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CEREBELLUM-SEEDED FUNCTIONAL CONNECTIVITY CHANGES IN TRAIT-ANXIOUS INDIVIDUALS UNDERGOING ATTENTION BIAS MODIFICATION TRAINING

Katherine Elwell
kelwell@nmu.edu

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By

Katherine A. Elwell

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Committee Chair: Dr. Joshua M. Carlson Date

07/08/2021

First Reader: Dr. Lin Fang Date

07/09/2021

Second Reader: Dr. Christina Hartline Date

07/12/2021

Department Head: Dr. Adam Prus Date

8/12/2021

Dr. Lisa Schade Eckert Date
Dean of Graduate Education and Research

ABSTRACT

CEREBELLUM-SEEDED FUNCTIONAL CONNECTIVTY CHANGES IN TRAIT-ANXIOUS INDIVIDUALS UNDERGOING ATTENTION BIAS MODIFICATION TRAINING

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Anxiety and anxiety related disorders are increasing at a drastic rate in the past decade, with the NIMH reporting that 31.1% of U.S. adults will experience an anxiety disorder at some point in their lives. Anxiety is commonly characterized by increased attention bias to threat. Attention Bias Modification (ABM) is a new treatment used to reduce individual's attention bias towards threat. The extent to which ABM leads to underlying neural changes is still unknown. The cerebellum is a neglected brain structure, with new research provides evidence that cerebellum's functional connectivity and shared networks with threat processing regions has a direct impact on anxiety etiology and symptomology. Therefore, the current study assessed functional connectivity changes seeded in cerebellum as an outcome of ABM training. The experiment consists of a 6-week ABM or control training period bookended by pre and post resting state functional magnetic resonance imaging (rsfMRI) sessions. Heightened trait anxiety was correlated with heightened connectivity from the cerebellum to threat processing regions. (i.e., the amygdala, ACC, and the thalamus). Decreased cerebellar connectivity to threat processing regions (i.e., the amygdala, ACC, and the thalamus) was observed following ABM training. This suggests that ABM may underlie neural changes within the cerebellum—resulting in decreased attention bias. This also suggests the cerebellum may contribute to the etiology and maintenance of anxiety and attention bias. Limitations and future directions concerned with both ABM and the functional role of the cerebellum are discussed.

DEDICATION

This thesis is dedicated to my parents, Amy Elwell (Rink) and Rom Elwell, as well as my twin brother William Elwell, my younger sister Emma Elwell, and my very close friends and family. These individuals have supported me tremendously thought my academic and personal endeavors—I would not be where I am today without them.

This thesis is also dedicated to all individuals inflicted with anxiety and anxiety disorders. It is my hope that my research can provide further contributions into the etiology of anxiety disorders.

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INTRODUCTION

Anxiety is a state of tension, worry, and apprehension regarding uncertain, and potentially negative, future events (Gallo et. al., 2012). Anxiety and anxiety related disorders are increasing at a drastic rate in the past decade, with the National Institution of Mental Health (NIMH) reporting that an estimated 19.1% of U.S. adults had an anxiety disorder in the past year, while 31.1% of U.S. adults will experience an anxiety disorder at some point in their lives (NIMH 2019). Reports from the NIMH indicate a higher prevalence rate for anxiety disorders in females (23.4%) compared to males (14.3%; NIMH 2019). Anxiety disorders have astronomical communal and economic impacts. Per Hoffman et. al. (2008),

The total cost of anxiety disorders was estimated to be approximately $42.3 billion in the United States alone. Anxiety disorders account for one third of all money spent on psychological disorders in the United States. This statistic does not include the cost of causal illness related to anxiety, as anxiety disorders have been proven to have a causal relationship with substance abuse, bi-polar disorder, depression, obsessive-compulsive disorder, etc. (Provencher et. al., 2012; Stein & Hollander, 2002; Sutton, 2011). The current therapies and treatments available for anxiety are not only time consuming, but restrictive in nature, as their efficacy and cost tend to be undesirable for the majority of individuals (Haratian & Karbasi, 2018; Hedman et. al., 2012; Hedman et. al., 2014). The need for easy-to-access and cost-effective anxiety therapies has never been more prevalent, as the burden of anxiety and its related disorders poses on society is monumental.

Attention Bias Modification (ABM) therapy is an emerging therapy for anxiety with the potential to eliminate monetary and efficacy problems currently inflicting current anxiety therapies. ABM therapy is similar to the most utilized therapy: Cognitive Behavioral Therapy

(CBT), as they both account for the well-known notion that cognitive bias is rooted in the pathology of anxiety disorders. CBT therapy elicited to combat attention bias utilizes an integrative process by employing verbalization, coupled with exposure to feared situations, allowing patients to interpret or learn that threatening stimuli are safe. (Bar-Haim et. al., 2007; Hakamata et. al., 2010).

ABM treatment differs from CBT in that its therapeutic action targets a specific bias in attention, extending work implicating threat-related attention bias in anxiety (Hakamata et. al., 2010). Despite it being a newly emerging therapy, preliminary studies (Britton et. al., 2015; Browning et. al., 2010; Taylor et. al., 2014) support ABM therapy as an effective treatment for the reduction of attentional bias to threat and anxious symptoms. Randomized control trials (Hakamata et. al., 2010) have shown ABM treatment to be as effective as CBT and medication (Hakamata et. al., 2010). Additional studies (Kuckertz, 2014; MacLeod et. al., 2007; See et. al., 2009) provide evidence indicating that ABM therapy can successfully be self-administered while maintaining long-term benefits associated with the reduction of anxiety-related symptomatology.

Despite the current literature supporting the effectiveness of ABM treatment, there is a lack of knowledge encompassing the extent to which ABM results in long-term changes in brain structure that persist after the treatment has been terminated, as well as the neuroplastic effect ABM therapy has on specific brain regions and neural circuitry. The aim of the current study is to assess the effects of an anxiety reduction intervention on initiating long-term changes in brain circuitry; specifically, the current study assessed the degree to which attention bias modification training leads to sustained changes in the cerebellum and its neural circuitry and function post-treatment, and the extent to which such changes are linked to long-term symptom reduction. The cerebellum is an often-neglected brain structure, with its functional role in psychological,

psychiatric, and neuropsychological disorders only recently being investigated (Fair, 2018; Moreno-Rius, 2018; Phillips et. al., 2015; Shakiba, 2014;).

New and converging research provides empirical evidence that not only is the cerebellum involved in higher cognitive functions such as attention, working memory, associative learning, and sensory processing (Smet et. al, 2015; Baumann & Mattingley, 2012; Dickson et. al., 2017), but that its functional connectivity and shared networks with threat processing regions (i.e the limbic system and amygdala) have a direct impact on anxiety related symptoms (Etkin et. al., 2009; Baumann & Mattingley, 2012; Talati et. al., 2015). Likewise, the current study aims to provide confounding evidence for the role of the cerebellum in anxiety related symptomatology, as well as contribute to the newly emerging research supporting the role of the cerebellum outside of its emblematic functions.

Hypotheses:

It was hypothesized that

1. Heightened levels of trait anxiety would be associated with statistically significant, widespread cerebellar functional connectivity with regions previously implicated in both motor and cognitive processing involved in various resting-state networks linked to the cerebellum.
2. Functional connectivity between the cerebellum and threat and emotion processing regions (i.e., amygdala, insula, caudate nucleus, cingulate gyrus) would decrease in the ABM training condition following training.

Review of Literature

Anxiety and Fear. Anxiety disorders have one of the highest prevalence rates of all psychological disorders, with the National Institution of Mental Health (NIMH) reporting that an

estimated 19.1% of U.S. adults had an anxiety disorder in the past year, while 31.1% of U.S. adults will experience an anxiety disorder at some point in their lives (NIMH 2019). Reports from the NIMH indicate a higher prevalence rate for anxiety disorders in females (23.4%) compared to males (14.3%; NIMH 2019). Anxiety, a commonly experienced affective state, can be characterized by sustained levels of arousal, apprehension, avoidance, and vigilance (Linetzky et al., 2015; Xu et al., 2015). These characteristics arise from all three levels of the triune forebrain: primal (neomammalian), emotional (paleomammalian), and instinctive (reptilian; Kroes et al., 2006; Price, 2003;).

The forebrain is historically attributed to the display of emotions, and has been proven to be at the forefront of the evolutionary development of the implementation of escalating and de-escalating strategies. From an evolutionary standpoint, Anxiety is a component of de-escalating strategies mediated by the paleomammalian and reptilian forebrains (Corbetta & Shul, 1998; Gardner, 2002; Price, 2003). Anxiety is attributed to the inability of the neomammalian brain to effectively process conspecific danger; thus, continuously initiating primitive de-escalating situations. Anxiety is thought to be evolved from this defect in the neomammalian brain, and can currently be attributed to the over-attenuation to threatening stimuli seen in anxiety and its disorders. From an evolutionary perspective, the detection of threat is critical for the survival of a species. This rapid and imprudent mechanism likely survived as an adaptive advantage, and is consistent with current models of threat processing (Green & Philips, 2003; Price, 2003).

Clear definitional distinctions between fear and anxiety have been elusive. There is also ambiguity in relating clinical classifications to preclinical laboratory models. The functional purpose of anxiety and fear is to trigger responses, both adaptive and intrinsic in nature, to signals of danger or threat (Carlson et al., 2013). Although fear and anxiety are similar in their

implementation and execution, there are differences in their etiologies, allowing for a distinction between the two. Anxiety is classified as a response to an unknown threat or internal conflict, whereas fear is rooted in external dangers known to the individual experiencing the (Hakamata et. al., 2010). Trait fear is the result of an individual over-attenuating to several distinct threat cues, while also avoiding any situational circumstances involving such threats. Trait anxiety is the result of an individual's lack of ability to avoid any prolonged fearful situations while also overestimating the fear itself, the impact it may have, or experiencing disarray between expectations and reality surrounding the threat. Models of both trait and state anxiety suggest that the neural correlates of state and trait anxiety differ. Some literature (Sylvers et al., 2011) suggests that fear is an emotional response that results from the interpretation of specific environmental cues as threatening and manifests itself in avoidance and escape behaviors.

Other literature regards anxiety as a product of one of three causes. The first construct identifies anxiety as a result of a disruption in the avoidance of a fearful stimulus (Fadardiet al., 2016). In this case, anxiety is rooted in the inability to avoid fearful stimuli (Öhman, 2008). Overestimation is another construct of anxiety, and occurs when an individual grossly overestimates the potential for threat in situations that are ambiguous. In this case, the treat is often nonspecific. This concept is regarded in ample literature (Carlson & Mujica-Parodi, 2015; Carlson & Reinke, 2008; Fadardiet al., 2016), and stems from anxious individuals associating a benign feature of a prior dangerous experience with actual danger. The third construct occurs when one's expectations of an environment or situation do not match. In this regard, anxiety is classified as hypervigilance in the face of uncertainty (Carlson & Aday, 2018; Fox, 2002). Nonetheless, the classifications of both fear and anxiety are similar yet inherently different. Öhman (2008) suggested that fear and anxiety share similar underlying processes and are

differentiated based on perceived avoidance options. Supporting this, (Fadardi, et al., 2016), suggest that trait fearful individuals who are concerned primarily with physical threat react more strongly than healthy individuals to physically threatening stimuli. Literature supports this concept, as fearful individuals tend to not experience elevated trait anxiety as one actively avoids perceived threat whereas individuals whose trait fear is concerned primarily with social threat also show elevated levels of trait anxiety (Delchau, et al., 2019). Therefore, the relationship between trait anxiety and fear differs according to whether the fear is primarily physical or social.

Other literature identifies trait anxiety as aversive arousal in uncertain situations where avoidance does not seem possible and, in contrast, conceptualized trait fear as hypersensitivity to danger cues leading to avoidance behavior (Graham & Labar, 2012). Fischer (2008) found that trait fear (as assessed by a "Harm avoidance" scale) and trait anxiety (as assessed by a "Stress Reaction" scale) are separable and nearly orthogonal constructs in the development of the Multidimensional Personality Questionnaire (Patrick, et al., 2002). Tellegen (1985) also found that, when embodying this conceptualization of trait anxiety and fear, trait fear loads on a higher-order Constraint factor. However, trait anxiety loads on a higher-order Negative Emotionality factor (see also Watson et al., 1994). Individuals who score highly on the Constraint factor "convey caution, playfulness, a tendency to avoid danger, conventionality, and adherence to traditional values (Tellegen, 1982). Individuals who scored high on the Negative Emotionality factor, in contrast, "describe themselves as often stressed and harassed, prone to respond with strong negative emotions to everyday vicissitudes, and as enmeshed in adversarial relationships (Tellegen, 1982). These findings suggest that anxiety and fear relate to, and stem from, different etiological classifications.

Attention Bias Modification. The rationale underlying this manipulation is that the covert allocation of spatial attention to one of the two lateralized cues will result in facilitation of the response to a subsequent probe that appears at the congruent ("attended") location. Accordingly, with the neutral-threat cue pairs typically used, researchers compare response times for trials in which the probe replaces a threat cue and trials in which the probe replaces a neutral cue. Relatively faster responses to probes replacing threat cues are interpreted as an attention bias toward the threatening stimulus (Yiend et al., 2013**).**

Threat is viewed as a physiological and behavioral response to the actual or anticipated occurrence of an explicit threatening stimulus (Phan, 2015). Anxiety crucially involves uncertainty as to the expectancy of threat (Phan, 2015), and is triggered by less explicit or more generalized cues (Helbig-Lang, et al., (2014). Attentional Bias towards threat refers to the phenomenon of hyper-attention to threatening material. This simply means that a person selectively attends to a certain category or certain categories of stimuli in the environment while tending to overlook, ignore, or disregard other kinds of stimuli (Fadardi, et al., 2016). Anxious individual's tendency to excessively attend to threatening stimuli has been demonstrated in different forms of anxiety via attentional tasks (Bar-Haim et. al., 2007). Attentional bias towards threat has been slated to have a causal relationship with the development of anxiety symptoms and disorders (Eldar, et al., 2008; MacCleod et al., 2002), and is known to be a hallmark symptom of anxiety disorders (Fox, 2002; MacLeod & Mathews, 1988; Mogg & Bradley, 2002).

Literature regarding the role of cognitive models of anxiety provide ample evidence that anxious individuals show increased attentional bias to threatening stimuli, and are more likely to interpret emotionally ambiguous stimuli in a threat-related manner. It has been suggested that these cognitive biases are implicated in the maintenance, and possibly even the etiology, of

anxiety (MacLeod et. al., 2002; Matthews & MacLeod; 2002). Although it is evident that anxious individuals elicit a threat-related attention bias, the underlying mechanisms of this bias is not particularly understood (Cisler & Koster, 2010; Ouimet, Gawronski, & Dozois, 2009; Pergamin-Hight et. al., 2015).

Models of attention bias. A common disaccord surrounding literature is whether attentional bias to threatening stimuli is a top-down or bottom-up mechanism. The notion that attentional bias to threat is a bottom-up process is rooted in perspectives concerning evolution, as the main justification for this mechanism is concerned with the development of adaptive purposes for the attentional biases (Kenrick et al., 2010; LoBue et al., 2010; Mogg & Bradley, 1998; Öhman, 2007). In bottom-up processing, it is understood that selective attention to threatening stimuli plays a causal role in anxiety; thus, ample research has been done to identify potential models for this form of selective attention. Early models of attention, threat, and anxiety are centered around evolutionary perspectives concerning the adaptive necessity of the latter. Previous literature has indicated that our visual-attention system is selectively adapted to rapidly attenuate to stimuli that offer a biological significance, such as stimuli indicating a threat (i.e., a predator) as well as stimuli indicating reward and survival (i.e., food; Kenrick et al., 2010). Bottom-up processing of these stimuli is instantaneous, and is designated to triage the stimuli being presented to initiate a quick response to the threat being presented (Busse et al., 2008; Delchau et al., 2019). The operations surrounding bottom-up processing are considered automatic; that is, they are only concerned with immediate stimuli—no considerations are utilized for factors such as competing goals, individualistic intentions, or deductive reasoning.

Bottom-up processing of threat detection can be classified as simplistic, as it only attenuates to simple features (i.e., shape, color, size, movement, etc.) Because of its lack of

intricacy, one must consider the deficits that ensure when stimuli which are multidimensional are presented. “Threatening” stimuli can take ample forms, and can be specific to the individual eliciting the response; thus, providing difficulty in the attenuation to complex stimuli (O’Kearney & Goodhew, 2019). Literature shows that attentional biases elicited in the bottom-up processing of threats are induced by specific features known to be associated with generalized threatening stimuli (LoBue, 2014; LoBue et al., 2017; LoBue & Larson, 2010). For example, LoBue & Larson (2010) demonstrate that anxious individuals, when compared to non-anxious individuals, have a more rapid attenuation to downward “V” and triangle shapes—this is noted to be similar to the shape of angry eyebrows on a face (Kenrick et al., 2010), which also has been shown to elicit attentional biases in anxious individuals (O’Kearney & Goodhew. 2019). These biases draw further support for the idea that threat detection, along with attentional bias towards threat, is both automated and a result of evolutionary adaptations.

Although it has been established that bottom-up processing plays a role in attention bias to threat, recent literature has indicated that top-down processing not only modulates this process, but also, it may completely direct it. Unlike bottom-up processing which is innate and automatic, top-down processing is endogenous and is context or goal-driven. This means that this type of processing is more individualized, and is largely up to the individual to interpret the threat and react accordingly, rather than simply reacting. Top-down processing predominantly involves the role of visual perception by which predictive models are entirely constructed implementing previous experiences, along with current sensory information (Gregory, 1968; Summerfield et al., 2006). According to this model, prior experiences are constantly evolving our perception while refining both the accuracy and speed at which we react to stimuli.

Top-down processing encompasses the idea that preemptive biases impact threat detection and processing, and is consistent which current literature that shows the operation of threat detection and processing occurs prior to the encounter with the threatening stimulus (Chen & Zelinsky, 2006; Sussman et al., 2016; Wolfe et al., 2003). These biases that exist before the stimulus is even presented is of particular importance to the conceptualization and understanding of anxiety, as anxiety has been shown to be associated with the over-perturbation of potential negative occurrences (Aue & Okon-Singer, 2015; Grupe & Nitschke, 2013). This notion has been established by studies identifying that cues perceived as threatening, which occur in anxious individuals at a rate upwards of five times more than non-anxious individuals (Aue & Okon-Singer, 2015), substantially impacts rates of anxiety (Sussman, Szekely et al., 2016). Top-down processing in anxiety disorders has been indicated as having a causal role in both developing and maintaining biases in one's perception. Anticipating future negative occurrences, one of the most-common anxiety symptoms, is thought to be a direct result of over-regulation of top-down processing (Grupe & Nitschke, 2013). This over-regulation results in anxious individuals continuously scanning their environment for threats that their convoluted perception has made imminent to them—even if they are nonexistent. Thus, this over-regulation creates a perpetual loop of never-ending anxiety and biases.

