

## ABSTRACT

Title of Thesis: LPP INDEXES BASELINE AND  
TREATMENT-RELATED CHANGES IN  
ANXIETY SENSITIVITY

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Anxiety sensitivity (AS) refers to an individual's tendency to be fearful of anxiety-related bodily sensations (the symptoms that accompany feelings of anxiety)(Reiss et al., 1986). These symptoms can be cognitive (i.e., fear of losing control of mental processes), physical (i.e., fear of catastrophic physiological outcomes such as heart attack or stroke), or social (i.e., concern about negative social judgment and subsequent observable symptoms of anxiety). AS is a well-understood risk factor for Internalizing psychopathology (INT). Cognitive Anxiety Sensitivity Treatment (CAST) (Schmidt et al., 2014) is a technology-based intervention shown to be efficacious in reducing AS, as well as INT. CAST is a fully-computerized brief intervention with two core components: psychoeducation and interoceptive exposure (Craske et al., 1997). In recent work by Schmidt, nontreatment seeking participants with elevated AS cognitive concerns participated in one session of CAST, which produced significant reductions in AS at posttreatment, relative to controls ( $d=0.57$ ).

The primary purpose of this study is to assess the late positive potential (LPP) event-related potential (ERP) component as an index of baseline AS, as well as treatment-related change in AS in response to CAST. In this study 263 participants (with complete EEG data at 1-month follow-up) received either an anxiety reduction intervention (Anxiety; CAST + cognitive bias modification interpretation [CBM-I] with an anxiety focus; N = 65), a mood intervention (Mood; mood psychoeducation + CBM-I with a mood focus; N = 66), or combined ANX and MOOD interventions (Combined; N = 68), as well a repeated contact control group (RCC; N= 64). Prior to the intervention, baseline LPP was measured via exposure to unpleasant, and baseline AS recorded using the ASI-3. Increased LPP amplitude was associated with higher baseline AS ( $r=.184$ ,  $p < .001$ ). We found that the LPP was sensitive to treatment effects in that at month 1, as across treatment groups, baseline LPP amplitude was associated with change in AS from baseline to month 1, with higher amplitude associating with greater reductions in AS ( $r = -.247$ ,  $p < .001$ ). In this study, there were no differences between treatment groups in this relationship between amplitude and treatment change, and there were no significant effects of the decrease task instruction on amplitude. These findings could be indicative of a larger pattern to be assessed in future work, or could be a product of low power. Overall, this work's findings have potential to demonstrate the efficacy of CAST in reducing AS, and given both CAST's and AS's implications in psychopathology measures such as internalizing, we can integrate transdiagnostic approaches and develop novel treatment targets for populations in need.

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ANXIETY SENSITIVITY

by

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## Chapter 1: Introduction

### *Anxiety Disorders: Real-World Implications and Importance of Treatment*

Anxiety is one of the most common and prevalent mental health problems in the United States (Shiele, 2020; Kessler et al., 2012). Wittchen and colleagues (2011) took estimates of 12-month prevalence of mental disorders in Europe and found anxiety disorders to be the most frequent—at 14%—, with depression the third-most frequent at 6.9%. Gustavsson and colleagues (2011) used a metric that estimated total cost per person for a variety of different diseases, as well as total cost per disorder in Europe, and found that anxiety disorders cost an estimated 74 billion Euros annually. Anxiety pathology is a significant factor that, through strong association with debilitating symptoms, high medical costs, and suicidal ideation and behavior, necessitates a great deal of individual and societal burden (Stanley et al., 2018). Advances in diagnostic models and cognitive-neuroscience based treatment targets provide opportunities to develop a low-burden, neuroscience-informed transdiagnostic treatments. Such treatments can have stronger impact with marginalized populations (e.g., those with low-socioeconomic status, substance users, and any other stigmatized group that otherwise are generally less likely to access and receive traditional treatment).

