precisely because of the repeated presentations (Beard, Weisberg, & Primack, 2012).

At-home training app: The task is similar to the one you completed in the lab. Each trial of the session will start with a small '+' (plus sign) in the center of the screen. At all times, keep your eyes fixated on the plus sign. After an initial period of fixation, two stimuli will be briefly presented: one on each side of the screen. After these stimuli disappear: a small dot will appear either on the left or on the right side of the screen. Your task is to locate this dot as quickly as possible. Each test should take between 5-10 minutes.

Concentration is very important when you are building a new habit. Therefore, please take the training task in a quiet distraction free environment. So, while doing the task, please do not listen to music, watch videos, and please silence all notifications in other apps. In other words please put your phone on do not disturb. To acquire a habit in a correct form, please respond as quickly and accurately as possible. Over the six-week period, your goal is to decrease your response time to the location of the dot. You may not see a decrease in reaction time from each session to the next, but the overall trend from start to finish should be a decrease in reaction time. Remember that the study requires you to complete 6 sessions per week (no more than 3 trials in a single day) for a total of 6 weeks. You are also encouraged to discover any clues of the task or use any strategies that could help you perform better.