Neuro-cognitive models of attention attribute difficulty regulating and allocation attention; specifically, threat-related attention, as a rationalization for attentional bias towards threat (Bishop, 2007; Eysenck et.al., 2007; Pergamin-Hight et. al., 2015). These models have elaborated on biased competition models of attention (Desimone, 1995), claiming that selective attention to threat has a causal relationship with the relative signal strength from a pre-attentive threat evaluation mechanism versus that from top-down control mechanisms (Mathews, 1998).

The ideology of attentional threat in anxiety is formed by the notion that increasing the output from the threat evaluation mechanism causes a biased attentional competition in a threat-related direction, even when conscious awareness of the threat-related stimuli(s) is not present (Bishop, 2007). Studies have shown that individuals with anxiety exhibited a poorer performance on attention control tasks involving threat-stimuli compared to non-anxious individuals (Bitton et. al., 2015; Monk, 2006). For instance, it was found that anxious individuals showed poorer performance on attention control tasks with threat stimuli relative to non-anxious individuals (Bishop, 2004; Monk et al., 2006).

Attentional bias towards threat can not only be attributed to attention itself, but also, the way the threatening memories are stored, interpreted, and judged (Bar-Haim et. al., 2007). Other models of threat processing encompass individual-specific biases in threat evaluation processes by which attention allocation to threat is impacted. These models are largely theorized around schema-driven processing based on substantiated associations to learning and memory which comprises the role of content specific aspects of attention bias. (Bar-Haim et al., 2007; Mogg and Bradley, 1998; Öhman, 1996; Pergamin-Hight et. al., 2015). These models are driven by a specific threat to an individual which are idiosyncratically relevant to that individual's anxiety. This is referred to as attention bias specificity, and is explored by testing whether disorder-congruent stimuli (e.g., socially relevant stimuli for social phobia or trauma-related stimuli for posttraumatic stress disorder) render larger threat-related attention bias than do general threat stimuli, or stimuli that are congruent with the threat content of a different anxiety disorder (i.e., disorder-incongruent stimuli; Pergamin-Hight et. al., 2015). Most studies, including the current one, compare the magnitude of threat-related attention bias of disorder-congruent and disorder-incongruent stimuli using response times in the classic visual attention task, the dot-probe task.

Neural correlates of Attention Bias in Anxiety. A hallmark symptom of anxiety is attention bias to threatening stimuli (Beck et. al., 1985), and an abundance of studies have indicated a significant relationship between attention bias and the maintenance of anxiety disorders—with similar neural mechanisms driving them. The majority of neuroimaging studies have fixated on the roles of the anterior cingulate cortex (ACC), the prefrontal cortex (PFC) and the amygdala as key regions for attention bias apparatus (Hakamata et al. 2018). Cognitive theories of attention bias, which are the most widely accepted, elucidate that biases towards perceived threatening stimuli in anxious individuals occurs by increasing the sensitivity of threat evaluation by the amygdala while coincidentally diminishing attentional control within the ACC and PFC (Bishop, 2007; Carlson, et al., 2013; Yun et al., 2017).

This notion is supported by functional magnetic resonance imaging (fMRI) studies which demonstrate an increase in activation in the amygdala and ACC and a stark increase in activation in the PFC during the presentation of threatening stimuli (Britton et. al., 2015). Britton et al. (2015) and Månsson et al. (2013) revealed increased amygdala activation to threatening stimuli in anxious individuals undergoing ABM, compared to non-anxious control groups, which did not demonstrate increased amygdala activation. Furthermore, additional studies have indicated resting-state strength in both ACC and amygdala-based functional connectivity networks to the insula and PFC have been reported to predict ABM treatment response, which increased resting-state connectivity associated with greater response to treatment (White et. al., 2017).

Previous literature implementing both fMRI measures and the dot-probe task have indicated a disarray in their findings. Britton et al. (2012), Fani et al. (2012), Monk et al. (2006, 2008), and Telzer et al. (2008) show that there are ample differences in brain regions uncovered via functional connectivity measures relating to anxiety (i.e., the amygdala, ACC, and insula)

and attention processing (ventrolateral prefrontal cortex [vlPFC], dorsolateral prefrontal cortex [dlPFC], the orbitofrontal cortex [OFC], etc.). Monk et. al., 2008 indicates that attention bias is deeply rooted within increased amygdala activation, which is associated with both anxiety and attention bias. Meta analyses concerning the matter are just as varied. Hakamata et al., 2010 asserts that attention bias, above all, is predominantly housed within the amygdala, and is demonstrated by an associated linear increase between the amygdala and levels of anxiety. However, Beard et al., 2012 states that attentional bias towards threat is primarily housed within the lateral PFC—demonstrating duplicate linear increases between functional connectivity within lateral PFC and anxiety levels. The vast array of discrepancies regarding attention bias in anxiety has brought to attention the need for further investigation into its neural correlates.

The Cerebellum. The cerebellum is a fascinating neural structure, which contains 10% of our brain's volume while accommodating about half of all of the brain's neurons (Villanueva, 2012). The cerebellum is composed of two hemispheres, which are mirror structures of each other, contain three nuclei, and are divided into several sections: Crus I, Crus II, and lobules I-X (Guell et al., 2018). The cerebellum is typically divided into two hemispheres with a midline region (the vermis) separating them. These hemispheres are further subdivided into 10 lobules. These lobules are organized into an anterior lobe (lobule I-V), a posterior lobe (lobule VI-IX), and then flocculonodular lobule (lobule X; Brissenden & Somers, 2019, see *Figure 1* for further details). Afferent fibers from the cerebral cortex reach the cerebellum via the pons and the inferior olivary nucleus (Brissenden & Somers, 2019). Efferent connections are sent to the cerebral cortex via the thalamus (Evarts & Tach, 1969).

Despite its large mass and ample neural connectivity, there is little research concerning the role of the cerebellum outside of its emblematic functioning. Typically, the cerebellum has

been established as having roles in muscle movement, coordination, balance, and spatial orientation (Guell et al., 2018). Much of what we understand about functional aspects of the cerebellum is due to findings within tasked-based neuroimaging studies. Previous literature shows that the vermis, along with lobules I-V, are responsible for facilitating motor processing (Debaere et al., 2001; Ouchi et al., 1999, 2001; Sang et al., 2012); lobules VI and VII mediate fine-motor movements (i.e., eye movements; Nagel, 2001); lobules III-V direct pain-related processing (Dimitrova et al., 2003, 2004; Maschke et al., 2002); and lobules IX-X are involved in both balance and spatial orientation (Walker et al., 2010; Yakusheva et al., 2008). Previous research efforts focused predominantly on the cerebellum's role in mortar functioning. Thus, there is little research regarding the cerebellum outside of its emblematic role.

Imaging studies repeatedly indicate significant changes in cerebellar activity of patients with anxiety disorders compared to healthy controls. Close examination of the reported data reveals significant changes in the cerebellum during resting state and anxiety-provoking tasks in anxiety disorders (Blair et al., 2018; Chen, 2011). New and converging research has identified the cerebellum as having a causal role in higher cognitive functions such as attention, working memory, associative learning, and sensory processing (Baumann & Mattingley, 2012; Dickson et al., 2017, Smet et al., 2015) and that the cerebellum has widespread functional connectivity across the brain, as seen in the default mode network (DFN), attention networks, as well as to a wide array of brain structures (i.e., the prefrontal cortex, limbic system, hippocampus, visual cortex, etc. (Lee et. al, 2020). This functional connectivity may have a direct impact on maintaining anxiety and its symptomatology.

There is converging evidence supporting the role of the cerebellum from both animal and human studies in anxiety circuity. Studies show that the cerebellum has robust connectivity to

the amygdala, insula, basal ganglia, and the ventral tegmental area, as well as other well-established brain regions for their role in anxiety (Kelly & Strick, 2003; Llinás, 1985) The role of the cerebellum is apparent, as there is cerebellar connections to cortical areas that are responsible for both perception and the anticipation of stimuli—particularly those that are perceived as fearful (Stoodley & Schmahmann, 2009)—providing further notion for the non-emblematic roles of the cerebellum in anxiety. In fact, the dentate nucleus of the cerebellum is referred to as the "limbic cerebellum" for its connectivity to the mesolimbic dopaminergic pathway which originates from the VTA (Lee et al., 2020). Dopamine is known as one of the key neuromodulators of both fear and anxiety, with literature suggesting that the mechanisms underlying this pathway are responsible for varying aspects of affective memory—most notably fearful memory formation, expression, retrieval, and extinction (Pezze & Feldon, 2004). The mesolimbic dopaminergic pathway, via the VTA, is one of the key structures that is associated with an over-activated salience network (Le, Pardo, & Hu, 1998). The projections originating from this pathway also project to the pre and postcentral gyrus, which also has been linked to aberrant cerebellar seeded functional connectivity in anxious individuals (Lee et al., 2020).

Previous studies concerned with functional connectivity in the cerebellum to areas concerned with cognition implicate that functional connectivity within the dentate nucleus of the cerebellum correlates with changes in regions such as the: the parietal cortex, the amygdala, thalamus, and hippocampus (Allen et al., 2005). Connectivity between the cerebellum and anterior cingulate cortex, a region typically associated with error detection, anticipation, attention, and emotional responses, has also been reported in other resting state studies (Yan et al., 2009). Corroborating this is evidence is other research indicating that the cerebellum contributes to the intrinsic connectivity networjks, a series of brain structures that correspond to

basic functions such as vision, audition, language, episodic memory, executive functioning, and salience detection (Habas et al., 2013). Other studies have identified that cerebellum-seeded functional connectivity is correlated with activity in the default mode network, the executive network, and the salience network, providing further evidence that the cerebellum has contributions to resting-state networks (Heath & Harper, 1974). Novel research shows us that resting state functional connectivity (rsFC) occurs between several regions within the cerebellum and the amygdala, indicating that the cerebellum has some involvement in emotional processing—specifically fear (Dickson et al., 2017). The rsFC demonstrated between the cerebellum and the amygdala indicate a possible involvement of the cerebellum in emotional memory.

Other studies have shown patterns of functional connectivity between the cerebellum across varying structures in the limbic system as well as the hippocampus (Sacchetti et al., 2005), all of which are structures responsible for producing and facilitating emotional behavior. Both prior (Reiman, 1997) and recent (Dimitrova et al., 2004) studies indicate there is a functional role of the vermis in the processing of affective and fear related emotions, such as anxiety.

Previous neuroimaging studies (see Kelly & Strick, 2003; Schmahmann et al., 2019) have focused on the plausible role of the cerebellum in anxiety disorders. These studies have indicated increased, hyperactive functional connectivity in the cerebellum when presented with angry faces, such as in the current study (Allen et al., 1997) relative to non-anxious, healthy control subjects. This is supported by rsFC studies which show increased activation within the cerebellum in anxious individuals (Kirschen et al., 2005). When compared to healthy, non-anxious individuals, those with anxiety have shown increased cerebellar-seeded functional connectivity changes to brain regions already implicated in heighted anxiety and anxiety

disorders (i.e., the limbic system and prefrontal cortical areas). For example, previous studies have shown that those clinically diagnosed with generalized anxiety disorder show enhanced connectivity from the cerebellum to the amygdala—a key brain region that has been implemented for its role in negative affective processing, and has been reported as a key region in the etiology of anxiety and anxiety disorders (Kirschen et al., 2005; Lee et al., 2020; Schmahmann, 2019).

The cerebellum has also displayed increased, aberrant connectivity within both the salience network (Lee et al., 2020; Stoodley & Schmahmann, 2009) and the default mode network (DMN; Guell et al., 2019). The salience network is housed within the insular cortex, and is known for its role in the detection and subsequent response to behaviorally and emotionally relevant stimuli (Shakiba, 2014). Aberrant connectivity within the salience network is linked to dysregulated attention allocation and affective response—such as what we see in anxious individual's attention bias towards threat (Hiler et al., 2019). The default mode network is a resting-state network that is most active when an individual is at rest. Several studies have investigated the role of increased connectivity in the DMN in the psychopathology of anxiety disorders (Kim and Yoon, 2018; Peterson et al., 2014), with other studies indicating that high trait-anxious individuals show significant increases in the connectivity within both the default mode network and the cerebellum (Modi et al., 2015). Functional connectivity increases within the cerebellum, as well as the DMN, have been found in non-clinical, high trait-anxious individuals (Guell et al., 2019; Lee et al., 2020) suggesting that the cerebellum may have a role in the predisposition of anxiety.

Attention bias, specifically to stimuli perceived as potentially threatening or fearful, is one of the hallmark symptoms of anxiety. Schmahmann and Sherman (1998) were the first to

suggest the role of the cerebellum in attention abnormalities. They described the occurrence of 'cerebellar cognitive affective syndrome' in adolescents and adults exhibiting behavior, emotion, and attention deficits. This syndrome is described as exhibiting impairments in psychopathological areas of what we now know contribute to anxiety, such as executive functions, disturbances in spatial cognition, language deficits, and personality changes (Schmahmann and Sherman, 1998). The deficits linked to these abnormalities are attributed to disruptions within neural circuits linking the cerebellum to threat and affective processing regions, such as the amygdala, limbic cortices, the thalamus, and the cingulate cortex (Lee et al., 2020). These brain regions are known for their importance in the role of attention; thus, making the close anatomical connections to the cerebellum ever relevant. Yet, there are few studies that investigate the cerebellum and both its connections to such areas and its role in attention deficits, such as attention bias. It is important to note that the cerebellum has vast connectivity to the neocortex, making its role in attention bias even more plausible.

Previous research indicates there are associations between prefrontal areas, which are critical for focused attention, and are connected to the cerebellum via the central pontine nuclei (Roš et al., 2010). These connections are modulated by ponto-cerebelar projections—with aberrant functional connectivity within this system being linked to dysregulated attention control (Salmi et al., 2010; Timmann & Daum, 2007). This notion is supported by current neuroimaging studies--showing increased functional activation of the cerebellum during attention tasks (Lee et al., 2020; Moreno-Rius, 2018; Schmahmann, 2019). Increased activity within the cerebellum has also been shown in neuroimaging studies that require shifting attention and focused attention--both of which are known to be dysregulated in anxious individuals (Lee et al., 2020; Moreno-Rius, 2018; Schmahmann, 2019).

Attention bias to fearful or threatening stimuli in anxious individuals may, in part, be modulated by specific cerebellar regions. The right cerebellum, especially lobule V, is a region that has been shown to have a preference for aversive stimuli, as indicated by hyperactivation to fearful stimuli, as compared to neutral stimuli (Lanius et al., 2018; Terpou., 2019). The observed pattern of increased activation in the cerebellum is exceedingly similar to that of the amygdala—providing support to their co-involvement and activation during adverse states Baumann & Mattingley, 2012; Eippert et al., 2007). This co-activation may be a result of amygdala activation maintaining the aversive affective state, while the cerebellum maintains attenuations to appreciate affective responding (Shutter & Van Hon, 2009; Terpou., 2019). Nonetheless, although there is a lack of literature particularly focusing on the role of the cerebellum in attention dysregulation and biases, there is enough evidence to infer that the cerebellum may play a role in modulating attention bias seen in anxious individuals.

Rationale

This study is an extension of the National Institution of Mental Health (NIMH) grant: R15MH1109051. (See *Appendix A, Appendix B, Appendix C*). The funds will be used to assess the effects of an ABM-training cell phone application, elicited via an altered version of the dot-probe task. Previous research has identified structural changes in ACC grey matter following ABM treatment (Hakamata et al., 2010). Previous studies have implemented the use of MRI scans to assess structural changes in the brain following treatment; however, previous studies have not addressed the use of fMRI following ABM treatment in anxious individuals, as well as assess the functional role of the cerebellum in anxiety and its symptomatology. fMRI scans work by detecting the changes in blood oxygenation and flow that occur in response to neural activity – when a brain area is more active it consumes more oxygen and to meet this increased demand

blood flow increases to the active area. fMRI can be used to produce activation maps showing which parts of the brain are involved in a neurological process. New and converging research has identified the cerebellum as having a causal role in higher cognitive functions such as attention, working memory, associative learning, and sensory processing (Baumann & Mattingley, 2012; Dickson et al., 2017; Smet et al., 2015) and that the cerebellum has widespread functional connectivity across the brain. This functional connectivity may have a direct impact on maintaining anxiety and its symptomatology.

Methods

Participants

Participants were recruited through advertisements across the NMU campus and Marquette community. The current study is an extension of the project NIMH R15MH110905; thus, participants were subject to the same inclusion criteria. Participants had to be between the ages of 18-42, be right-handed (not ambidextrous), and have normal and/or corrected to normal vision. Participants had to have a trait anxiety score of 40 or more (STAI-T) as well as an attention bias score of 7 ms or greater (measured by the dot-probe task). Participants were excluded if they had any known neurological disorders, a recent head injury or loss of consciousness (6 months or less), were currently or had recently taken any psychoactive medications, or if they were currently seeking counseling/therapy. Due to the MRI portion of this study, participants were also excluded if they did not meet the criteria to undergo an MRI. One-hundred-and-one (102) men and women between the ages of 18-38 (M = 21.83, SD = 4.82) were recruited to partake in this study. Participants were chosen at random to be placed either in the control group (N=32) or the experimental group (N=56). Sixty-one (61) participants were not included in the final results due to attrition from the study (N=18), excessive motion or missing

50% or more of either their sMRI or fMRI (N=10), and missing data due to quarantine as a response to the COVID-19 pandemic (*N*=33). This left the current study with 41 participants (control group *N*= 23; experimental group *N*=18) included for data analyses.

General Procedure

Participants that met inclusion criteria (see *Appendix D and Appendix E,* for a full list of inclusion and exclusion criteria) underwent a fMRI scan and then immediately began six weeks of at-home ABM (or control) training. Following their six weeks of training, participants underwent another fMRI scan followed by a post-screening implementing the same measures as their initial screening. If participants did not meet the inclusion criteria, their participation ended following the screening, and they were compensated $10. Participants meeting inclusion criteria were compensated $65 following the completion of their initial fMRI, 6-week app training, and post-fMRI (see *Appendix F* for full protocol of the screening; *Appendix G* for the consent form).

Screening

The screening was performed on a 60 Hz 16” LCD c Dell 570L computer within the CABIN laboratory. The screening process consisted of the dot-probe task followed by three self-report measures—the State Trait Anxiety Inventory (STAI), the Depression and Stress Scale (DASS), the Cognitive Emotion Regulation Questionnaire (CERQ). Participants were required to have an AB incongruent - congruent score of 7 ms or greater on the dot-probe task as well as a trait anxiety score (STAI-T) of 40 or greater to be eligible for inclusion in the current study.