### *Transdiagnostic Structure of Psychopathology: HiTop and Internalizing*

Transdiagnostic models of psychopathology describe latent dimensions theorized to underlie and cause related disorders. Research spanning decades has now investigated common symptoms, behaviors, and diagnoses in children and adults, and an underlying transdiagnostic structure has been widely replicated. This work is

represented in the current hierarchical topology of psychopathology (HiTOP) model (Kotov et al., 2017) that defines an empirically-based hierarchical structure. This model provides high-level dimensions characterizing related disorders (Kotov et al., 2018; Kotov et al., 2021). At the top levels, psychopathology is characterized into factors of related disorders: externalizing (e.g., disinhibition and aggression), internalizing (e.g., fear, anxiety, depression, PTSD), and thought disorder (e.g., psychotic disorders, schizoaffective, schizophrenia). Subsequently, the shared variance among these three factors can be understood as the highest dimension, a general psychopathology (*p*) factor (Krueger, 1999; Krueger et al., 1998; Lahey et al., 2012; Caspi et al., 2014). The core elements of this structure account for genetic and environmental risk factors and have demonstrated invariance across several covariates such as age, gender, culture, ethnicity, and more (Krueger et al., 2003; Kessler et al., 2011, Vollebergh et al., 2001; Eaton et al., 2012; Eaton et al., 2013).

A key benefit of transdiagnostic approaches is in developing treatment targets because they better reflect underlying systems, with empirically validated referents in the brain and physiology (McTeague et al., 2020; Sha et al., 2019; Sprooten et al., 2017), more accurately than traditional diagnostic systems. Thus, these models provide more parsimonious representations, as well as stronger empirical bases for treatment target development. Assessment can then be conducted to demonstrate change in those targets, and then whether change in the transdiagnostic target (e.g., INT) produces change in the outcome symptoms (e.g., depression symptoms). As will be described below, interventions with transdiagnostic targets have the potential for broader impact by addressing multiple disorders. Taken together, this evidence

suggests that in assessing treatment interventions, transdiagnostic approaches could provide important advances. The current study seeks to utilize this understanding of the interrelationships across mental disorders and relate it to underlying neural mechanisms in a transdiagnostic framework. Thus, underlying transdiagnostic factors, or factors that contribute to onset and/or maintenance of multiple different disorders, represent an important avenue for identifying effective treatment targets. Broadly, transdiagnostic intervention approaches provide deeper understanding of psychopathology overall, underlying neural mechanisms, and the development of treatment interventions.

#### *Anxiety Sensitivity: An Overview*

Anxiety Sensitivity (AS) is one of the earliest transdiagnostic constructs, first developed in 1986 by Reiss (1986), and it indexes a fear of fear. AS represents a cognitive predisposition, or inclination, to general fearfulness. More specifically, AS is defined as the extent to which a person is fearful of anxiety-related sensations due to intense beliefs that these sensations will have negative social, physical, and cognitive ramifications. Individuals high in AS have a higher tendency to misinterpret bodily symptoms related to arousal (shortness of breath, trembling, or any form of respiratory distress) as a sign of real and impending danger (Shiele, 2020). Anxiety Sensitivity is conceptualized as a general factor made up of 3 lower-order factors: the cognitive concerns subfactor refers to the misinterpretation that cognitive difficulties are indicative of one “going crazy”, physical concerns refer to the belief that anxiety-related physical symptoms (e.g. increased heart rate) are indicative of serious physical maladies, and the social concerns factor refers to the fear that anxiety symptoms will

lead to social rejection (Stanley et al., 2018, Schmidt, 2006, Zinbarg et al., 1997). AS, as described by Ghisi and colleagues (2016), can be understood as an “anxiety amplifier”: people high in AS disproportionately misinterpret their interoceptive sensations and thus worry about them, and this subsequent worry manifests in increasing the intensity of the experienced anxiety, creating a dangerous and overwhelming cycle of anxious despair for an individual.

*Anxiety Sensitivity as an Anxiety Disorder Risk Factor and Suitable Treatment Target*

Productive development of treatment interventions should focus largely on identifying causal risk factors (Freyd, DePrince, & Zurbriggen, 2001). In line with emerging transdiagnostic formulations of psychopathology, Fernandez (2016) states that risk factors for one disorder can confer risk for other highly comorbid disorders. Anxiety Sensitivity (AS) is an ideal intervention target for treatment of anxiety and mood pathology, as AS is a causal risk factor for both (Narragon-Gainey, 2010). AS is one of the most well-researched transdiagnostic risk factors for psychopathology (Narragon-Gainey) and has been demonstrated to be associated with a number of different INT symptoms and disorders, as it prospectively predicts clinical diagnosis of related psychopathology such as anxiety, depression, panic, and posttraumatic stress symptoms (Sturges et al., 1998; Schmidt et al., 1997; Schmidt et al., 2007). The scope of long-standing, wide-reaching, and focused research regarding AS is exemplified in the fact that the Diagnostic Manual of Mental Disorders Fifth Edition recognizes Anxiety Sensitivity as a risk factor for anxiety psychopathology. AS and its lower order dimensions relate to anxiety and mood disorders; meta-analytic correlations by Narragon-Kainey showed that AS was broadly related to fear and