Questionnaires

*State-Trait Anxiety Inventory***.** The Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, et al., 1970) consists of two, 20-item scales and is implemented to assess both state and trait anxiety. The STAI utilizes a 4-point Likert scale, with 1 equating to “almost never” and

4 equating to “almost always”. This scale asks participants how much the question applies to them generally (trait anxiety) and how much it applies to them in the current moment (state anxiety). The STAI evaluates both short-term and long-term feelings of apprehension, tension, nervousness, and worry—with scores increasing in response to physical danger and psychological stress. A STAI score of 39 indicates clinically significant levels of anxiety (Julian, 2011)

Depression Anxiety Stress Scale. The Depression Anxiety Stress Scale (DASS) is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress. The DASS was constructed not merely as another set of scales to measure conventionally defined emotional states, but to further the process of defining, understanding, and measuring the ubiquitous and clinically significant emotional states usually described as depression, anxiety and stress. Each of the three DASS scales contains a total of 42 items, divided into subscales of 2-5 items with similar content. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The Stress scale is sensitive to levels of chronic non-specific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive and impatient. Subjects are asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state over the past week. Scores for Depression, Anxiety and Stress are calculated by summing the scores for the relevant items (Lovibond & Lovinbond, 1995; Parkinty & Mcauley, 2010).

Cognitive Emotion Regulation Questionnaire. The Cognitive Emotion Regulation Questionnaire (CERQ) is a 36-item self-report measure questionnaire that was designed to

identify nine different cognitive and emotion regulating strategies (i.e., coping strategies) one implements following the elicitation of a negative event. The CERQ is unique, as rather than differentiating the differences between one's thoughts and actions, this questionnaire is entirely focused on one's thoughts following a negative event. The CERQ utilizes nine different emotion regulation strategies: self-blame, other-blame, rumination or focus on thought, catastrophizing, putting into perspective, positive refocusing, positive reappraisal, and acceptance. Self-blame refers to implementing blame on oneself for experiences and situations out of their control. Rumination is describing the thoughts and feelings elicited by negative events. Catastrophizing is when ones thoughts are focused, or emphasized, on the negative feelings arising from experiences. Putting into perspective refers to the occurrence of dismissing the seriousness of an event relative to a prior event that occurred. Positive refocusing is when someone is able to shift his or her focus from thinking about a negative event to thinking about a positive one. Positive reappraisal is when one is able to identify positive meaning to an event to aid in his or her personal growth. Acceptance refers to accepting an experience for what it really is, along with the outcomes of this experience. Refocus is when one thinks about the proper way to handle a negative event (for a more elaborated explanation of the way the particular dimensions were chosen, see Garnefski et al., 2001; Garnefski, van den Kommer et al., 2002, Garnefski, Kraaij et al., 2002).

Dot Probe Task. The dot-probe task was implemented utilizing E-Prime 2.0 presentation software (Psychology Software Tools, Sharpsburg, PA). Responses were recorded via a button press on a Chronos response box (Psychology Software Tools, Sharpsburg, PA). Stimuli for the task utilized grayscale faces: 20 fearful and neutral, with 10 different actors from two databases—faces were half male, half female (Gur et al., 2002; Lundqvist, et al, 1998). Fearful

and neutral face stimuli were from actors: 207, 208, 213, and 217 (Gur et al., 2002) as well as AF14, AF19, AF22, AM10, AM22, AM34 (Lundqvist, et al, 1998). This task employed five blocks consisting of 90 trials in each block—for a total of 450 trials. Each block consisted of three different stimuli trials: incongruent trials, congruent trials, and neutral-same trials. During incongruent trials, the stimuli were always neutral-fearful paired, and the dot always appeared behind the neutral face.

During congruent trials, there was a neutral-fearful stimulus pairing, with the dot always appearing behind the fearful face. During neutral-same trials, the stimulus pairings were always neutral-neutral, with the dot appearing behind the neutral face. During incongruent trials, there was a neutral-fearful stimulus pairing, with the dot always appearing behind the neutral face. During each trial, a black screen with white fixation cue (+) at the center was displayed for 1000ms. This was then immediately followed by one of the three latter stimulus pairings. This stimulus appeared for 200ms, and was presented horizontally to the fixation cue. Following the stimulus presentation, a dot would appear behind one of the faces (dependent on the trial and stimulus pairing). This dot remained in place until the participant responded by indicating which side the dot was on via the use of the Chronos box. Participants were instituted to respond as quickly and as accurately as possible. An intertrial interval of 1000ms occurred following the participant's response (see *Figure 2*).

Attention Bias Modification Training. The only difference between the dot-probe task and ABM training is the frequency of congruent vs incongruent trials (see figure 2). Similar to the dot-probe task, each trial starts with a white fixation cue (+) centered on a black background. Two valanced stimuli (face or words) are then simultaneously presented to the left and right of fixation. Unlike the dot-probe task, however, ABM sessions only contain incongruent trials (i.e.,

target-dot – neutral stimulus 100% pairing). The rationale is that through repeated training, attention is implicitly reprogrammed to prioritize the neutral stimulus over the threat-related stimulus (i.e., due to the location of the task-relevant target dot). The app training featured both face and word stimuli and increased in difficulty as the training progressed. The words utilized for the training were implemented via the Affective Norms for English Words (ANEW) dataset (Bradley & Lang, 1999). Words within the ANEW dataset are classified via their valence and arousal into neural and fearful word pairs (30 pairs total). These pairings were based on frequency and length (Bradley & Lang, 1999).

Responses were recorded using touch screen technology on participant's cellphones. Participants performed a total of 36 training sessions (each session will contain 200 trials) over the course of six weeks (7200 total training trials) with each week containing six training sessions (no more than three in a single day). Prior to the start of the trial, a black screen appeared and instructed participants to set their phone to 'do not disturb', to turn their brightness to the highest level, and to find a distraction-free environment (see *Appendix H* for full instructions provided to participants at the beginning of the app training). Once the participants confirmed they had done the latter, they were issued a ten-item PANAS questionnaire utilizing the Likert scale, as previously mentioned. Following the completion of this questionnaire, the participants were presented with 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." Once the participants confirmed they had read the instructions, they were then presented with the instructions to complete their task "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!" Following these instructions, the training session began. Control groups partook in an

equal number of congruent and incongruent trials, whereas the ABM treatment group received only incongruent trials (see *Figure 3*). Participants were excluded from further participation in the study if they fell behind in their sessions by more than seven days.

Analysis

Behavioral Data Analysis

Trials that had an incorrect response and/or trials that had a RT < 150 ms or > 750 ms were excluded from 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. 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.

fMRI Acquisition and Analysis

Functional MRI data were collected with a 1.5 Tesla General Electric whole-body scanner within 1 week following the behavioral session. Two-hundred and forty functional volumes were collected in a 10-minute resting state scanning protocol using the following T2* weighted gradient echo pulse sequence: TR = 2500 ms, TE = 35 ms, flip angle = 90°, FOV = 220, matrix = 64 × 64, voxel size = 3.4 mm × 3.4 mm, slice thickness = 5 mm; see Appendix I for all fMRI parameters. In addition, high-resolution 3D Fast Spoiled Gradient Echo (FSPGR) T1-weighted structural images were obtained using the following sequence: TR = 5.6 ms, TE = 2.1 ms, TI = 450 ms, flip angle = 9°, FOV = 250, matrix =256 × 256, voxel size = 0.98 × 0.98 × 1.2 mm.

Resting-state fMRI scans were preprocessed by the functional connectivity toolbox in CONN via MATLAB (Math Works, Natick, MA). First, images were realigned to correct for head movement. Next, images were re-sliced to match the timing sequence of the first image. This subject motion was both calculated and removed via CONN's artifact detection (subject-motion threshold = 0.2 mm, global-signal z-value threshold = 5). Images were normalized to MNI space and smoothed with an 8-mm FWHM Gaussian kernel. First-level general linear model (GLM) analyses were conducted utilizing Pearson correlation coefficients for the following the time course for the seed region and the time course for all voxels across each participant's brain. Following the latter, scans were then Fisher transformed to z-scored for second-level analyses. The current study implemented cerebellar regions implicated in rsFC analyses as seeds in CONN. The results were coded to have an initial threshold at $p < .001$ (uncorrected) with a minimum cluster size of 20 voxels and then subjected to family wise error rate (FWE) correction $p < .05$ at the cluster level.

Analytic Plan

Hypothesis 1: Heightened levels of trait anxiety will be associated with significant, widespread cerebellar functional connectivity within regions and networks previously implicated in both motor and cognitive processing involved in various resting-state networks linked to the cerebellum. Heightened levels of trait anxiety will be associated with widespread cerebellar functional connectivity with regions previously implicated in both motor and cognitive processing involved in various resting-state networks linked to the cerebellum. This was assessed utilizing cerebellar seed regions of interest (ROIs) and functional connectivity analyses identified within the CONN software. The current study anticipated to see a main effect regarding functional connectivity; that is, there will be functional connectivity observed between

cerebellar cognitive regions (cerebellar vermis and Crus I and II), cerebellar non-cognitive regions (hemispheric areas VI, VIIb, and VIII) , threat processing regions (i.e., the limbic system; the ACC) emotion processing regions (i.e., the insula, thalamus, caudate, and cingulate gyrus) as well as within functional networks (i.e., the default mode network, the salience network, the frontoparietal network). The current study anticipated these associations would be greater in individuals with higher levels of trait anxiety.

Hypothesis 2: Functional connectivity between the cerebellum and threat/emotion processing regions (i.e., amygdala, insula, thalamus, cingulate gyrus) will decrease in the ABM training condition following their training. The current study anticipated that functional connectivity between the latter regions and networks will decrease in the ABM training group following the completion of their training.

Results

Effects of ABM on Behavioral Measures

A 2 × 2 mixed factors analysis of variance (ANOVA) was conducted to assess the impact of training session (pre vs post) and training group (ABM training vs control) on attention bias. There was a main effect of training session, $F(1, 39) = 20.49$, $p < .001$, $\eta_p^2 = .35$. Compared to pre-attention bias (M=17.20, SD=11.48), there was a decrease in attention bias scores following training (M = 6.75, SD = 8.86). There was no interaction effect of the training group $F(1, 39) = 0.95$, $p = .38$, $\eta_p^2 = .02$, as attention bias scores decreased for both the ABM group (Pre: M = 15.24, SD = 10.28; Post: M = 7.24, SD = 10.23) and the control group (Pre: M = 18.73, SD = 12.34; Post: M = 6.37, SD = 7.85; see *Figure 4*).

A 2 x 2 mixed-factors ANOVA was conducted to assess to assess the effect of training type on trait anxiety. No main effect of training session was observed $F(1, 39) = 0.11$, $p = .92$, η_p^2

= .000. There was no training session × group interaction, $F(1, 39) = 0.06$, $p = .85$, $\eta_p^2 = .001$, see *Figure 5*.

Hypothesis One: Heightened Levels of Trait Anxiety Will Be Associated with Significant Cerebellar Functional Connectivity to Threat-Processing Regions and Networks.

Seed-to-voxel analysis were implemented for analysis of hypothesis 1 ($N = 41$ participants; 18 ABM vs. 23 control). No associations were significant for cerebellar seeds at $p_{FWE} < .05$. Heightened levels of trait anxiety correlated with increased connectivity between the cerebellar vermis (Ver45; xyz = 6, 14, 32) and both the ACC (xyz = 42, -02, 40), $t(39) = 6.14$, $p < .001$, $k = 21$, and the right insular cortex (xyz = 40, -02, 40), $t(39) = 6.14$, $p < .001$, $k = 21$. Heightened trait anxiety was also linked to increased connectivity from the right cerebellum (Cereb3; xyz = 24, -82, 40) to the right insula (xyz = -34, 18, 4), $t(39) = 6.36$, $p < .001$, $k = 21$. Increased connectivity was also noted between the right cerebellum (Cereb3; xyz = 12, -35, -19) and the lateral occipital cortex (LOC; xyz = 52, -70, -02), $t(39) = 5.93$, $p < .001$, $k = 33$, as well as the lateral thalamus (Cereb10; xyz= -56, 32, 10), $t(39) = 5,07$, $p < .001$, $k = 28$. Heightened levels of trait anxiety also correlated with increased connectivity between the right cerebellum (Cereb8; xyz= 24, -82, 40) and the right insula via the salience network (xyz= 24, -56, -46), $t(39) = 5.93$, $p < .001$, $k = 21$). See *Figure 6* for rsFC associated with trait anxiety; see *Table 1* for further results.

Hypothesis Two: Functional Connectivity Between the Cerebellum and Threat/Emotion Processing Regions Will Decrease in the ABM Training Condition Following Training.

No associations were significant for cerebellar seeds at $p_{FWE} < .05$. Relative to control, ABM training resulted in decreased connectivity between the crus II (xyz=25 −75 −40) and the ACC (xyz= 06, -8, 30), $t(39) = 6.59$, $p < .001$, $k = 27$, as well as the posterior cingulate gyrus

(xyz = -04, -42, 02), $t(39) = 4.74$, $p < .001$, $k = 20$. In the training group, decreased connectivity in the vermis (Ver45; xyz = 1, -52, -7) was associated with decreased connectivity within the posterior cingulate cortex (PCC; xyz = 04, -60, 24), $t(39) = 5.86$, $p <. 001$, $k = 34$. The vermis, in the training group, was also associated with decreased connectivity to several other threat and emotion processing regions. The vermis (Ver6; xyz = 4, 44, 10) was associated with decreased connectivity to the right amygdala (xyz = 60, -58, 16), $t(39) = 4.80$, $p <.001$, $k = 26$. Decreased connectivity was also observed between the vermis (Ver45; xyz = 6, 14, 32) and the left parahippocampal gyrus (xyz= 36, -36, -10), $t(39) = 5.89$, $p <.001$, $k = 34$; the vermis (Ver9; xyz = 20, 0, 72; xyz = 18, -32, 30) and the left hippocampus (xyz = 28, -62, 64; xyz = -46, -74, 24), $t(39) = 5.70$, $p <.001$, $k = 29$; $t(39) = 5.56$, $p <.001$, $k = 25$; as well as the vermis (Ver6; Ver8; xyz = 1, -66,-16; xyz =11, -45, -76) and the right angular gyrus (xyz = 46, -62, 42), $t(39) = 4.97$, $p <.001$, $k = 26$; $t(39) = 4.58$, $p<.001$, $k = 21$.

ABM training also resulted in decreased connectivity between the left cerebellum (Cereb8 & Cereb10; xyz = 25, -56, -49; xyz = 26, -34, -41) and the thalamus (xyz = -16, -58, -30), $t(39) = 5.22$, $p <.001$, $k = 24$; (xyz =00, -02, -04), $t(39) = 5.86$, $p <.001$, $k = 27$. Decreased connectivity from the right cerebellum (Cereb10; xyz = 26, -34, -4) was also associated with decreased connectivity to the thalamus (xyz = -14, -05, -12), $t(39) = 5.86$, $p <.001$, $k = 27$. Decreased connectivity between the left cerebellum (Cereb3, Cereb7b Cereb8, & Cereb10) was correlated to decreased connectivity within varying threat and emotion processing regions (i.e., the ACC and postcentral gyrus; see *Table 2* for further results).

Lastly, cerebellar-seeded decreases in connectivity were noted between varying regions of the right cerebellum and threat/emotion processing regions, such as the thalamus (xyz= -16, -58. 64), $t(39) = 5.22$, $p <.001$, $k = 24$ and the ACC (xyz = -34, -58, 64), $t(39) = 4.80$, $p <.001$, $k =$

24 (*Table 2*). Decreases in connectivity within cerebellar-seeded regions were also observed across varying resting-state networks—most notably to hubs within the salience network and the default mode network (DMN). Connectivity between the left cerebellum (Cereb8; xyz=25, -56, -49) and the insula in the salience network (xyz = 32, -46, 36), $t(39) = 5.45$, $p <. 001$, $k = 31$, decreased in the ABM group. rsFC seeded in Crus I (xyz= 36, -10, 54) was also associated with decreased connectivity within the salience network (rooted in the left anterior insula; xyz = 34, -54, -34), $t(39) = 6.12$, $p <.001$, $k= 20$. rsFC between both the Crus I (xyz = 54, 06, -04), $t(39) = 5.84$, $p <.001$, $k = 27$, and the crus II (xyz = -02, -48, -42), $t(39) = 4,82$, $p <.001$, $k = 21$ was associated with decreased connectivity within the DMN (rooted in the posterior cingulate cortex and the lateral parietal region; see *Table 2* for further results).

It is important to note, that although not considered a threat or emotion processing region or network, the lateral occipital cortex (LOC) had noticeable interactions to the right cerebellum in the present study's sample. Relative to the control group, connections to the LOC decreased following ABM training from several cerebellar-seeded regions—most noticeably between the crus II (xyz = 48, -62, 04), $t(39)= 4.83$, $p <.005$, $k = 20$, the right cerebellum (xyz = -34, -58, 64), $t(39) = 4.80$, $p<.001$, $k = 24$, and the vermis (xyz = 28, -62, 64), $t(39)= 5.70$, $p<.005$, $k= 29$ (see *Table 2* for further results). No associations were significant for cerebellar seeds to the LOC at $p_{FWE} < .05$.

Discussion

Measures of Trait-Anxiety and Attention Bias Pre and Post Training

The aim of the current study was to provide further insight into the role of the cerebellum in anxiety while utilizing its functional connectivity patterns as an outcome-measure in attention bias modification training. The findings provide evidence that rsFC increases within the

cerebellum may be associated with, or may play a role in, the etiology of anxiety disorders. Both ABM and control training did not lead to an overall decrease in anxiety. This is inconsistent with previous literature, which shows that ABM is effective (compared to control groups) at reducing trait-anxiety (i.e., Kraft et al., 2019; Mogg, et al., 2017). Teng et al. (2019) demonstrated that ABM and control training resulted in the reduction of anxiety symptomatology. Cognitive theories concerning anxiety state that attention bias towards negative stimuli is associated with the onset and maintenance of anxiety (Disner et al. 2011; Lazarov et al., 2018). Previous studies are consistent with this concept, finding that ABM therapy modifies anxiety and reduces the severity of symptomatology among individuals with heightened levels of anxiety (Wells & Beevers, 2010; Yang et al. 2015) as well as with patients with diagnosed anxiety disorders (Browning et al. 2012).

Criticism of utilizing the STAI to assess trait anxiety have been noted, with some researchers claiming that the STAI actually assesses more depression-based symptomatology than that of anxiety (Beck et al., 1998; Knowles & Olatunji, 2020). In fact, ABM has also been shown to decrease depressive symptoms (Browning et al., 2012; Julian, 2011). Knowles & Olatunji (2020) conducted a meta-analysis to assess the STAI and how effective it is to evaluate levels of anxiety. Their results from 388 published studies indicate that depressed individuals have higher STAI-T scores than anxious individuals, anxiety and depressive symptoms are both significantly correlated with STAI-T scores, the STAI-T does not appear to specifically measure trait anxiety, and the STAI-T should be considered a nonspecific measure of negative affectivity Knowles & Olatunji (2020). Further studies should implement differing measures (i.e., the Worry Domains Questionnaire; WDQ or the Penn State Worry Questionnaire; PSWQ, see

Meyer, Miller, Metzger, & Borkovec, 1990; Tallis, et al., 1994) to explicitly assess anxiety symptomatology.

Both ABM and control training led to decreases in attention bias scores. The current study's findings may be attributed to the desired outcomes of both control training and ABM training. Previous studies (Kuckertz & Amir, 2015; Kuckertzet al., 2019; Mogg & Bradley, 2018) have shown that both ABM and control conditions resulted in reductions in attention bias. It has been noted by the authors of these studies that varying aspects of the training were not made clear to their participants (i.e., no understanding of control training mechanism vs ABM training mechanisms)—as did the current study. It can be argued that an observed effect in both training and control groups is a result of the outcomes of both control and ABM training.

The aim of ABM training is to reduce attention bias to threat, a key trait noted in anxiety disorders; thus, decreasing overall levels of anxiety. The control training in the current study was a version of the dot-probe measure. The dot-probe paradigm was originally designed to assess selective attention towards threat (MacLeod et al, 1986), but utilizing it for training has been shown to have generalized outcomes in increases in top-down control to threat, as inhibited top-down control has been associated with anxiety disorders (Sussman, et al., 2016). The two similar outcomes of these types of training may be as a result of differing neurocognitive mechanisms implemented by both trainings in which a similar outcome is observed. Britton et al. (2015) and Kuckertz et al. (2014) argue that similar training outcomes in both ABM and control groups is a result of the similar cognitive loads they implement, in which resulting implicit learning occurs--even in the absence of explicit learning outcomes (Mogg & Bradley, 2016). This suggests that engaging implicit systems may elicit anxiety, and that anxiety may be a result of poor regulation of implicit association and learning.

It is important to note that mechanisms underlying the changes in attention bias prior to and following training is hard to assess, as all of the mechanisms underlying it co-occur. It is unknown to the extent in which both ABM and control training influence other mechanisms underlying anxiety (i.e., attentional control and allocation); because of this, the observed attention bias reduction may be a result of increased attentional control and allocation (rather than being a result of anxiety reduction). The current study supports this notion, as a decrease in trait-anxiety was not observed—but a decrease in attention bias was observed. Attention control is the ability to use cognitive resources selectively to inhibit the processing of certain stimuli (Najmi et al., 2015). Impairments in attentional control have demonstrated effects of poor emotion regulation Gross & Barrett, 2011; Rothbart et al., 2004).

Previous literature indicates that poor regulation of emotional control results in attention bias towards threat (Rothbart, et al., 2004). For example, anxious individuals tend to divert most of their attention towards stimuli they perceive as threatening stimuli. These threatening stimuli compete for attentional resources with non-threatening information—by either attending preferentially to threatening information (Rothbartet al., 2004). This lack of attentional control away from stimuli perceived as threatening has a direct effect on anxiety and its symptomatology (Najmi et al., 2015; Reinholdt-Dunne et al., 2012). This notion implies that increased ability to regulate attentional control may allow one to inhibit the involuntary attention to threat (Derryberry & Reed, 2002; Reinholdt-Dunne, et al., 2012). Further studies should assess changes in attention bias in terms of both changes in anxiety and changes in attentional control. It is important to note that the similar effects seen in both groups could, in part, be due a regression to the mean effect.

Hypothesis One: Heightened Levels of Trait Anxiety Will Be Associated with Cerebellar Functional Connectivity to Threat-Processing Regions and Networks.

Resting state functional connectivity (rsFC) refers to the measurement of the temporal correlation of spontaneous blood oxygenation level dependent (BOLD) signals arising from brain structures and regions, with the assumption that the BOLD signals arising from these structures and regions correlate with neural activity (Woodward & Cascio, 2015). This simply means that brain structures or regions with functional connectivity while at rest are thought to contribute to certain cognitive processes (Decoet al., 2011). Statistically significant widespread connectivity seeded within the cerebellum associated with heightened levels of trait anxiety was no overly apparent. However, an array of resting-state connections between the cerebellum and threat-processing regions in high trait-anxious individuals were observed (see *Figure 6* & *Table 1* for rsFC results).

Associations between the cerebellum and right precentral gyrus, ACC, thalamus, and insular cortex were noted. The cerebellum has been shown to have roles in the neurocognitive mechanism pertaining to anxiety disorders, while also previously showing connectivity to threat and emotion processing regions known to be associated with anxiety disorders (Hilber et al., 2019; Lee, et al., 2020). The precentral gyrus, ACC, and the insular cortex are structures that have been well-established as having roles in the development, maintenance, and etiology of anxiety and its related disorders (Robinson et al., 2019; Xu et al., 2019), and meta-analyses have shown that abnormal functional connectivity between these structures is associated with dysregulated emotion regulation, emotional expression, attention allocation, and anxiety-induced physiological reactions (Shang et al., 2014), which are factors that are thought to contribute to the onset of anxiety disorders.

Tovote, et al. (2015) found that stimulation of the vermis elicited varying complex patterns of attention-to-threat behavior, heightened stress and anxiety, as well as increased connectivity from the vermis to the ACC and the insular cortex—indicating that increased connectivity between these structures may, in part, have a causal role in the development of anxiety and its symptomatology. Similar to the current study, research indicates that heightened connectivity between the cerebellar vermis and the ACC and the insula in individuals with generalized anxiety disorder is linked to abnormal fear processing, heightened trait-anxiety, and attention bias (Roy et al., 2013; Sacchetti, Sacco & Strata, 2005; Sacchetti, Sacco & Strata, 2007). This suggests that increased rsFC connectivity within the cerebellar vermis correlated with dysregulated rsFC connectivity within the ACC and insula—thus, plausibly contributing to anxiety disorders. Ample research has unveiled the potential role of the precentral gyrus in anxiety disorders. Yet, there is some dispute as to whether hypoactivity or hyperactivity within this structure correlates with anxiety (Boshuisen et al., 2002; Kitls et al., 2006; Li et al., 2019; Picó-Pérez et al., 2017).

Trait-Anxiety and Increased Cerebellum-Thalamus rsFC

The current study found connectivity from the right cerebellum, which is responsible for both motor and cognitive functioning (Lee et al., 2020; Moreno-Rius, 2018), to the lateral thalamus. The lateral thalamus has been associated with negative reactions to visual threats, and has been attributed to heightened levels of trait anxiety (Salayet al., 2018). The dentate nuclei directly project to the thalamus—allowing for streamlined connectivity between the cerebellum and the thalamus (Lee et al., 2020; Middleton & Strick, 1994). Previous meta-analyses have indicated that functional connectivity between the cerebellum and the thalamus may contribute to

anxiety etiology (Chavanne & Robinson, 2021; Leicht & Mulert, 2020; Pergamin-Hight et al., 2015)—with the current results supporting this prior work.

The thalamus has ample projections to various brain regions via their nuclei (including the anterior nucleus, the mediodorsal nucleus, and the pulvinar nucleus; Asami et al., 2018). The thalamus has shared connection with both the amygdala and the medial prefrontal cortex, both of which appear to have a are linked to the development of anxiety (Gorman, 2000; Ironside et al., 2019). Although the thalamus has literature regarding its role in the development of anxiety and anxiety disorders, the cerebellum does not. Given the vast rsFC between the thalamus and cerebellum in anxious individuals (Lee et al., 2020; Moreno-Ruis, 2018; Phillips et al., 2015), as well as support arising from the results of the current study, it is apparent that the cerebellum may have contributions to the etiology of anxiety. The decrease in rsFC from the cerebellum to the thalamus following ABM training supports the notion that the cerebellum may be a relay station for areas, such as the thalamus, that contribute to anxiety disorders. The current finding provides further precedent for the role of the cerebellum in anxiety.

Trait-Anxiety and Increased Cerebellum-Inferior Frontal Gyrus rsFC

New research shows that trait-anxiety is linked to the right inferior frontal gyrus (IFG)—specifically when selectively trying to reallocate attention away from threatening stimuli (Shadli et al., 2020). A meta-analysis conducted by Chavanne & Robinson (2021) demonstrates increased connections between the cerebellum and the inferior frontal gyrus in individuals with clinical anxiety, as well as recruitment of the inferior frontal gyrus and cerebellum in allocation of attention towards threat. Li et al. (2020) found that the functional connectivity between the right cerebellum (cereb 8) and the left inferior frontal gyrus was related to levels of trait anxiety. The rsFC noted in previous literature, as well as the rsFC in the current study, provide further

corroboration regarding the role of the cerebellum as a "hub" for connections to regions well established as having a causal role in the etiology of anxiety. Other studies indicate that aberrant functional connectivity between the cerebellum and the inferior frontal gyrus has a direct relationship with dysregulated attention control and increased inhibitions of top-down control—both of which are known factors of anxiety and attention bias (Brissenden et al., 2016; Liew et al., 2018; Schmahmann, 2019).

The findings in the current study may demonstrate the role of the cerebellum in threat perception—particularly allocating resources within the brain to determine how much attention is being granted to threatening vs non-threatening stimuli. Disruptions of allocation of attention to threatening stimuli, also known as attention bias to threat, is a hallmark symptom of anxiety (Britton et al., 2014; Hakamata et al., 2010). Thus, the rsFC observed between the cerebellum and the right inferior frontal gyrus further contribute to the notion that rsFC seeded within the cerebellum may contribute to anxiety.

Trait-Anxiety and Increased Cerebellum-Insula rsFC

An individual's perceived control over negative events has been thought of as important to the psychopathology of certain cognitive schemas that are linked to experience emotion, such as fear (Rapee et al., 1996), and is thought to be a mediator between high trait-anxiety and over-activation of certain enroll processing of emotionally aversive events and stimuli (Strigo, Matthews, & Simmons, 2013). Previous functional neuroimaging studies utilizing non-clinically diagnosed, high-trait anxious individuals (such as in the current study) suggest that insular cortex hyper activation is correlated with the anticipation of potentially aversive events and stimuli, including negatively valence pictures (Andrzejewski, Greenberg, & Carlson, 2019; Nitschke et al., 2006; Simmons et al., 2004). Although these same previous studies suggest that increased

activation to the insula is involved in the anticipation surrounding anxiety, more specific studies suggest that weighted insular activation occurs during the anticipation of unpredictable, adverse events (Carlsson et al., 2006; Shankman et al., 2016). These findings suggest that the insula has a critical role in the anticipation of aversive events—most notably, this is supported by evidence of hyperactive insular activation in individuals with both anxiety and dysregulated moods and attention (Avery et al., 2014; Paulus & Stein, 2010; Shin & Liberzon, 2010).

Trait-Anxiety and Increased Cerebellum-ACC rsFC

The ACC has been shown to be involved in monitoring and resolving emotional conflicts—particularly those conflicts related to threat and fear (Kim et al., 2016). Given its direct anatomical associations to the amygdala and higher cortical areas, it is no surprise that the ACC may have a role in modulating response to negative events (Etkin et al., 2006). Previous studies show that high trait anxious individuals display heightened functional connectivity with the ACC and ACC networks (Carlson et al., 2012; Carlson & Reinke, 2010). This hyperconnectivity has been associated with dysregulated prioritization of visual processing and localization to potential threat— resulting in hyperactive attention to irrelevant stimuli (Carlson & Reinke, 2010). ACC hyperactivation has been associated with predisposition of individuals to focus their attention to stimuli they perceive as threatening, even when no threat is present (Carlson, et al., 2013; Greenberg et al., 2012).

Tovote et al. (2015) found that stimulation of the vermis elicited varying complex patterns of attention-to-threat behavior, heightened stress and anxiety, as well as increased connectivity from the vermis to the ACC and the insular cortex—indicating that increased connectivity between these structures may, in part, have a causal role in the development of anxiety and its symptomatology. Similar to the current study, research indicates that heightened

connectivity in vermis-based ACC-cerebellar networks and vermis-based insula-cerebellar networks in individuals with generalized anxiety disorder is linked to abnormal fear processing, heightened trait-anxiety, and attention bias (Roy et al., 2013; Sacchetti, et al., 2005; Sacchetti, et al., 2007). This suggests that heightened rsFC connectivity seeded in the cerebellar vermis impacts rsFC connectivity within the ACC and insula—thus, plausibly contributing to anxiety disorders.

Trait-Anxiety and Increased Cerebellum-Precentral Gyrus rsFC

Ample research has unveiled the potential role of the precentral gyrus in anxiety disorders—yet there is some dispute as to whether hypoactivity or hyperactivity within this structure correlates with anxiety, as there are studies supporting sides to this notion. Boshuisen et al., 2002; Kitls et al., 2006; Li et al., 2019; Picó-Pérez et al., 2017). The precentral gyrus is mainly a motor region that is related to body movement (Li et al., 2019). Nonetheless, similar to the role of the cerebellum, little research has been conducted to assess its role in cognition and psychological disorders. There has been miniscule investigation into the functional connectivity between the precentral gyrus and the cerebellum: specifically, the role of this connectivity in terms of anxiety or attention bias to threat. This connectivity may play a role in biasing defensive anxiety-related behaviors. Hadj-Bouziane et al. (2008) uncovered evidence for the role of the precentral gyrus in emotional regulation—specifically when it comes to fear. Pagliaccio et al. (2015) uncovered increased connectivity between the postcentral gyrus, the ACC, and the amygdala in non-anxious individuals, indicating the possibility of greater emotion regulation. Picó-Pérez et al. (2017) found that individuals with clinically diagnosed anxiety had increased activations and connectivity between other cortical regions such as the precentral gyrus, the cerebellar vermis and the left anterior insula.

Individuals with anxiety have been shown to elicit increased activation of the precentral gyrus, as compared to non-anxious individuals (Makovac et al., 2016). This hyperactivation has been linked to dysregulated top-down control of attentional focus (Hopfinger et al., 2000). Previous research shows that increased trait anxiety is correlated with increased activation of the precentral gyrus, which in turn, increases activation in the left cerebellar gyrus (Geng et al., 2018; Li et al., 2019). Given these findings, it is plausible that hyperactivation in such regions is associated with attentional deficits that are linked to excessive worry, which is what we observe in individuals with anxiety Eysenck et al., 2007).

The current findings, coupled with previous investigations into rsFC connectivity between the cerebellum and precentral gyrus, may indicate that dysfunctional connectivity between these two structures may have a causal relationship with the lack of cognitive control and negative-emotion regulation seen in anxiety disorders. Abnormal hypoactivation or hyperactivation between these two structures may result in disrupted connectivity between other, more notable regions responsible for anxiety and attention bias (i.e., the amygdala, the ACC, etc.). This disrupted connectivity may be a consequence of, or compensation for impaired cognitive function as a result of the connectivity between the cerebellum and the precentral gyrus. Further investigation into the functional relationship between the cerebellum and the precentral gyrus is needed to further explore this assumption.

Trait-Anxiety and Increased Cerebellum-Salience Network rsFC

The right cerebellum was noted to have rsFC to the right insula via the salience network. The salience network, which is primarily seeded within the ACC and the insula, is involved in detecting, integrating and filtering relevant interoceptive, autonomic, and emotional information (Seeley, 2019). Prior research has shown that heightened connections within the salience

network plays a pivotal role in attention bias to threat (Hilland et al., 2019). Previous investigation into the role of the salience network in anxiety disorders shows increased resting-state connectivity between the amygdala and insula in individuals with anxiety, as well as significant intra-network BOLD correlations within the salience network, indicating potential involvement of the salience network in anxiety disorders (Caulfield et al., 2016; Bernard et al. 2012; Buckner et al. 2011; Habas et al. 2009; O'Reilly et al. 2010; Seeley et al., 2019).

Of more importance, these same studies show that specific regions of the cerebellum (Crus I, Crus II and vermis) have direct contributions to salience network activity, as well as direct connectivity to the amygdala and insula, indicating that the cerebellum may have a role in attention bias to threat (Minlanyuan et al., 2017). Supported by the functional connectivity patterns noted in the current study, it appears that the rsFC in the cerebellum may have contributions to the salience network, potentially modulating observed increases in anxiety symptomatology.

There was an overall pattern of increased activation associated with trait anxiety to brain regions and networks implicated for their role in anxiety and affective processing. The current study saw a correlation between high trait anxiety associated with several cerebellar-seeded regions—mostly the Crus I, Crus II, and vermis (see *Table* 1 for further results). This increased cerebellar-seeded connectivity associated with trait anxiety was connected to several brain regions and networks which have previously been implicated in their roles for the etiology and maintenance of anxiety (i.e, the ACC, thalamus, insular cortex, precentral gyrus, and the salience network). The heightened rsFC observed between the cerebellum and these brain regions and networks may have a causal role in the etiology of anxiety and the maintenance of the symptoms associated with anxiety. For example, increased cerebellar-ACC rsFC may, in part, explain why

anxious individuals exhibit abnormal, dysregulated fear processing by over-attenuating themselves to potentially threatening stimuli.

Cerebellar-insular hyperactivity may explain the anticipation of negative events—a hallmark symptom of anxiety; whereas increased cerebellum-insula activation may also, in part, contribute to the lack of emotion regulation seen in anxious individuals. Dysregulated cerebellar-salience network activation may explain why anxious individuals have trouble with properly filtering relevant interoceptive, autonomic, and emotional information. The cerebellar-seeded rsFC in anxious individuals may contribute to anxiety and provide a target for future therapeutic avenues. However, further research into these associations is required to better understand how hyperactive cerebellar connectivity may contribute to the etiology and maintenance of anxiety.

Hypothesis Two: Functional Connectivity Between the Cerebellum and Threat/Emotion Processing Regions Will Decrease in the ABM Training Group Following Training.

The current study compared pre to post-training changes in rsFC in both the ABM and control training groups. Compared to changes in the control group, the ABM group had decreased rsFC from the cerebellum to several key brain regions and networks. The decrease in functional connectivity from the cerebellum to these regions may indicate that ABM results in neural changes, which in turn, may result in changes in behaviors linked to these regions. Connections from the left crus, right cerebellum, left cerebellum, and vermis to the ACC and amygdala decreased in the ABM group relative to the control group. Previous research suggests that the cerebellum, especially the left cerebellum, is involved in oculomotor control as well as control in covert visual attention (Townsend et al., 1999; Baier et al., 2010; Striemer et al., 2015; see *Figure 7* and *Table 2* for rsFC results).