distress disorders, especially panic, generalized anxiety disorder, and posttraumatic stress disorder. AS is well-positioned as a transdiagnostic target for interventions, having been first introduced and developed decades ago by Reiss (1986). Anxiety Sensitivity has been a well-researched, widely-accepted, and validated transdiagnostic construct that is strongly related to internalizing problems.

A meta-analysis by Olatunji & Wolitzky-Taylor (2009) showed that AS is elevated in patients across anxiety diagnoses, and their findings suggest AS is central to the phenomenology of anxiety disorders such as panic disorder and posttraumatic stress disorder. AS not only predicts anxiety and mood disorder onset, it also plays a fundamental role in the maintenance of these INT problems (Ghisi et al., 2016). Sturges and colleagues studied anxiety sensitivity in response to a hyperventilation task and found those with elevated AS levels tended to rate their subjective anxiety as greater (misinterpretation of anxiety-related sensations). In an experiment that showed evidence of CO<sub>2</sub> as a cue for laboratory fear onset, anxiety sensitivity levels moderated fear response in participants (Forsyth et al., 2000). This research shows that not only has AS been studied in relation to internalizing disorders (causal risk factor for anxiety, mood, and suicide symptoms), but that treatment for AS has been demonstrated to reduce AS, and that reductions in AS produce reductions in current and prospective INT symptoms.

In 2014, Schmidt and colleagues followed up on work done by Schmidt and Eggleston to replicate AS reductions in all domains after a brief, computer-based anxiety sensitivity intervention, further validating the notion that these reductions can have broad beneficial outcomes in all anxiety psychopathology. Further, treatment-

related changes in AS can mediate changes in symptoms (Schmidt et al., 2014; Schmidt et al., 2017; Capron et al., 2017; Schmidt et al., 2007). Schmidt and colleagues developed the core parts of a cognitive AS treatment (CAST) (2007) that requires little training to use and has been demonstrated to reduce AS and an array of internalizing problems, as well as prospectively reducing new internalizing symptoms. Stanley et al. (2018), in a meta-analysis, concluded that AS is related to suicidal ideation and suicide risk: AS amplifies stress and augments suicidality (Capron et al., 2013), but reductions in AS through anxiety sensitivity treatment is associated with lower suicidality (Schmidt et al., 2017). Cadron and colleagues, along with Schmidt and colleagues in 2017, showed again that reductions in AS are associated with reductions in anxiety and mood pathology.

It is notable that at this point, most preventative interventions for anxiety disorders currently aim to modify AS (Shiele 2020). AS is one of the most well-researched transdiagnostic risk factors, has been demonstrated to be associated with an array of INT symptoms and disorders, and is validated as a construct to target to reduce a variety of INT symptoms. The INT-EXT/p-factor structure is emerging as a compelling model of psychopathology, while AS is one of the most well-studied, validated transdiagnostic constructs with demonstrated relationship to internalizing problems. Treatment outcomes have reflected that changes in AS result in changes in internalizing symptoms. This places the current study in a privileged position of evaluating treatment on a construct that is already proven to be productive and fruitful in our understanding of anxiety pathology. The construct of INT is newer, while the construct of AS is more established, well developed, with demonstrated relationships

to INT problems. Focusing intervention programs around AS, a great transdiagnostic construct that is clearly well-suited as an intervention target, can have beneficial broader impacts on people in need of mental health care of anxiety and mood pathology, as this work is seeking to address.

#### *Computerized Anxiety Sensitivity Treatment (CAST) Overview*

Cognitive anxiety sensitivity treatment (CAST) is a technology-based intervention (Schmidt et al. 2014). CAST was originally designed to target the cognitive concerns subfacet of AS, but the aforementioned work by Schmidt and colleagues showed that it was efficacious in both overall AS at the general factor level as well as each of the other subfacets (social concerns and physical concerns) (Schmidt, 2014). Schmidt and colleagues (2014) showed that AS is modifiable using this brief, computer-based interventions aimed at targeting maladaptive cognitions and behaviors, such that reductions in AS led to reductions in anxiety and mood pathology.