Attention bias, specifically towards threat, heavily relies on the brain to rapidly attend to stimuli and elicit responses to stimuli that are relevant. In anxious individuals who exhibit attention bias, we typically see this attention heavily biased towards stimuli the individual sees as threatening, even when that stimulus is not an actual threat. Both the left crus and the vermis are thought to contribute to prediction and prediction errors when selecting relevant stimuli to attend to. Specifically, these regions of the cerebellum contribute to prediction errors when attending to fearful stimuli (Aps et al., 2018; Ernst et al., 2019). The right cerebellum plays a role in cognitive processing whereas the vermis is thought to be the 'limbic cerebellum' for its role in affective processing (Gawda & Szepietowska, 2016). The cerebellar-seeded rsFC observed from these regions has been shown to have a causal role in the adjustment of emotional and cognitive processes to situational context; specifically, research shows that these two regions play a critical role in rapid detection and response to negative/fearful stimuli. (Gawda & Szepietowska, 2016; Parvizi et al., 2001). Similar research indicates that abnormal connectivity or disruptions within these neural circuits subserving sensorimotor, cognitive, or emotional processing disrupts connectivity from the cerebellum to threat-processing regions (i.e., the amygdala and ACC) causing accompanying cognitive-affective and attention-regulation deficits (Gawda & Szepietowska, 2016; Schmahmann, 2004). It is important to note that the mechanism underlying behavioral changes in the ABM group, and differing mechanisms could potentially underly the same behavioral changes in the control group.

Cerebellum-ACC rsFC Decreases Following ABM

The ACC is among one of the core regions that indicates a preference when responding to negative stimuli in non-anxious individuals, and functional connectivity to the ACC has repeatedly been reported across a range of experiments that use emotional tasks with cognitive

demand and negative or fearful stimuli, such as the current study (Hilland et al., 2020; Lindquist et al., 2016). Neural responses to negative stimuli in the ACC are more pronounced in anxious individuals than in healthy controls (Hilland et al., 2020). The ACC translates an individual's intentions into conceivable and appropriate responses—doing so by combining motor control, arousal state, and attention to relevant stimuli translating intentions into action, by integrating motor control, motivational drives/arousal state, and cognitive messages (Aviram-Friedman et al., 2018; Stevens et al., 2011). Increased connectivity to the ACC has been shown to result in abnormal biobehavioral processing in anxious individuals with an attention bias towards threat (Bar-Haim et al., 2007; Britton et al., 2014; Carlson et al., 2013; Lazarov et al., 2019). This may be, in part, due to impaired affective processing when presented with emotionally laden stimuli (i.e., fearful faces), often resulting in failure of the ACC to regulate attentional control. The ACC has been well-established in regard to its role in anxiety disorders (Carlson, et al., 2013; Kim et al., 2016; Stevens et al., 2011). There are ample studies that note functional connectivity patterns from the cerebellum to the ACC in anxious individuals (see Aminto et al., 2013; Klumpp, et al., 2018; Seo et al., 2017), yet there has been insufficient discussion regarding this connectivity and how it's increase may be contributing to anxiety disorders and how these changes may be related to treatment, such as ABM.

One explanation for this heightened connectivity is the neural circuitry underlying the functional connectivity between the cerebellum and the ACC. These two brain regions are connected through the cingulate–pontine–cerebellar neural circuit (Aminto et al., 2013; Clausi et al., 2017). This neural circuit connects the cingulate gyrus to the cerebellum, and is responsible for recognizing the underlying characteristics and intentions of social stimuli and producing appropriate responses via affective response to these stimuli (Olson et al., 2007). Treatments

targeting attention bias and abnormal attention allocation, similar to ABM, have been shown to decrease functional connectivity within this circuit (see Fortenbaugh et al., 2017; Kim et al., 2016; Shao et al., 2016), making it plausible why a decrease in attention bias was only seen in the ABM training group and not the control group

Hyperactivation in this circuit has been linked to anxious symptomatology, impulse control, and attention regulation deficits (Aminto et al., 2013). It is presumed that heightened rsFC between the cerebellum and the ACC is modulated by heightened rsFC within the circuit that connects it: the cingulate–pontine–cerebellar neural circuit—leading to decreased emotion regulation and disruptions with attention allocation: two hallmark symptoms of anxiety. This notion is consistent with the results of the current study, as decreased connectivity between the cerebellum and the ACC decreased following ABM training in anxious individuals, leaving speculation as to whether this decrease was modulated by the latter neural circuit. Further studies should focus their efforts on the cingulate–pontine–cerebellar neural circuit to further investigate precisely how the cerebellum may be contributing to anxiety through its connections within this circuit.

Functional connectivity between the ACC and the amygdala are believed to be the hallmark indicator of attention bias towards threat (Hilland et al., 2020). Cognitive models concerned with the neural correlates of attention bias claim that the amygdala non-consciously monitors and evaluates stimuli for their threat potential, whereas the ACC monitors conflict between threatening and non-threatening stimuli competing for attention (Carlson & Aday, 2018). Disruptions in ACC-amygdala networks result in attention bias towards threat, which may be due to the inability of the network to properly differentiate what stimuli deserve attention allocation. The ability of the cerebellum, the amygdala, and ACC to potentially modulate more

goal-directed cognitive control over attention allocation allows the anxious individual to better control their attentional regulation to threat-relevant stimuli; thus, decreasing the amount of time and attentional control expended upon threatening stimuli. When compared to control training, ABM has been shown to underlie more neural changes (Delchau at al., 2020; Lee et al., 2020; Mogg et al., 2017)—in turn, these neural changes increase the ability to elicit goal-directed attention allocation. ABM training may modulate more neural-based changes compared to control training, as concluded by the results of the current study. These underlying neural changes may be why we see decreased rsFC from the cerebellum to the ACC and the amygdala in the ABM group and not the control group.

Cerebellum-Amygdala rsFC Decreases Following ABM

The amygdala is one of the most-well known structures when it comes to the neural correlates of anxiety and attention bias. The amygdala is crucial to the rapid detection of emotionally salient stimuli—most notably threatening stimuli (Carlson & Aday, 2018; Carlson, et al., 2013; Ledoux and Muller, 1997). The amygdala unconsciously detects and evaluates visual stimuli that are perceived as threatening (Liddell et al. 2005; Roy et al., 2013). Previous studies indicate that the amygdala initiates increased responses to threat-relevant stimuli—even when these stimuli are not at the forefront of one's attention (Roy et al., 2013; Vuilleumier, 2005), suggesting the amygdala mediates attentional bias to threat. The amygdala has bidirectional connections to sensory and attention-regulation areas, indicating the amygdala may be responsible for the early, automatic response to attention to threat (Freese and Amaral, 2009; Jenks et al., 2020; LeDoux, 2007, Vuilleumier, 2005). Other neuroimaging studies indicate that the amygdala response to fearful faces is enhanced in individuals with anxiety (Jenks et al., 2020; Rotshtein et al., 2010, Vuilleumier et al., 2005).

Given the perceptible role of the noted cerebellar regions in attention bias, as well as its decreased rsFC to the amygdala, it is intelligible why we see cerebellar-seeded functional changes in individuals who re-trained their attention bias via ABM. The results of the current study suggest the recruitment of the cerebellum aids in varying aspects of cognitive control and attention allocation. The attenuated connectivity from the cerebellum to the amygdala in the ABM training group suggests that anxious individuals may engage the cerebellum, alongside the amygdala to direct attention to threat-relevant stimuli. Since anxious individuals who exhibit attention bias are known to favor negative/fearful stimuli versus other types of stimuli (Carlson & Aday, 2018; Fani et al., 2012), it is presumed that ABM training (compared to control training) underlies relevant neural changes in critical regions to reduce attention bias to threat. This is believed to be, in part, due to the communication between the cerebellum and amygdala-ACC networks in order to elicit more goal-directed control versus aberrant threat related attentional-control, as seen in attention bias.

It is important to note that it is unclear whether the cerebellum is a direct inhibitor of the amygdala and the affective responses it elicits towards negative or fearful stimuli (Baumann & Mattingley, 2012; Moreno-Rius, 2018) or whether the amygdala has a moderating effect on the cerebellum (Lee et al., 2020). Nonetheless, the cerebellum has extensive functional connectivity to areas such as prefrontal cortex and other limbic regions. Coupled with the results observed in the current study, amygdala-cerebellar connectivity may play a role in the pathophysiology of both anxiety and attention bias. It is no surprise that functional connectivity between the cerebellum and the amygdala decreased following ABM in the current study. Individuals with anxiety eliciting an attention bias to threat may be activating the cerebellum in order to engage in regulation of attenuation and response deployment of threat reactivity via allocation of attention

to support performance following the initial limbic response. This supports the notion that ABM treatment, when compared to control, may be more effective at modulating response deployment of threat reactivity; thus, decreasing rsFC between the cerebellum and amygdala (and greater limbic system).

Cerebellum, Thalamus, and Hippocampus rsFC Changes Following ABM

There were observed decreases in rsFC between the right cerebellum, as well as the vermis, to the thalamus. The right cerebellum has been correlated with mechanisms involved in cognitive processing, whereas the vermis has been shown to have a role in affective processing (Gawda & Szepietowska, 2016), allowing the cerebellum to have a role in the detection and response of negative and fearful stimuli. (Gawda & Szepietowska, 2016; Parvizi et al., 2001). The thalamus and hippocampus, are regions which have ample research to procure their role in attention bias towards threat. The thalamus has direct anatomical and functional connectivity to the cerebellum (Allen et al., 2005; Gornati et al., 2018; Hintzen et al., 2018). Yet, the connectivity between these structures has hardly been investigated—especially in terms of anxiety and attention bias.

Research suggests that the thalamus may represent the junction between regulation of mnemonic and control functions, such as action or attentional selection of relevant stimuli (Kirouac, 2021). This regulation involves focusing a spotlight on important information, as well as inhibiting unnecessary background information (De Bourbon-Teles et al., 2014). The thalamus has been shown to filter un-attended emotional stimuli, with increased rsFC linked to threat related attentional bias and attentional control (Hakamata et al., 2016). The thalamus prioritizes processing based on affective significance of the stimuli. In the case of anxious individuals with attention bias towards threat, the decreased regulatory ability of the thalamus to evaluate stimuli

may result in increased rsFC to other areas of the brain (i.e., the amygdala, cerebellum, and hypothalamus) for aide in attenuating to relevant stimuli (Kirouac, 2021; Todd et al., 2012).

Individuals with anxiety exhibit functional connectivity abnormalities in brain regions involved in attention and reward during attention allocation tasks (Oldrati & Schutter, 2018). This suggests a dysfunctional interplay between attention allocation and cognition in individuals with anxiety, whereas anxious individuals appear less capable of upregulating attention networks relative to non-anxious individuals—hence why we see attention bias deficits in anxious populations. In studies concerned with rewarding sustained attention away from aversive (i.e., negative, fearful) stimuli (Chantiluke et al., 2012; Oldrati & Schutter, 2018), there was an observed decrease in functional connectivity within neural circuits concerning the thalamus, ACC, cerebellum, and hippocampus (i.e., the fronto-striato cerebellar network; the cingulate–pontine–cerebellar circuit). Furthermore, similar studies show a decrease in sustained attention from aversive stimuli is modulated by a decrease in cerebellar activation (Chantiluke et al., 2012).

Brain activation deficits between the cerebellum, thalamus, and hippocampus in individuals with anxiety are more pronounced during attention control tasks relating to negative, aversive stimuli, presumably reflecting poor upregulation of attention allocation within attention networks. ABM treatment has been shown to target neural changes within networks associated with the cerebellum, thalamus, and hippocampus (Britton et al., 2014; Lazarov et al., 2018; Liu et al., 2018). The results of the current study extend these previous findings by showing decreased rsFC between these regions and the cerebellum.

Cerebellar-seeded rsFC changes in resting-state networks following ABM

Altered functional connectivity in resting state networks have been shown to sustain cognitive and affective deficits in anxiety. However, little research has explored the effects of ABM on these neural networks, and associated decreases in symptomatology—such as decreased attention bias. There was several cerebellum-seeded resting-state decreases in the ABM training group within resting state networks following their training. Left cerebellum and the right crus rsFC decreases within the salience network, whereas left cerebellum and left crus rsFC decreases within the DMN. Abnormalities in both the salience network and the DMN have been linked with anxiety and its symptomology—most notably attentional control deficits (Kaiser et al., 2015; Sharma et al., 2017).

The current study provides further evidence that these cerebellar-regions are connected to the salience network. This network to two main regions within the cerebellum: the lateral portion of the left lobules VI and the right crus I. Lobules VI–VII (crus I) are connected, through the pontine and dentate nuclei, with posterior and lateral hypothalamus (Habas et al. 2009; Sharma et al., 2017). As the lateral cerebellum is mainly connected to associative cortices, it is postulated that the cerebellum-insula functional connectivity clusters detected within the salience network in the current study are preferentially linked with lobules VI– crus I of the cerebellum.

Previous research confirmed the role of vermal lobule VI and the hemisphere of lobules VI– crus I in threat-related processes like, fear, and startle reactions, and attention deficits (attention bias) concerned with threat (Dimitrova et al., 2004; Sang et al., 2012). rsFC studies indicate that neural-circuit changes housed within the salience network were positively related to state anxiety (Kim & Whalen., 2011; Baur et al., 2013), suggesting that increased connections

within this network reflects an increased sensitivity to salient events, which allows for biased, inaccurate attentional and perceptual processing (Baur et al., 2013; Geng et al., 2016).

In the current study, the heightened cerebellum-insula rsFC prior to ABM treatment within the salience network may be associated with weaker cognitive control, which is consistent with an anxiety theory that suggests that trait anxiety includes an impoverished recruitment of prefrontal attentional mechanisms to trigger the allocation of attentional resource (Bishop, 2009). This may result in problems with attention control and emotion regulation (Geng et al., 2016). Other studies (see Hakamata et al., 2018; Hilland et al., 2018) have found functional connectivity changes within the salience network following attention bias modification in both depressed and anxious individuals. These studies particularly found changes from insula within salience functional connectivity.

Similarly, the current study predominantly saw decreased rsFC from the cerebellum to the insula within the salience network. These studies failed to report or investigate any functional changes within the cerebellum. However, given the ample connections the cerebellum has within the salience network, as well as the current studies observed rsFC decreases within the cerebellum following ABM training, we can speculate that the cerebellum may modulate attention-changes in these trait-anxious individuals. Taken together, these findings indicate that ABM treatment may enact general changes to attention-control via the salience network—specifically modulated by connections from the cerebellum to the insula.

Attention bias towards threatening stimuli has been linked to increased rsFC within the DMN (Xiong et al, 2020). Grimm and colleagues showed that anxiety disorders are characterized by impaired activation in the anterior DMN during attention-control tasks (Carlson et al., 2017; Grimm et al., 2009). The DMN known as set of brain areas that are more activated when an

individual is at rest, is well-established for its role in spontaneous cognitive events (i.e., the elicitation of spontaneous thoughts and reactions; Imperatori et al., 2019, Whitfield-Gabrieli & Ford, 2012). Among the subregions of the cerebellum, Crus I is thought to be linked to the DMN, with increased Crus I–DMN connectivity is observed in treatment-resistant depression and anxiety (Guo et al., 2015). Moreover, individuals with anxiety show disrupted functional connectivity between the posterior cerebellum and the cerebral cortex (Lee et al., 2020; Xiong et al., 2020); mainly including the DMN and the limbic system indicating that the cerebellum might be associated with the onset of anxiety.

Typically, the DMN elicits decreased activation and functional connectivity during attention-demanding or stimulus dependent tasks (such as the training implemented in the current study). However, in the case of anxious individuals, activations and connectivity are increased during these tasks (Buckner et al., 2008; Imperatori et al., 2019). This can potentially be attributed to failure of a high trait-anxiety individual's ability to synchronize brain areas within the DMN (i.e., the cerebellum) when they're in a resting state. This explanation is in-line with the attention control theory (Eysenck et al., 2007), which suggests that high trait-anxious individuals tend to over-control situations by allocating excessive attention resources to scan for potential threat. This results in a constant state of over-attenuation to their environment as well as attention bias to stimuli they perceive as threatening. Hyper-activation of the DMN may result in deficits of attention regulation, which in turn, results in attention bias. (Berggren and Derakshan, 2013). This notion aligns with the findings in the current study, as we saw decreased activation of cerebellar-seeded rsFC in the DMN, as well as a decrease in attention bias, in the ABM training group.

Cerebellar-seeded rsFC to the Lateral Occipital Cortex

Such as with the cerebellum, the lateral occipital cortex (LOC) has been implicated in ample literature concerned with anxiety and attention bias. Yet, there has been little discourse surrounding its role in the etiology of anxiety and its link to anxious symptomatology. The current study saw the most cerebellar-seeded rsFC changes to the LOC. Specifically, rsFC between the right cerebellum and the LOC was correlated with heightened levels of trait-anxiety, while decreases in rsFC from the left cerebellum, right cerebellum, and the vermis to the LOC were associated with decreases in attention bias in the ABM training group. The LOC is well known from previous studies in regards to its role in object perception (Malach et al., 1995; Lerner et al., 2008), as well as a visual area important for processing shape information (Grill-Spector et al., 2000; Kourtzi & Kanwisher, 2001), as well as facial recognition and processing (Karten et al., 2013; Walz et al., 2014).

Although the LOC in individuals with anxiety and depression has exhibited structural and functional abnormalities (Modi et al., 2015; Nagy et al., 2012; Schreiner et al., 2019; Walz et al., 2014) how this brain region interacts with other regions and networks still needs some clarification. In previous rsFC studies, the LOC of individuals with anxiety and depression had increased interaction with the DMN, as well as heightened rsFC to areas such as the amygdala, thalamus, and hypothalamus, as compared to non-anxious and depressed individuals (Nagy, Greenlee, & Kovács, 2012; Pannekoek et al., 2013; Walz et al., 2014). However, other studies have shown activation in LOC to the DMN where high trait-anxious individuals showed significant decreases in rsFC—compared to low trait-anxiety groups (Modi et al., 2015), as well as decreases in rsFC from the cerebellum to the LOC (Westlund et al., 2019).

These theories provide a plausible explanation for the observed rsFC to the LOC from the cerebellum. However, they still do not explain contributions of the LOC, as well as cerebellum-

LOC connectivity that may be contributing to anxiety symptomatology—including attention bias. ROI-based rsFC studies demonstrate widespread interconnections between the cerebellum, specifically lobule VII and VIII and occipital cortices, such as the LOC. These functional connections might rely on cortico-pontine afferents and/or cerebello-thalamo-cortical afferents in agreement with anatomical tracing from human tractography studies (Habas, 2020; Habas & Manto, 2018). These pathways have long been implicated for their role in attention deficits (Olson et al., 2007). Treatments that aim to better control these deficits, such as ABM training, have been shown to decrease functional connectivity within these circuits (Fortenbaugh, DeGutis, & Esterman, 2017; Kim et al., 2016; Shao et al., 2016). As such, we also saw a decrease in connectivity between the cerebellum and LOC in the ABM training group.

Attention allocation is a cognitive process that enables us to focus on certain aspects of the environment for the benefit of improved performance (Cameron et al., 2002; Guggenmos et al., 2015). However, for individuals with anxiety, this focus is misguided, resulting in biased attention to threatening stimuli, as well as decreases in attention resources to for the processing of goal-relevant information. One way in which attention has been found to impact neural processing in anxious individuals is through an amplification of neural responses to attended spatial locations, objects, or features (Treue, 2003), which may explain why many studies concerned with attention bias have seen functional connectivity in the LOC.

The role of the LOC may, in part, explain why there was ample connectivity from the cerebellum to this region, as the current study implemented the use of facial stimuli in our attention bias training, In ABM training, participants see threatening faces paired with a non-threatening face—triggering biased attention towards the threatening faces as opposed to the non-threatening faces. However, participants are immediately thereafter required to engage in

another visuospatial task (identifying the location of the probe), which may limit processing of these images. Perhaps the reduction in attention bias variability associated with ABM training (Abend et al., 2019; Badura-Brack et al., 2015) is evidence of a reduced tendency to fluctuate between over- and under-attending to threat in response to involuntary attention allocation processes. This normalization may include increased LOC activity and reduced posterior occipital responses in individuals with anxiety treated with ABM training, as observed in the current study.

Given that both the cerebellum and the LOC are not typically implicated in disorders such as anxiety, the realm of rsFC between these two brain regions needs further investigation to determine how it may impact the etiology and subsequent symptomatology of anxiety disorders. Nonetheless, the results of the current study, coupled with the results of previous studies, indicate that reduced stability of LOC connectivity, particularly rsFC changes seeded within the cerebellum, may be an important factor underlying neurocognitive dysfunctions and symptom severity, such as attention bias, in anxiety disorders.

Overall, there were vast amounts of cerebellar-seeded rsFC decreases following ABM training. The cerebellar seeded decreases were to regions already established for their roles in the etiology and maintenance of anxiety. The current study found decreases from across varying regions of the cerebellum to key brain regions such as the amygdala, ACC, thalamus, and hippocampus. Attention bias may result from failure of the ACC to regulate attentional control. The current study saw decreases from the cerebellum to the ACC following ABM training. Given the role of the ACC in attention control, the connectivity from the cerebellum may provide further understanding for the underlying neural circuitry modulating dysregulated attention. The results provide further evidence for the potential of the cingulate–pontine–cerebellar neural

circuit, seeded within the cerebellum and projecting to the ACC, in dysregulated attention control.

The amygdala is one of the most nitrous structures in terms of the etiology of anxiety disorders—yet its role in the symptomatology of attention bias is largely unexplored. the decreased connectivity from the cerebellum to the amygdala in the ABM training group may, in part, provide support for the notion that anxious individuals exhibit attention bias towards threat, and that ABM underlies changes in attentional bias resulting from ABM. The amygdala is known for increased responses to threat-relevant stimuli, whereas the cerebellum is known to potentially modulate attention control. These results suggest that anxious individuals engage the cerebellum, alongside the amygdala to attenuate to threat-relevant stimuli.

This notion is also supported further by the observed rsFC decreases from the cerebellum to the thalamus and hippocampus: two other critical regions implicated in aberrant attention regulation and control. The thalamus has been shown to filter un-attenuated emotional stimuli, with increased rsFC linked to threat related attentional bias and attentional control. The hippocampus has been shown to aid in attention control. Cerebellar rsFC to these regions is thought to help modulate up regulation of attention; thus, we see a decrease in cerebellar-seeded rsFC to these areas after ABM training.

Decreased connectivity from the cerebellum to both the DMN and the salience network may help underlie the proposed neural changes. In the current study, the cerebellum-insula rsFC within the salience network in anxious individuals may be associated with weaker cognitive control. The rsFC from the cerebellum to the DMN may provide further evidence for the role of the cerebellum in modulating attention control.

Overall, these results provide evidence for the role of the cerebellum in attention deficits: specifically, those related to anxiety disorders. The results provide further notion for further research to target the neural substrates of the cerebellum in disorders associated with dysregulated attention. Lastly, the results provide further support in implementing the cerebellum as a potential target for ABM treatment. Given the results of the current study, future clinical efforts aimed at increasing one's attention regulating may wish to further investigate the role of the cerebellum.

Clinical Implications

The current study provides further evidence for the neural substrates of ABM training. Thus, aiding in the understanding of how this treatment works and modulates functional brain changes. In particular, the current study focused on the underlying biology of anxiety, and how this in turn may lead to symptom reduction. The cerebellum, although overlooked, may be a critical target for future therapeutic efforts concerned with symptom reduction in anxiety and attention disorders. The results from this study alone do not provide enough evidence to justify sole investigations into rsFC in the cerebellum as an outcome of ABM treatment. Although the current study did not see a decrease in trait-anxiety following ABM treatment (although other studies did, see Britton et al., 2014; Hakamata et al., 2018; Mogg, Watters, & Bradley, 2017), it did see a stark decrease in attention bias following the completion of training. Changes in attention bias in anxious individuals may provide some further treatment courses concerned with altering biased attention.

The observed functional connectivity abnormalities may help psychologists, therapists, and other professionals recognize the functional importance of specific cues, both explicit and implicit, for their clients with anxiety or other varying clinical disorders. Looking away from, or

diverting attention away from, or preferring certain stimuli (attention bias) is likely to reduce threat for a social-phobic patient because it makes it more difficult for other people to engage the patient in a conversation and thus provides a psychological escape (or relief) for the patient (see Chen et al., 2002; Mobini & Grant, 2007). It is important to note that such deliberate therapeutic intervention can be counterproductive without proper execution, as it can engage the participant in both safety-seeking and avoidance behaviors—rendering such treatment as ineffective (see Thwaites & Freeston, 2005).

Nonetheless, targeting attention allocation deficits in clinical populations may also grant clinicians with information they can utilize to elicit negative automatic thought and responses associated with both implicit and explicit anxiety-inducing stimuli in real-life situations. Once these cures provoke observable defects and symptoms that can be identified by the clinician, more targeted therapeutic interventions to counter these deficits and symptoms can be utilized and tailored to the clients. It is important to identify specific attentional preferences of the clients to formulate a more effective treatment plan.

The observed attention bias deficits and resolution following ABM treatment can allow clinicians to better understand attention bias, but also, what may be modulating symptomology in their own clients. This further aids clinicians in developing treatment plans for their clients—aiding in more beneficial outcomes. It is important to note that the observed attention bias changes are not limited to just anxiety disorders. Many other psychological and neurological disorders (i.e., attention deficit hyperactivity disorder (ADHD), schizophrenia, bipolar disorder (BPD), major depressive disorder (MDD), and autism spectrum disorders) exhibit some sort of attention bias, as well as trouble with attention allocation (Amianto et al., 2013; Lee et al., 2020;

Shakiba, 2014;). The findings in the current study, coupled with previous literature, may denote ABM a therapeutic target for clinical outcomes of disorders other than anxiety.

Providing support for the results in the current study, there is growing evidence implicating the cerebellum in not only its emblematic motor, balance, and involuntary movements (Buckner et al., 2011; Parvizi et al., 2001); but also, its role in cognitive and affective processes, as well as attention modulation (Lee et al., 2020; De Smet et al., 2013; Moreno-Rius, 2018; Schmahmann, 2019). The functional involvement of the cerebellum in both psychological and neurological disorders is supported by the current study, as well as other functional neuroimaging studies (Clausi et al., 2017; Shakiba, 2014; Villanueva. 2012) As previously discussed, the cerebellum was found to be associated with not only anxiety, but also psychological and neurological disorders (Amianto et al., 2013; Baumann & Mattingley, 2010; Phillips et al., 2015; Shakiba, 2014).

Advances in the understating of the functional role of the cerebellum provides further clinical implications for the etiology and symptomatology in such disorders, and may aid in future advances in therapeutic and pharmaceutical interventions. Future research utilizing varying motor and cognitive tasks in different types and subtypes of psychological and neurological disorders is still needed to further investigate the exact role the cerebellum has in the etiology and symptomatology of these disorders.

General Limitations

The current study was not without limitations. To begin, this study lacks statistical power. The initial number of participants was estimated to be around 120. However, due to the COVID-19 pandemic, as well as attrition from the study, and insufficient data for some of our participants, the current study had 41 participants. The COVID-19 pandemic imposed executive

orders to close the schools, laboratories, and imaging centers in which data was collected. Due to these circumstances, many post-treatment fMRIs were not collected, rendering the data for these participants unusable for this study. Attrition is a common limitation of multisession ABM studies (see Enock et al., 2014) the unfortunate reality is that at-home based ABM training has an even higher attrition rate, as it is administered remotely and done at-will by the participants (see Beard et al, 2012; Enock et al., 2014; MacLeod & Clarke, 2015).

In line with other multi-session, at-home ABM studies, this study saw a large impact on data collection due to attrition, resulting in a smaller sample size. It is also important to note that the sample of participants used for this study was not a clinical sample; rather, participants were recruited if they exhibited high levels of both state and trait anxiety (although the current study only assessed trait anxiety). If a clinical population with clinically diagnosed anxiety was used, the results could be further implemented and generalized to such populations. Furthermore, there were restrictions as to the assessment of anxiety symptomatology due to the implementation of the STAI-T and STAI-S surveys. The STAI surveys are self-reported, and have been shown to be less effective at measuring anxiety alone; rather, it measures generalized symptomology of both anxiety and depression (Beck et al., 1998; Knowles & Olatunji, 2020). Other surveys, such as the Worry Domains Questionnaire (WDQ), should be implemented in further studies to accurately assess anxiety symptomatology and any subsequent changes observed. The first hypothesis may have been limited by only using high anxious individuals, which further limits the range of anxiety values assessed. Lastly, the results of the current study were limited due to the small significance of the observed changes. No results were significant at the $p_{FWE} < .05$ level, with small voxel changes still noted after riding the analyses of this correction. The small observed changes may, in part, be due to the methodological limitations already discussed previously.

Future Directions

Future studies concerned with assessing the role of the cerebellum in anxiety disorders, or the role of the cerebellum in attention bias, should implement more strict measures to assess changes. Other than implementing different methodology to assess anxiety (as mentioned previously), future studies would also benefit from a non-anxious control group. That is, a control group that does not have any reported levels of anxiety, as opposed to the anxious control group used in the current study. This will allow researchers to narrow in on whether observed effects are changes to anxiety themselves, and what changes are simply regression to the mean. The current study intended to implement a third rsfMRI to assess long-term modulated changes in the cerebellum following ABM treatment, but was unable to incorporate this due to attrition and the COVID-19 pandemic. Future studies should also assess any long-term rsFC changes in order to assess if any observed changes are short-term or long-term. Other studies implementing ABM treatment have reported that although participants seem eager to begin training, this optimism can subside, leading to high rates of attrition (Beard et al., 2012; Kuckertz et al., 2019). This, in part, can be attributed to the repetitive nature of a dot-probe paradigm, such as the one implemented in the current study. Future efforts should focus on ways to further engage participants in their training—hopefully resulting in less attrition.

Furthermore, most studies concerned with the role of the cerebellum in anxiety disorders indicate increased functional connectivity to and from the cerebellum may have a role in the etiology and symptomatology; however, this hyperactivity is also observed in a wide-array of other psychological and neurological disorders. This may, in part, be due to the observed attention impairments across these disorders. However, it would be beneficial to further investigate which, if any, areas are contributing to specific, contrasting deficits particular to

anxiety. For example, comparing functional connectivity in the cerebellum during acute episodes of anxiety with episodes of MDD may help research efforts concerned with the role the cerebellum plays in each respective disorder. Further investigation into psychotherapeutic interventions on cerebellar function as a target of anxiety therapies is still warranted and necessary. In addition, future studies would benefit from investigating cerebellar functional connectivity across varying anxiety disorders as well as symptom clusters in each particular anxiety disorder. This would aid in specific therapeutic targets for each disorder, rather than a generalized target aimed for all anxiety disorders.

Conclusion

The current study found that trait anxiety is correlated with increased cerebellar-seeded rsFC to several key brain regions (i.e., the ACC and the thalamus). These results provide further evidence for the notion that the cerebellum may represent a neural correlate of the etiology and maintenance of anxiety. The cerebellum has vast projections across the cerebral cortex, making its role outside its emblematic functioning plausible. Connections to threat and affect processing regions from the cerebellum were linked to heightened levels of trait anxiety—supporting the results from previous literature. Providing evidence for the role of the cerebellum in anxiety may warrant further clinical efforts to target neural changes within the cerebellum. Since there is still little research surrounding the role of the cerebellum in anxiety disorders, future research efforts should target functional connectivity changes within the cerebellum in anxious and non-anxious populations in order to implement further understanding of its role.

The current study also uncovered vast decreases in rsFC from the cerebellum to key brain regions and networks (i.e., ACC, thalamus, amygdala, hippocampus, salience network, and DMN). There is more research that supports the cerebellum's role in attention deficits than in

anxiety, so it is plausible why the current study saw the most changes in this regard. Areas such as the ACC and thalamus have ample support for their role in dysregulated attention. Given the decreased rsFC from the cerebellum to these areas, we can speculate that the cerebellum has a role in modulating attention deficits. Coupled with the results of previous research, this study provides further evidence for the role of the cerebellum in anxiety disorders, and may extend its findings as evidence for the role of the cerebellum in attention-related disorders. To the knowledge of the author, this was the first study that investigated cerebellar-seeded rsFC as an outcome of ABM training in highly anxious individuals.

The results may contribute to the wide array of new, up-and-coming literature that is concerned with the role of the cerebellum in neuropsychological disorders. This study investigated rsFC in the cerebellum prior to and following ABM training in highly anxious individuals. These individuals were recruited for both their preexisting attentional biases to threat, as well as high levels of trait anxiety in order to thoroughly investigate the effectiveness of ABM training. Although the observed cerebellar-seeded rsFC was not apparent utilizing the strict FWE correction, the vast array of cerebellar connectivity observed, specifically to threat and affective processing regions, may suggest underlying modulations of the cerebellum in support of the hypotheses.

The results provide further notion that ABM might have the potential to reshape the abnormal patterns of spontaneous cerebellar-seeded brain activity in relevant neural circuits, which are thought to be associated with a predisposition for anxiety. The rsFC between the cerebellum and other brain networks and regions were regarded as mainly constituting as having a pivotal role in attentional control, and salience monitoring and detection, as well as anxiety symptomatology. Dysregulation between these brain regions and networks in anxiety disorders

may explain the negative bias and abnormal cognitive control and attention allocation deficit—all of which are common in attentional bias towards threat and anxiety. Despite the limitations of the current study, there is enough evidence to support the role of the cerebellum as a plausible underlying neural substrate of anxiety disorders. Since this is not a clinical sample, rather a general sample of anxious individuals, further investigation into the role of the cerebellum in anxiety disorders should utilize clinically diagnosed individuals to generalize the effects noted into such populations.

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APPENDIX A

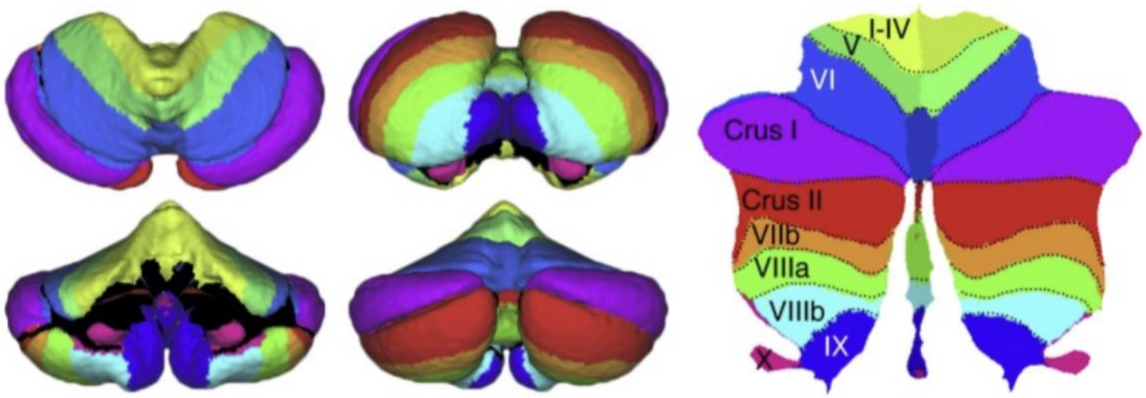

Figure 1. Pial surface representation of the cerebellum from superior (top left), anterior (bottom left), inferior (top middle), and posterior (bottom middle) views. Cerebellar lobules are organized into an anterior lobe (lobule I–V), a posterior lobe (lobule VI–IX), and a flocculonodular lobe (lobule X). Colors denote lobular boundaries. Flat map representation of the cerebellum is shown on the right with corresponding lobular labels (Brissenden & Sommers, 2019).

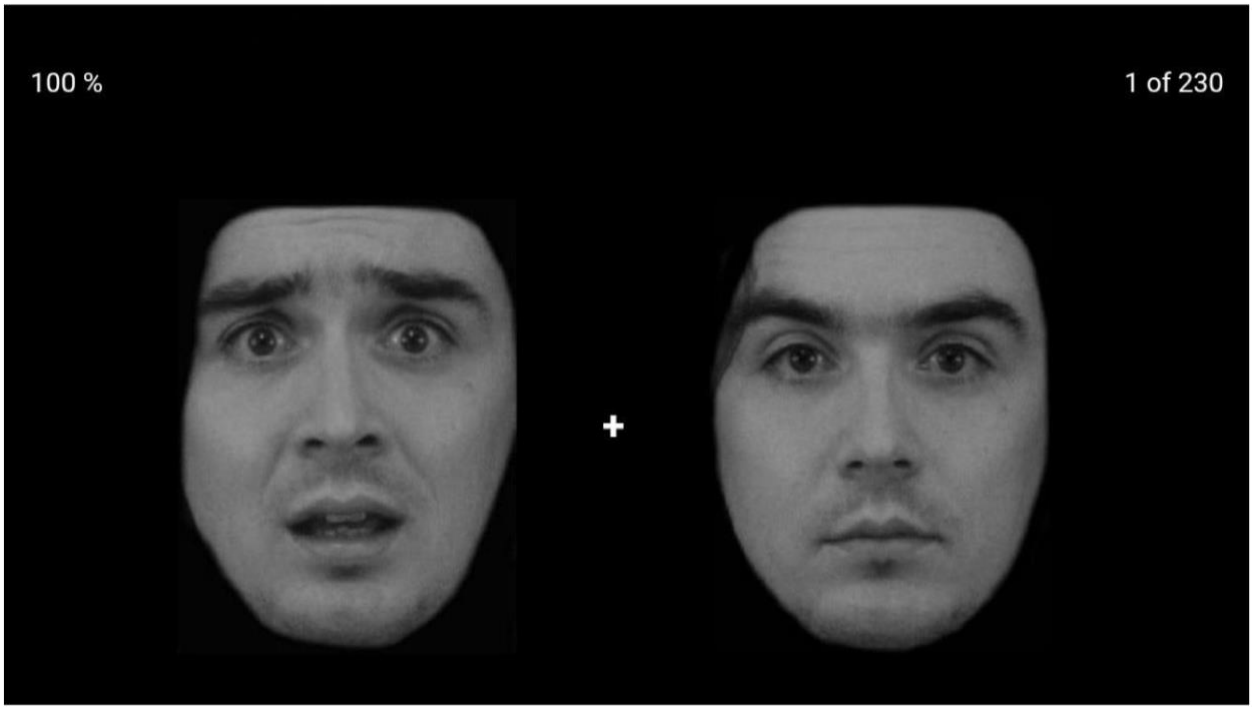

Figure 2. An example of what participants see in the ABM training application. The participants accuracy is displayed in the top left, whereas their progress is displayed in the top right.