CAST is a fully-computerized brief intervention with two core components: psychoeducation and interoceptive exposure (IE) (Schmidt and Trakowski, 2004). The psychoeducation section provides corrective information regarding the nature of symptoms brought on by stress and anxiety (e.g., elevated heart rate, difficulty concentrating). Individuals are taught (using audio and video presentations, as well as interactive features) that physiological arousal and bodily sensations resulting from stress/anxiety are not dangerous, and that their elevated level of AS suggests they may have developed a conditioned fear of this arousal. This conditioned fear is then modified through the use of repeated IE exercises (i.e., computer guided

hyperventilation) to attenuate the fear response to these bodily sensations. Several additional IE exercises are described and participants are encouraged to complete on their own.

#### *Efficacy of CAST Targeting AS*

Computer-based strategies (including psychoeducation strategies, cognitive bias modification (CBM), and their combination) are attractive preventative intervention strategies due to cost effectiveness, scale, and accessibility. Computer-based strategies such as CAST, cognitive bias modification (CBM), and their combination, have the potential to be particularly useful in going forward for treatment and prevention of anxiety and mood pathology. Technology-based interventions have shown the ability in previous work to be successful in reducing psychiatric symptoms (Griffiths et al., 2006), and these interventions have even been suggested to be equally-effective as face-to-face interventions (van't Hof et al., 2009). Schmidt's CAST treatment is brief and easily-implemented, as it does not require therapist or experimenter participation. They have found that nontreatment seeking participants with elevated AS cognitive concerns that participated in one session of CAST produced significant reductions in AS at posttreatment, relative to controls (Schmidt et al., 2014).

Finding significant AS reductions immediately following CAST treatment, provides further evidence for CAST as a potent intervention. In 2020, Shiele and colleagues successfully established CAST as an effective intervention in reducing AS, and this came after translating the intervention into German. They also found that reduction in AS mediated declines in separation anxiety. CAST has been shown to

reduce a variety of INT symptoms, including anxiety, PTSD, depression, insomnia, and suicidal ideation (Mitchell et al., 2014; Raines et al., 2015; Short et al., 2015), thus further supplanting AS as a potent treatment mechanism. Overall, treatments targeting changes in AS appear to have the most positive potential if using CAST, a treatment specifically designed for modifying AS, while simultaneously being practical in use, affordable, and accessible.

#### *Broader Impact and Motivation for Current Study*

Psychoeducation interventions and CBM interventions have evidence of effectiveness, and with AS being known as a validated transdiagnostic construct for anxiety pathology, targeting the modification of AS through computer-based intervention could yield very fruitful treatment outcomes for many people. The potential to reach individuals with lower access to care with effective intervention programs is incredibly powerful, and, for me personally, motivating and exciting. The ability to eliminate the barrier of access to quality mental health treatment to the diverse ethnic and cultural groups that tend to be underserved and underrepresented in this field (children, elderly, those with low socioeconomic status, people of color, etc.) could mean a substantial increase of those in need actually receiving care. A low-resource, neuroscience-validated intervention, specifically CAST, has potential to reach stigmatized populations such as substance users. In fact, the breadth of research over the past few decades relating AS to INT symptoms has also identified associations with externalizing. Elevated levels of AS have been shown to increase substance use (Norton et al., 1997), as it increases internalizing-related motives for an individual to use. Lejuez et al. (2008) found AS to be a unique predictor of treatment

dropout for cocaine users; it is suggested in work by McDermott and colleagues (2009) that among cocaine users, AS is associated with variation in the relationship between PTSD and emotion regulation.

Brief technology-based interventions have prominent scalability, affordability, autonomy, convenience, flexibility, and acceptability to consumers (Kazdin, 2015). Technology-based interventions have the potential to serve many individuals who might not normally have the opportunity to seek treatment, be considered an acceptable and reasonable form of treatment, and expand the setting and providing areas of treatment, among the other reasons of convenience, affordability, scalability, and overall access. Altogether, technology-based interventions provide an elegant solution to diminish multiple barriers due to their convenience, potential to reach a wide variety of individuals with lower access to care, and reduction or elimination of face-to-face meetings while not compromising the quality of care received. Along with the effectiveness of CAST to reduce AS, the ability to disseminate efficacious treatment to a broader community, perhaps a community in need that has been neglected, as I know myself and others like me have felt all too well, is an invaluable opportunity that I hope to seize with this study.

#### *Current Proposal: Culmination of Concepts to New Proposed Research*

To recap, it is understood that AS is a validated transdiagnostic risk factor for anxiety and mood pathology, and that technology-based interventions have shown the ability to deliver effective treatment for mental health care broadly. The brief, computer-based CAST intervention that targets maladaptive cognition and behavior, has been shown to decrease AS, which causally reduces anxiety and mood symptoms.

The current study will include this CAST treatment, measured at two separate timepoints: baseline, and after one month of treatment. The literature on CAST effects is commonly framed immediately after treatment, or up to one month post-treatment (Fitzgerald et al., 2020). In Fitzgerald's meta-analysis, over 70% of the studies (focused on brief treatments for AS) only assessed effects up to 1-month post-intervention (M1). As such, this research will focus on baseline AS scores and 1-month post-intervention.

In my proposed research, I aim to integrate transdiagnostic frameworks: psychopathology, CAST targeting AS, and underlying neural mechanisms. Validating underlying neural mechanisms is innovative in that it provides a possibility of neuroscience-informed intervention for anxiety and mood pathology. Research now suggests that brain activity varies across broad arrays of diagnostic groups, consistent with transdiagnostic formulations of psychopathology (McTeague et al., 2020; Sha et al., 2019). This work identified a pattern of neurocircuit disruptions across psychiatric disorders in brain regions and networks pivotal in emotion processing and regulation, and found meta-analytic evidence of shared modulation of functional connectivity in 3 brain networks of interest across psychiatric disorders. These studies suggest shared mechanisms of network interactions in association with psychiatric disorders.

Overall, the work showed that transdiagnostic psychopathology constructs, like the ones discussed above, have direct referents in neuroscience, and that merging our understanding of psychopathology and treatment with ERP measures could lead to a characterization of separable transdiagnostic systems underlying problem behavior. However, these meta-analyses focused on whole-brain neuroimaging

techniques and/or resting state fMRI. My proposed research is suggesting EEG research, with two event-related potentials (ERPs) elicited in response to emotional stimuli. As Hajcak and McNamara et al. (2010) point out, ERPs directly reflect neural activity, and have excellent temporal precision to index early and rapid changes in neural processes. In work focused on modulating anxiety and mood symptoms, validated and clinically translatable measures of emotional processing, reactivity, and regulation are vital to producing novel research and replicable findings. Further, Dr. Bernat's lab has been engaged in continued efforts to relate ERPs sensitive to transdiagnostic measures of psychopathology on numerous occasions (Hall et al, 2007; Bernat et al., 2020), showing that there is a demonstrated record of using ERP measures from task protocols to index transdiagnostic measures. This work is evidence of the effectiveness of utilizing EEG and ERP measures in order to adequately assess the transdiagnostic concepts this proposed work seeks to address. There are validated ERP measures sensitive to the psychopathology measures of interest in this proposed research.

This project integrates transdiagnostic approaches, including the intervention target (AS), psychopathology measures (INT problems), and underlying neural mechanisms in order to assess the utility, and underlying mechanisms, of an established transdiagnostic AS treatment (CAST) in reducing AS and INT symptoms. Culminating transdiagnostic approaches from these domains through a low-burden and effective technology-based delivery is in line with the goal to develop more coherent interventions with strong impact.

### Emotion Regulation Task and ERP Measures

Most definitions of psychopathology contend that modulated emotion regulation is an important factor (Hajcak and McNamara et al., 2010; Phillips, Ladouceur, & Drevets, 2008b). Recent review work (Phillips et al., 2008) showed a neural model of emotion regulation developed as a framework to identify a relationship between neural abnormalities and a predisposition to developing bipolar disorder, a major psychiatric disorder characterized by severe emotion dysregulation. To better study emotion regulation with a laboratory task, Jackson and colleagues (2000) developed a task including an emotional stimulus (picture), followed by a cue to modulate emotional response: either suppress their response to the stimuli, enhance their response, or passively view without modulating emotional response to the emotional stimuli. Later implementations, including the one currently proposed in this research, show the cue first and then the emotional stimulus (Bernat et al., 2011; Moser et al., 2006; Krompinger et al., 2008).