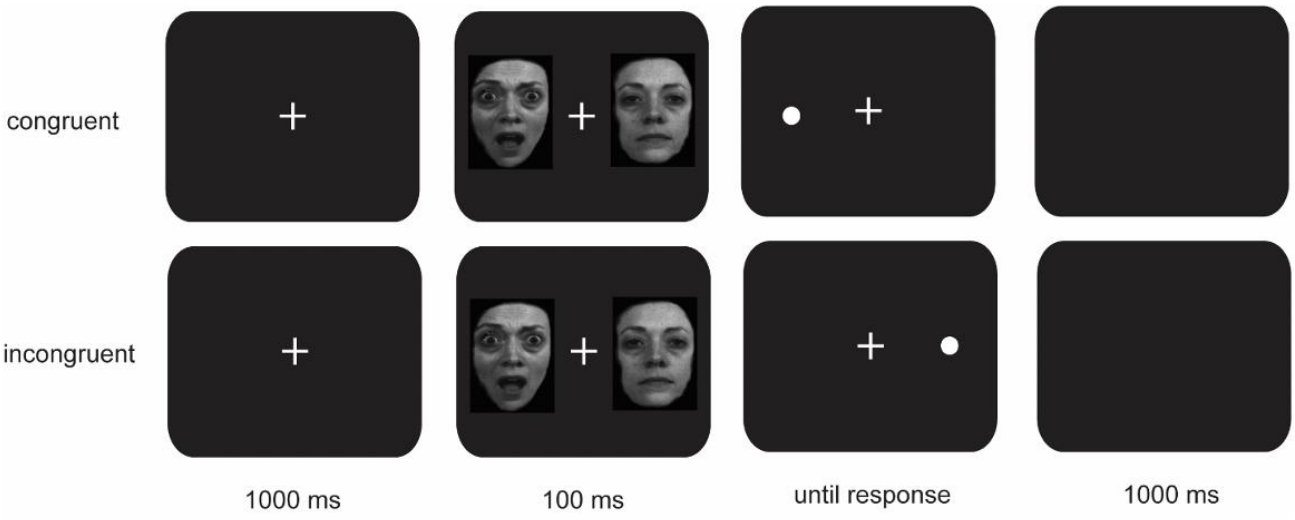

Figure 3. An example of a congruent (top) trial and an incongruent (bottom trial). In congruent trials, the dot was on the same side as the emotional face. In incongruent trials, the dot is on the same side as the neutral face.

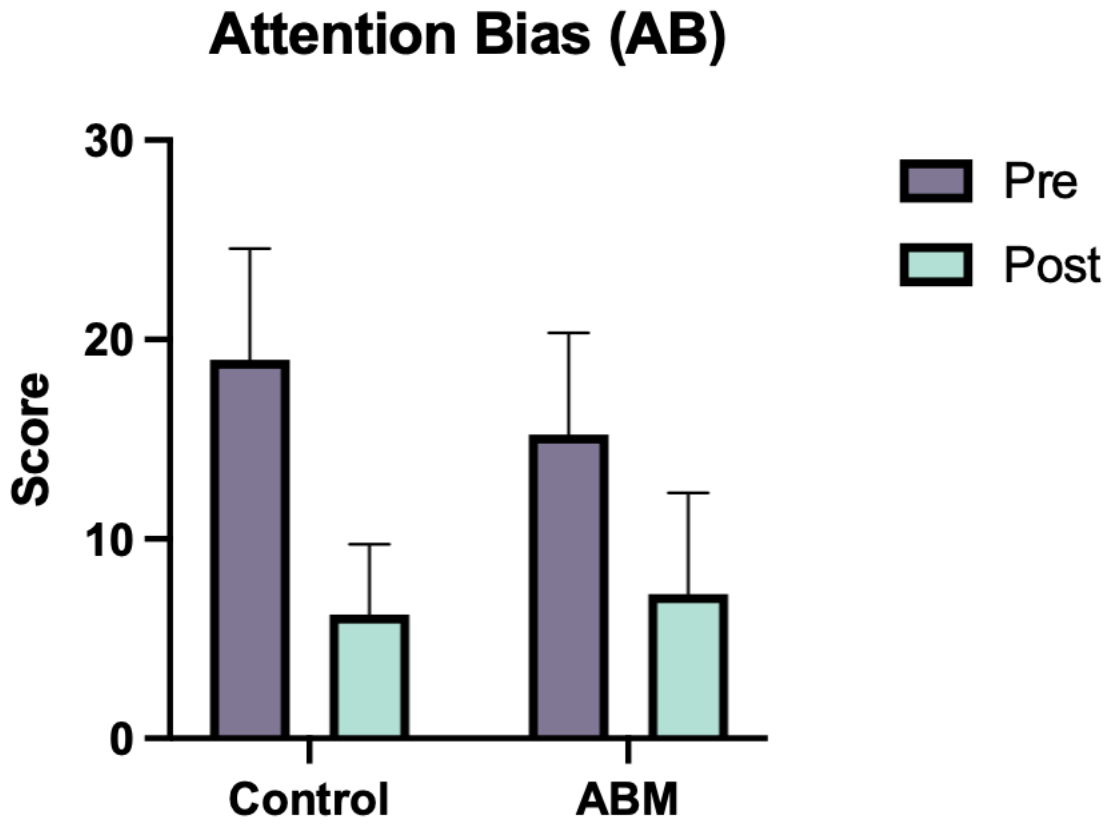

Figure 4. Overall attention bias (AB) score changes across groups pre and post training. There was a strong decrease in AB in both the control group and the ABM following six weeks of at-home app training. Error bars represent the standard deviation

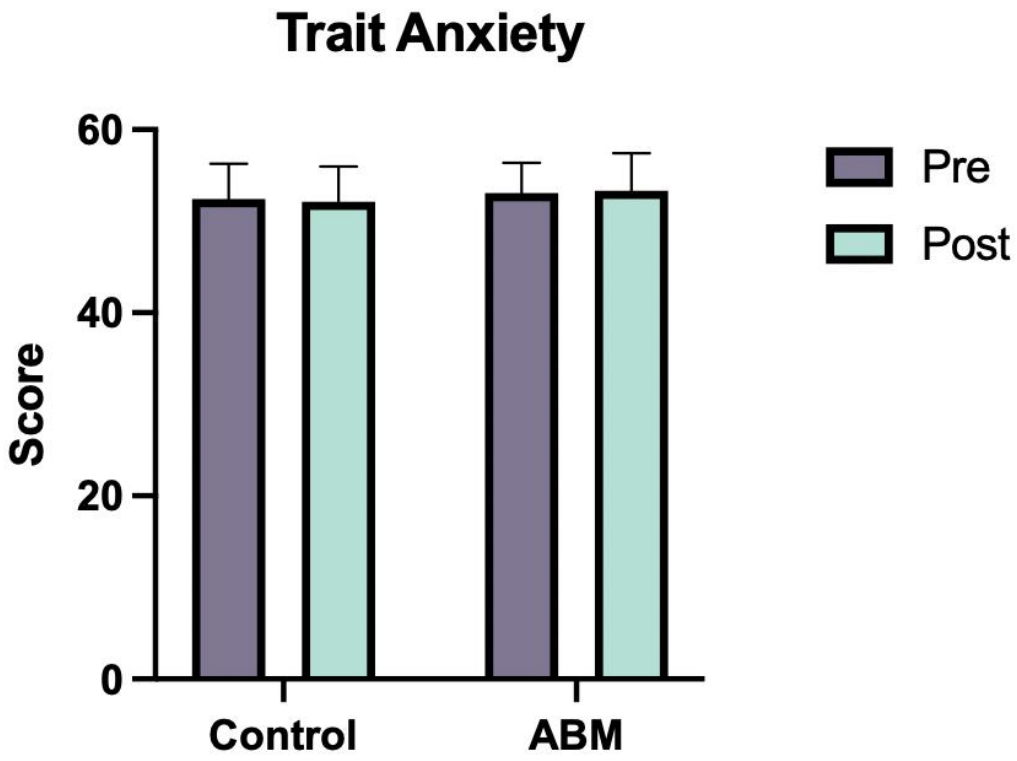

Figure 5. Overall trait anxiety scores (assessed via the STAI) across groups pre and post training. There was no significant decrease in trait anxiety for both the control group and the ABM group following their six weeks of at-home app training. Error bars represent the standard deviation.

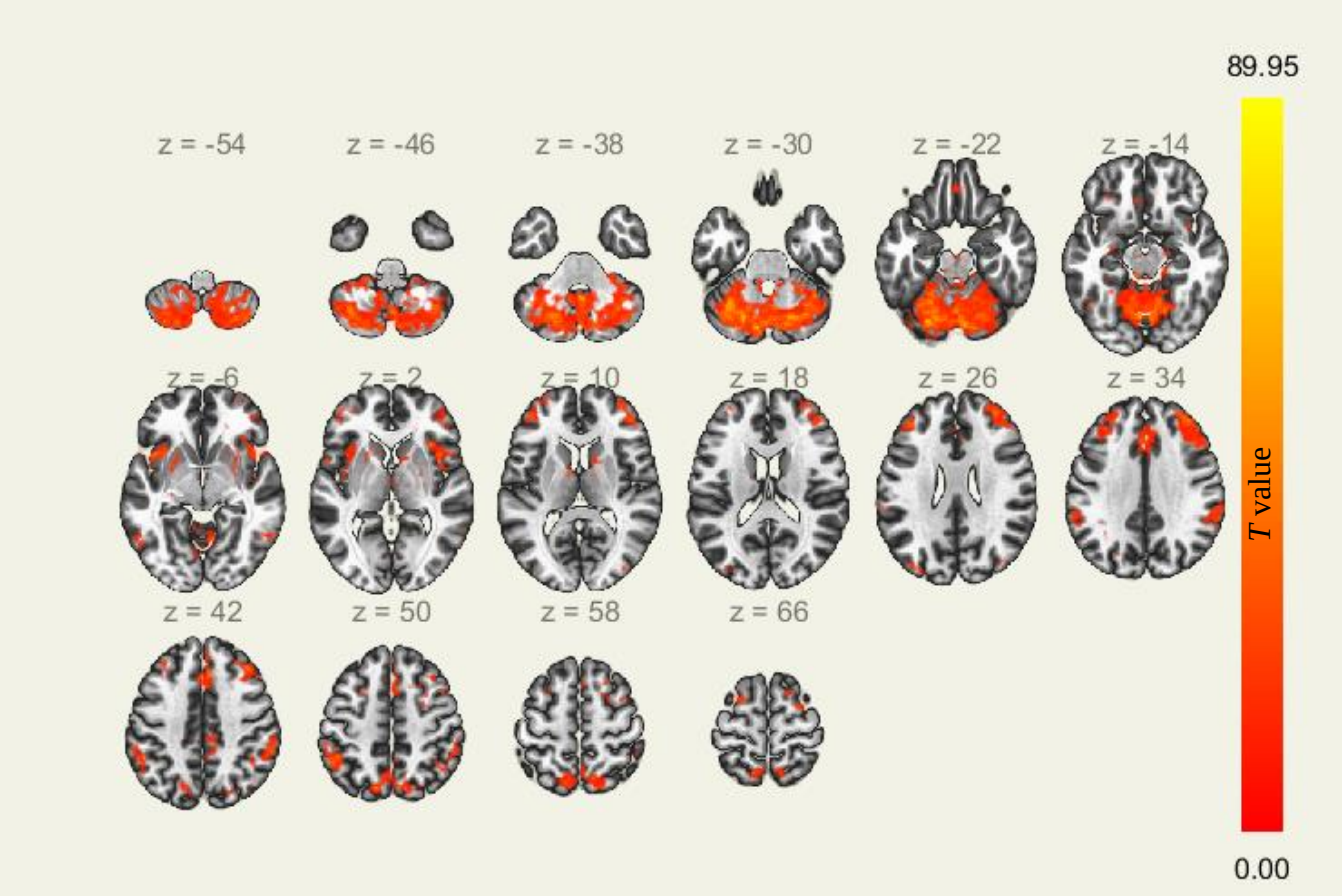

Figure 6. Cerebellar-seeded rsFC correlated with rsFC increases, which were associated with increased trait-anxiety. rsFC in the cerebellum (ROI seed regions: Cereb3, Cereb10, Ver45, Ver45, Ver45, Cereb8) correlated with trait anxiety was linked to rsFC in several areas (i.e., the ACC, the LOC, and the thalamus). Results displayed are an uncorrected at $p < .005$, 20 voxel threshold

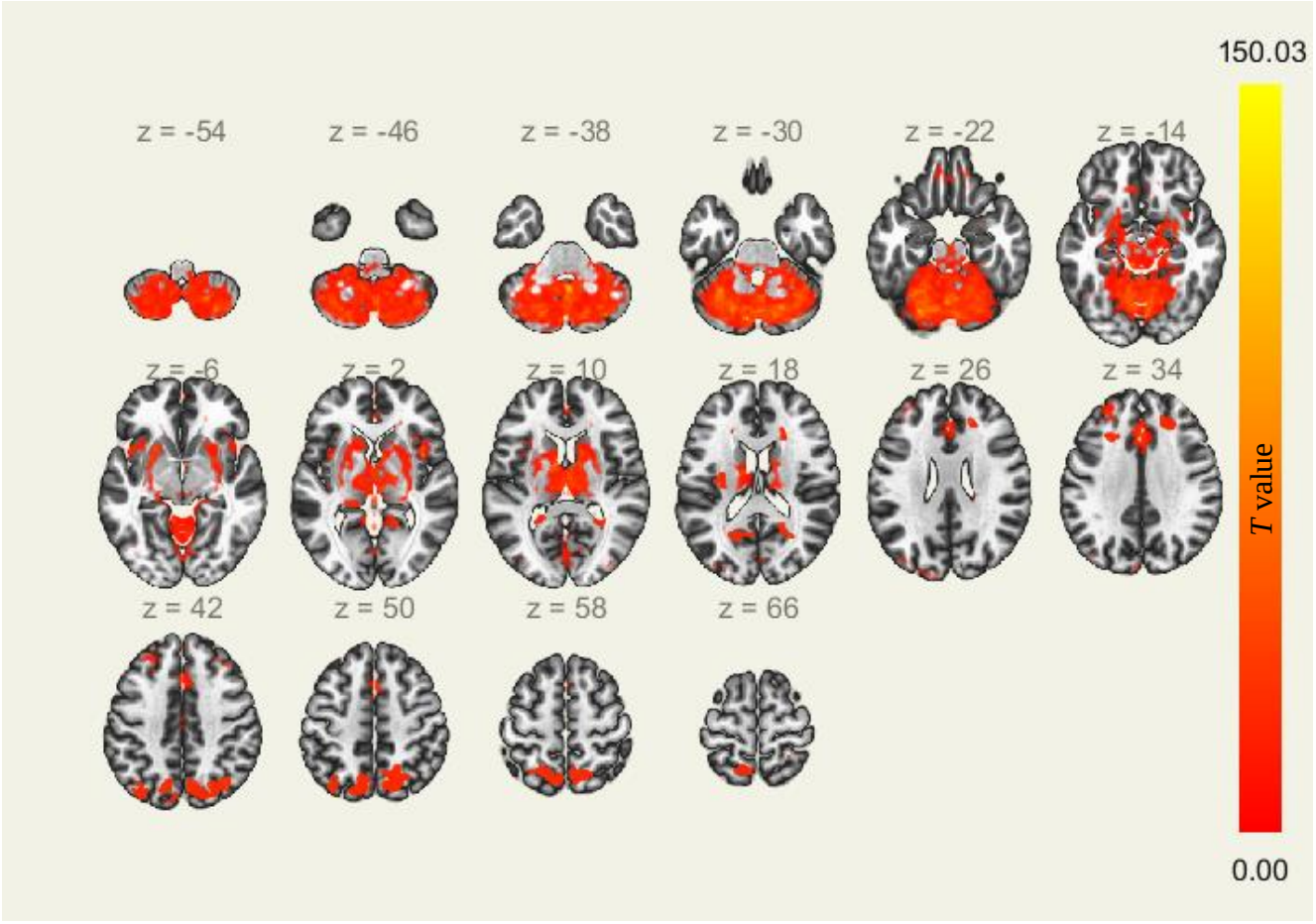

Figure 7. Decreases in cerebellar-seeded rsFC correlated with widespread brain rsFC decreases, along with attention bias decreases, in the ABM training group. Decreases in rsFC in the cerebellum (ROI seed regions: Cereb1, Cereb2, Cereb3, Cereb45, Cereb7, Cereb 8, Cereb10, Ver45, Ver6, Ver8, Ver9, Ver10) correlated with a decrease in attention bias in the ABM training group was linked to decreases in rsFC in several areas (i.e., the ACC, the LOC, the amygdala, the hippocampus, and the thalamus). Results displayed at an uncorrected $p < .005$, 20 voxel threshold.

Seed region (ROI)	Connected to	Hemisphere	MNI Coordinates X	Y	Z	Voxels*	Peak *t* value
Cereb3	Lateral Occipital Cortex (LOC)	R	52	-70	-02	33	5.93
Cereb10	(l)Thalamus	R	12	32	10	28	5.07
Ver45	Anterior Cingulate Cortex (ACC)	L	-42	-02	40	21	6.14
Ver45	(r)Insular cortex	L	-34	18	4	21	6.36
Ver45	Precentral Gyrus	L	-60	8	24	24	6.18
Cereb8	Salience Network (A)Insula	L	-24	-56	-46	21	5.97

* At $p < .001$ uncorrected, $k > 20$.

Table 1. The results from hypothesis one. Heightened trait anxiety was associated with rsFC from the cerebellum to several threat and emotion processing regions and networks. Most notably, there was cerebellar seeded rsFC associated with heightened trait-anxiety from the vermis to the ACC and the insular cortex.