Importantly, the two measures of interest in this proposed research, the ERP components P300 and Late Positive Potential (LPP), can be useful in understanding the processing of emotional stimuli (Hajcak and McNamara). Both the P300 and LPP are commonly assessed from picture viewing and emotion regulation tasks. The P300 is defined as a broad positive deflection maximal between 300-500 milliseconds post-stimulus onset (Hajcak & McNamara; Johnston et al., 1986). The LPP is another positive deflection that starts around 300ms, but it is much more sustained, with some characterizations of average activity defined from multiple timepoints until 2000ms post-stimulus presentation (Cuthbert et al., 2000; Foti & Hajcak, 2008). Due to the temporal overlap, there is some difficulty sometimes in parsing the two measures. In

conventional emotion regulation tasks, cognitive control of emotion can be assessed as well as simple affective responding.

The LPP in recent years has become a primary measure in studying emotion regulation, whereas modulating the P300 was heavily centralized in early studies reporting on increased positivity following emotional stimuli, the deflection remaining active beyond the traditional P300 window led to the LPP as the more updated focus (Johnston et al., 1986; Lang et al., 1997; Palomba et al., 1997). Both the P300 and LPP show increased positivities following emotional stimuli relative to neutral stimuli, and work further supports the prevailing notion that affective modulation of the LPP measure is quite typical (Bernat et al., 2011; Cuthbert et al., 2000; Schupp et al., 2000). This work found that cognitive control responses (defined as efforts to increase or decrease emotional responding), did show significant relationships to all the measures included in their study (valence and arousal-based measures such as startle blink, heart rate, skin conductance response, etc.), including the ERP measures. Increased positivity to emotional stimuli during the P300/LPP is described as a marker of motivated attention/incentive salience, and Bradley and colleagues defined motivated attention as the notion that emotion directs attention and guides subsequent processing (Bradley et al., 2003). The P300/LPP showing a larger positive peak to emotional stimuli relative to neutral might reflect automatic processing of emotional stimuli due to intrinsic motivational significance, and thus the P300 is modulated.

Further research has elaborated on the fact that the LPP may be particularly useful in studying emotional disruptions (Albanese et al., 2019): it provides a measure

of responding to specific emotional images, and can be increased or decreased when participants are up-regulating and down-regulating their emotional responses (Hajcak and Nieuwenhuis, 2006; Moser et al., 2006). LPP reflects stimulus detection and categorization that occurs every time a sensory stimulus is presented; therefore, the LPP remains robustly detectable even when stimuli are repeated (Parvaz et al., 2016). In fact, Hajcak and Nieuwenhuis (2006) found that the LPP is highly sensitive to the emotional intensity of stimuli, and given this finding combined with the temporal precision of ERPs, the LPP is an ideal candidate to study the time course of emotion regulation. Altogether, P300/LPP amplitude during an emotion regulation task can reflect the extent to which an individual is able to modulate their emotional response.

#### *Emotion Regulation Task Utility in Assessing Treatment Efficacy and Mechanisms*

Assessing effects during an emotion regulation task is important for this proposed research because difficulties in emotion regulation have been associated with various forms of psychopathologies, including INT problems previously discussed such as anxiety and depression (Sheppes, 2015). There is a body of research that shows when one is able to mitigate the emotional impact of a stimulus, like by reappraisal (consciously and intentionally changing the meaning of an emotional stimulus), self-reported negative experience levels decrease (Gross, 2002; Hajcak and Nieuwenhuis, 2006; Hajcak and McNamara et al., 2010). In fact, there is evidence that reappraisal can alter emotional responses to unpleasant stimuli, as shown through an association between neural activity and phenomenological experience (Moser et al., 2006).