Seed region (ROI)	Connected to	Hemisphere	X	Y	Z	Voxels*	*t* value
Cerebr2	Anterior Cingulate Cortex (ACC)	L	-06	-08	-02	27	6.59
Cereb2	Posterior Cingulate Cortex (PCC)	L	-04	-42	02	20	4.74
Cereb3	Lateral Occipital Cortex (LOC)	L	-48	-62	04	20	4.83
Cereb45	Anterior Cingulate Cortex (ACC)	R	34	-58	-30	24	4.80
Cereb45	Lateral Occipital Cortex (LOC)	L	-46	-58	-8	24	5.21
Cereb7	Anterior Cingulate Cortex (ACC)	L	-00	10	36	20	4.74
Cereb8	(l) Postcentral Gyrus	L	-12	-38	78	23	5.53
Cereb8	(l)Thalamus	R	16	-58	-30	24	5.22
Cereb10	(l)Thalamus	L	-00	-02	-04	27	5.86
Cereb10	(r) Thalamus	R	14	-05	-12	27	5.86
Ver45	Posterior Cingulate Cortex (PCC)	R	04	-60	24	34	5.35
Ver45	(l) Parahippocampal Gyrus	R	36	-36	-10	34	5.89
Ver6	(r)Amygdala	R	60	-58	16	26	4.80
Ver6	(r)Angular Gyrus	R	46	-62	42	26	4.97
Ver6	Lateral Occipital Cortex (LOC)	R	38	-46	60	26	5.94
Ver8	Anterior Cingulate Cortex (ACC)	L	-56	-56	22	23	5.38
Ver8	(r)Angular Gyrus	L	-02	-48	64	21	4.58
Ver8	Lateral Occipital Cortex (LOC)	L	-47	-59	-7	21	4.22
Ver9	(l) Hippocampus	L	-28	-62	64	29	5.70
Ver10	(l) Hippocampus	L	-46	-74	24	25	5.56
Ver10	Lateral Occipital Cortex (LOC)	R	59	-53	2	25	5.94
Cereb8	Salience Network (A)Insula	R	32	-46	36	31	5.45
Cereb7	Salience Network (A)Insula	L	-34	-54	-34	20	6.12
Cereb1	Salience Network (l) SMG	L	-54	06	04	27	5.84
Cereb1	Default Mode Network PCC	L	-02	-48	-42	21	4.82
Cereb2	Default Mode Network (r) LP	L	-44	-64	40	21	4.63

* At $p < .001$ uncorrected, $k > 20$.

Table 2. The results from hypothesis two. Decreases in attention bias in the ABM training was associated with vast decreased connectivity from the cerebellum to several threat and emotion processing regions and networks. Most notably, decreased AB in the ABM training group was noted from Crus I, II, and the vermis to the ACC, LOC, thalamus, amygdala, hippocampus, and throughout resting-state network.

APPENDIX B

NORTHERN MICHIGAN UNIVERSITY

OFFICE OF GRADUATE RESEARCH AND EDUCATION
1401 Presque Isle Avenue
Marquette, MI 49855-5301
906-227-2300 | Fax: 906-227-2315
www.nmu.edu/graduatestudies

Memorandum

TO: Joshua Carlson
Principal Investigator
Psychological Science

DATE: November 21, 2017

FROM: Robert Winn, Ph.D. RJW
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 <u>for all investigators listed on the application</u> 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

APPENDIX C

NORTHERN MICHIGAN UNIVERSITY

OFFICE OF GRADUATE EDUCATION AND RESEARCH
1401 Presque Isle Avenue
Marquette, MI 49855-5301
906-227-2300
906-227-2315
www.nmu.edu/graduatestudies

MEMORANDUM

TO: Joshua Carlson
Psychological Science Department

FROM: Lisa Schade Eckert
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.

APPENDIX D

NORTHERN MICHIGAN UNIVERSITY

MEMORANDUM

OFFICE OF GRADUATE EDUCATION AND RESEARCH
1401 Presque Isle Avenue
Marquette, MI 49855-5301
906-227-2300
906-227-2315
www.nmu.edu/graduatestudies

TO: Joshua Carlson
Lin Fang
Department of Psychological Science

Taylor Susa
Hayley Gilbertson
Katie Elwell
Haley Gaboury
Justine Nelson
Jacquie Cammarata
Hannah Kaull
Natalie Strand
Nathan Schmitz
Mason Steinhauer
Madeline Voltz
Diego Ulloa
Abigail Schaedig
Abbey Zigarac
Analise Osgood

DATE: September 5, 2019

FROM: Lisa Schade Eckert
Dean of Graduate Education and Research

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

Your modification for the project "Characteristics of Attention Bias Modification - New Title: "R15MH1109051: Neuroplasticity in an Extended Amygdala Network as a Target Mechanism for Attention Bias Modification Outcome" has been approved by the Northern Michigan University Institutional Review Board. Please include your proposal number (HS13-555) on all research materials and on any correspondence regarding this project.

Any additional personnel 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 have any questions, please contact the IRB at hsrr@nmu.edu.

APPENDIX E

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

RADIOLOGY - OTHER

Please Print
Name (include middle initial) _____ Weight _____ #

1. Have you had back surgery? ☐ Yes ☐ No Date: _____ Neck, Mid Back, Lower (Circle One)
2. Have you had heart surgery? ☐ Yes ☐ No Date: _____ Type: _____
3. Have you had brain/head surgery? ☐ Yes ☐ No Date: _____ Type: _____
4. Have you had other surgery? ☐ Yes ☐ No Date: _____ Type: _____
5. Ear or eye surgery/implant? ☐ Yes ☐ No Date: _____ Type: _____
6. **Have you at any time had any metal fragments in your eyes? ☐ Yes ☐ No (Worked with metal/grinding/keymaking etc.)**
7. Are you pregnant? ☐ Yes ☐ No
8. Are you breast feeding? ☐ Yes ☐ No
9. Are you allergic to any medications and/or contrast dye? ☐ Yes ☐ No
   If yes, please list: _____

10. Do you have any of the following?

	Yes	No		Yes	No
Cardiac Pacemaker/Defibrillator	☐	☐	Wound Dressing (anticoat 7)	☐	☐
Bladder Stimulator (card for copying)	☐	☐	Internal Wires, Location _____	☐	☐
Loop Recorder	☐	☐	Small Bowel Endoscopy Capsule	☐	☐
Artificial Heart Valves (card for copying)	☐	☐	Metal Foreign Body (gunshot wound, BB shrapnel)	☐	☐
Insulin Pump	☐	☐	Aneurysm or Vascular Clips	☐	☐
Infusion Pump	☐	☐	Drug Delivery Patches (stop smoking, pain, birth control, nitroglycerin, etc.)	☐	☐
Stent, Date:_____ Location:_____	☐	☐	Seizure Disorder	☐	☐
Shunt (brain)	☐	☐	Cancer: Type: _____	☐	☐
Neurostimulator (Tens Unit)/Electrodes	☐	☐	Diabetic, High Blood Pressure, Liver Disease, Liver Transplant	☐	☐
Breast Tissue Expanders	☐	☐	Renal Dialysis/Insufficiency	☐	☐
Grafts or Mesh Repairs Clips	☐	☐	Tattoos or body piercing, Date:_____	☐	☐
Metal Rods, Pins, Plates, Screws, Location:_____	☐	☐	Lifeline	☐	☐
Joint Replacements or Harrington Rod	☐	☐	Removable Dental Work	☐	☐
Metalic Implant or Prosthesis (includes penile & IUD)	☐	☐	Removable Hearing Aid	☐	☐
Mediport	☐	☐	Other: _____	☐	☐

11. Did your doctor give you special medication for todays test? Yes ☐ No ☐

    If yes, drug name(s) _____ Dose: _____ Time: _____

I have answered the above questions to the best of my knowledge.

Signature of Patient or Legal Guardian _____ Date _____

Staff Signature _____ Date _____ Time _____

UP HEALTH SYSTEM MARQUETTE
A Duke LifePoint Hospital

MRI OUTPATIENT HISTORY FORM

Approved: 5/30/19
RADO-0009 (5/19)

Page 1 of 1

APPENDIX G

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)

ii.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 NOT 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.

APPENDIX H

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 2030min 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

78 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

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

79 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 _____

APPENDIX I

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.

Protocol: adult_head_NMU RESEARCH 2018

3-pl T2* FGRE

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*Head*
Plane	*3-PLANE*
Series Description	*3-pl T2* FGRE*

SCAN TIMING	
Number of Echoes	*1*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*

MULTI-PHASE	
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

DIFFUSION	
Recon All Images	*On*

CONTRAST	
Contrast Yes/No	*No*

IMAGING PARAMETERS	
Imaging Mode	*2D*
Pulse Sequence	*Gradient Echo*
Imaging Options	*Seq, Fast*

SCAN RANGE	
FOV	*24.0*
Slice Thickness	*5.0*
Slice Spacing	*5.0*

ACQ TIMING	
Freq	*256*
Phase	*128*
Freq DIR	*Unswap*
NEX	*1.00*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*No*

FMRI	
PSD Trigger	*Internal*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
Tag Type	*None*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*Off*

3-pl T2* FGRE

Cal Head 24

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*Head*
Plane	*AXIAL*
Series Description	*Cal Head 24*
SCAN TIMING	
Number of Echoes	*1*
IMAGE ENHANCE	
Filter Choice	*None*
GATING/TRIGGER	
Auto Trigger Type	*Off*
MULTI-PHASE	
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*
DIFFUSION	
Recon All Images	*On*
CONTRAST	
Contrast Yes/No	*No*

IMAGING PARAMETERS	
Imaging Mode	*3D*
Pulse Sequence	*SPGR*
Imaging Options	*EDR, Fast, ZIP2, Calib*
SCAN RANGE	
FOV	*30.0*
Slice Thickness	*12.0*
ACQ TIMING	
Freq DIR	*R/L*
Auto Shim	*Auto*
Phase Correction	*No*
FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*
SAT	
Tag Type	*None*
TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*Off*

Cal Head 24

FSPGR 3D

PATIENT POSITION	
Patient Entry	Head First
Patient Position	Supine
Coil Configuration	Head
Plane	AXIAL
Series Description	FSPGR 3D

SCAN TIMING	
Flip Angle	9
TE	Min Full
Number of Echoes	1
TI	450
Receiver Bandwidth	125.00

IMAGE ENHANCE	
Filter Choice	None

GATING/TRIGGER	
Auto Trigger Type	Off

FMRI	
PSD Trigger	Internal
View Order	Bottom/Up
# of Repetitions REST	0
# of Repetitions ACTIVE	0

SAT	
Tag Type	None

TRICKS	
Pause On/Off	On
Auto Subtract	0
Auto SCIC	On

IMAGING PARAMETERS	
Imaging Mode	3D
Pulse Sequence	SPGR
Imaging Options	EDR, Fast, ZIP512, ZIP2, IrP

SCAN RANGE	
FOV	25.0
Slice Thickness	1.2
Location per Slab	128
Overlap Locations	0

ACQ TIMING	
Freq	256
Phase	256
Freq DIR	A/P
NEX	1.00
Phase FOV	0.75
Auto Shim	Auto
Phase Correction	No

USER CVS	
User CV23	100.00

MULTI-PHASE	
Seperate Series	0
Trigger Delay without AV	0
Mask Phase	0
Mask Pause	0

DIFFUSION	
Recon All Images	On

CONTRAST	
Contrast Yes/No	No

FSPGR 3D

TENSOR

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*Head*
Plane	*AXIAL*
Series Description	*TENSOR*

SCAN TIMING	
TE	*Minimum*
Number of Echoes	*1*
TR	*10025.0*
Number of Shots	*1*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
Tag Type	*None*
Fat/Water Saturation	*Fat*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*Off*

IMAGING PARAMETERS	
Imaging Mode	*2D*
Pulse Sequence	*Spin Echo*
Imaging Options	*EPI, DIFF, Asset*

SCAN RANGE	
FOV	*22.0*
Slice Thickness	*2.4*
Slice Spacing	*0.0*

ACQ TIMING	
Freq	*128*
Phase	*128*
Freq DIR	*R/L*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*Yes*

USER CVS	
User CV5	*1.00*
User CV17	*1.00*

MULTI-PHASE	
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

DIFFUSION	
Optimized TE	*Yes*
Diffusion Directions	*Tensor*
Number of Diffusion Directions	*30*
Number of T2 Images	*1*
Dual Spin Echo	*On*
Diffusion Tenser Processing Output	*No Selection*
Recon All Images	*Off*

CONTRAST	
Contrast Yes/No	*No*

TENSOR

Ax DWI 1000b 2 NEX ASSET

PATIENT POSITION	
Patient Entry	Head First
Patient Position	Supine
Coil Configuration	Head
Plane	AXIAL
Series Description	Ax DWI 1000b 2 NEX ASSET

SCAN TIMING	
TE	Minimum
Number of Echoes	1
TR	2000.0
Number of Shots	1

IMAGE ENHANCE	
Filter Choice	None

GATING/TRIGGER	
Auto Trigger Type	Off

FMRI	
PSD Trigger	Internal
Slice Order	Interleaved
View Order	Bottom/Up
# of Repetitions REST	0
# of Repetitions ACTIVE	0

SAT	
Tag Type	None
Fat/Water Saturation	Fat

TRICKS	
Pause On/Off	On
Auto Subtract	0
Auto SCIC	Off

IMAGING PARAMETERS	
Imaging Mode	2D
Pulse Sequence	Spin Echo
Imaging Options	EPI, DIFF, Asset

SCAN RANGE	
FOV	22.0
Slice Thickness	5.0
Slice Spacing	0.0

ACQ TIMING	
Freq	96
Phase	192
Freq DIR	R/L
Phase FOV	1.00
Auto Shim	Auto
Phase Correction	Yes

USER CVS	
User CV0	1.00
User CV5	1.00
User CV17	1.00

MULTI-PHASE	
Seperate Series	0
Mask Phase	0
Mask Pause	0

DIFFUSION	
Optimized TE	Yes
Diffusion Directions	All
Number of Diffusion Directions	3
Number of T2 Images	1
Dual Spin Echo	Off
Recon All Images	On

CONTRAST	
Contrast Yes/No	No

Ax DWI 1000b 2 NEX ASSET

Ax T1 MEMP

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*Head*
Plane	*AXIAL*
Series Description	*Ax T1 MEMP*

SCAN TIMING	
Flip Angle	*45*
TE	*Min Full*
Number of Echoes	*1*
TR	*585.0*
Receiver Bandwidth	*31.25*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*

FMRI	
PSD Trigger	*Internal*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
Tag Type	*None*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*On*

IMAGING PARAMETERS	
Imaging Mode	*2D*
Pulse Sequence	*Spin Echo*
Imaging Options	*EDR*
PSD Name	*t1memp*

SCAN RANGE	
FOV	*22.0*
Slice Thickness	*5.0*
Slice Spacing	*0.0*

ACQ TIMING	
Freq	*384*
Phase	*256*
Freq DIR	*R/L*
NEX	*2.00*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*No*

USER CVS	
User CV4	*1.00*

MULTI-PHASE	
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

DIFFUSION	
Recon All Images	*On*

CONTRAST	
Contrast Yes/No	*No*

Ax T1 MEMP

Ax GRE EPI fMRI BOLD

PATIENT POSITION	
Patient Entry	Head First
Patient Position	Supine
Coil Configuration	Head
Plane	AXIAL
Series Description	Ax GRE EPI fMRI BOLD

SCAN TIMING	
Flip Angle	50
TE	30.0
Number of Echoes	1
TR	2500.0
Number of Shots	1

IMAGE ENHANCE	
Filter Choice	None

GATING/TRIGGER	
Auto Trigger Type	Off

FMRI	
PSD Trigger	Internal
View Order	Bottom/Up
# of Repetitions REST	0
# of Repetitions ACTIVE	0

SAT	
Tag Type	None

TRICKS	
Pause On/Off	On
Auto Subtract	0
Auto SCIC	Off

IMAGING PARAMETERS	
Imaging Mode	2D
Pulse Sequence	Gradient Echo
Imaging Options	MPh, EPI, Asset

SCAN RANGE	
FOV	22.0
Slice Thickness	5.0
Slice Spacing	0.0

ACQ TIMING	
Freq	64
Phase	64
Freq DIR	R/L
NEX	1.00
Phase FOV	1.00
Auto Shim	Auto
Phase Correction	Yes

USER CVS	
User CV0	1.00

MULTI-PHASE	
Slice per Location	240
Phase Acquisition Order	Interleaved
Delay after Acquisition	0
Seperate Series	0
Delay after Acquisition without AV	0
Mask Phase	0
Mask Pause	0

DIFFUSION	
Recon All Images	On

CONTRAST	
Contrast Yes/No	No

Ax GRE EPI fMRI BOLD

Ax T2* GRE

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*Head*
Plane	*AXIAL*
Series Description	*Ax T2* GRE*

SCAN TIMING	
Flip Angle	*15*
TE	*Min Full*
Number of Echoes	*1*
TR	*400.0*
Receiver Bandwidth	*31.25*

IMAGE ENHANCE	
Filter Choice	*G*

GATING/TRIGGER	
Auto Trigger Type	*Off*

MULTI-PHASE	
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

DIFFUSION	
Recon All Images	*On*

CONTRAST	
Contrast Yes/No	*No*

IMAGING PARAMETERS	
Imaging Mode	*2D*
Pulse Sequence	*Gradient Echo*
Imaging Options	*FC, EDR*

SCAN RANGE	
FOV	*22.0*
Slice Thickness	*5.0*
Slice Spacing	*0.0*

ACQ TIMING	
Freq	*260*
Phase	*230*
Freq DIR	*R/L*
NEX	*2.00*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*No*

FMRI	
PSD Trigger	*Internal*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
Tag Type	*None*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*2*

Ax T2* GRE

Ax PROBE Multi Voxel 144TE

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*Head*
Plane	*AXIAL*
Series Description	*Ax PROBE Multi Voxel 144TE*

SCAN TIMING	
TE	*144.0*
Number of Echoes	*1*
TR	*1000.0*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*

FMRI	
PSD Trigger	*Internal*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
Tag Type	*None*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*Off*

IMAGING PARAMETERS	
Imaging Mode	*MRS*
Pulse Sequence	*Probe-P*
Imaging Options	*EDR*

SCAN RANGE	
FOV	*25.0*
Slice Thickness	*48.7*
Slice Spacing	*20.0*
Location per Slab	*1*

ACQ TIMING	
Freq	*16*
Phase	*16*
Freq DIR	*A/P*
NEX	*1.00*
Auto Shim	*Auto*
Phase Correction	*No*

USER CVS	
User CV3	*1.00*
User CV18	*7.00*

MULTI-PHASE	
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

DIFFUSION	
Recon All Images	*On*

CONTRAST	
Contrast Yes/No	*No*

Ax PROBE Multi Voxel 144TE