The concept of reappraisal is promising for targeting change in AS through CAST, because in reappraisal, similar lines of reasoning apply as with cognitive therapy: targeting maladaptive cognitions that can significantly influence emotion. Both Hajcak and Moser studies indeed found reappraisal-induced LPP modulation following unpleasant stimuli onset. Gross' (2014) process model of emotion regulation focuses on implementation of appropriate strategies that alter emotional response, and it shed light on failures in strategies that contribute to various psychopathologies, and Sheppes (2015) extended the model by removing the exclusive focus on implementation and reviewing other important regulatory stages, in which various psychopathologies (like panic attacks, depression, anxiety, OCD, and more) can subsequently manifest due to failure points at different regulatory stages. Emotion regulation, as defined by Fernandez and colleagues (2016), is the activation of a goal to influence emotion generation. The relationship between problematic selection of emotion-regulation strategies and psychopathology will be exploited in this proposed research, and emotion regulation is the core concept due to the clear link to cognitive control and AS. Individuals high in AS misinterpret anxiety-related sensations as dangerous, and the magnitude of the relationship between one's AS level, ability to modulate response to emotional stimuli, and CAST, CBM, or Combination treatment will be assessed through underlying brain mechanisms in this work. This proposed work is novel, innovative, transdiagnostic, and potentially very informative in terms of shaping future prevention and intervention approaches to anxiety and mood psychopathology.

### Current Study

The primary aim of this study is to examine the utility, and underlying mechanisms, of an established transdiagnostic AS treatment (CAST) in reducing AS. My hypotheses for this study are as follows: 1) Replicating previous work, “increase” instructions will result in increased P3 and LPP amplitude, while “decrease” instructions will result in decreased amplitudes, relative to viewing 2) treatment-related reductions in AS from baseline to 1 month post-treatment 3) At intake, AS will be correlated with amplitude, such that higher levels of AS are associated with higher P3 and LPP amplitude 4) There are differences in treatment-related effects between treatment groups; I am hypothesizing a sensitivity to change scores and 5) similar to the previous hypothesis, I am again hypothesizing a sensitivity to change scores in that there are differences in treatment-related effects, but that the effects vary between task instruction. Through measuring AS at baseline and at a 1-month post-intervention follow up, I will be able to fully examine underlying mechanisms in individuals elevated in AS, as well as the efficacy of treatments targeting AS, with aims to see AS reductions.

The proposed research is based on data collected during a conventional emotion regulation task, a task validated across ERP measures and in a transdiagnostic context to address the psychopathological focus of this research. This study aims to examine how the relationship between P3/LPP amplitude, AS, and CAST-related changes across affective stimuli, emotion regulation task instructions, as well as across treatment groups (to be described in more detail in methods). The proposed work is integrative in that it attempts to contain the major concepts and domains within a sensible, transdiagnostic framework that can inform future

interventions and dissemination of information to the general public: AS, CAST, emotion regulation, and Psychopathology are all connected either directly or indirectly, as evidenced by the bevy of evidence presented above. There is a strong need for low-burden interventions to increase the potential for broad dissemination in lower-SES and minority communities. This proposed research seeks to implement a computerized, brief intervention treatment that is efficient, effective, and accessible, and thus we will assess treatment related changes in AS, the transdiagnostic intervention target, as well as underlying neurophysiological mechanisms through the assessment of the P3/LPP during an emotional modulation task in hopes that reductions in AS lead to reduction in anxiety and mood symptoms; across all major domains of this work, transdiagnostic approaches are being applied, with the potential for broad dissemination and influencing novel treatment programs in the future.

## Chapter 2: Methods

### Participants

Participants (N = 263) were recruited from the community to participate in a computerized treatment study targeting risk factors relevant to Anxiety Sensitivity (AS). Participants' ages ranged from 18 to 79 years old, average age 35.89 years (SD = 16.13), 148 females. All participants were 18 years of age or older and were screened for neurological conditions, visual impairments, and/or traumatic brain injuries.

Other inclusionary criteria were included elevations on AS. The threshold was set to above average risk on Anxiety Sensitivity's cognitive concerns subfacet (>8) (Schmidt & Joiner, 2002). Other inclusionary criteria included: English-speaking participants; no evidence of uncontrolled psychotic-spectrum or bipolar disorders; no imminent suicide risk; no significant medical illness (e.g., cardiovascular disease) that would prevent the completion of interoceptive exposure exercises (i.e., repeated induction of bodily sensations); and/or not participating in psychotherapy at intake. Participants were allowed to be on medications if they were on a stable dose for at least six weeks. Education levels ranged from less than high school, high school, some college, four-year college degree, and graduate school or higher. The racial breakdown ranged as follows: Caucasian, African American, Asian, Native American, Pacific Islander, and other (e.g., biracial). Additionally, some of the sample identified as Hispanic.

### *Missing Data*

Participants were recruited approximately evenly into the ANX/CAST (n = 65), MOOD/CBM-I (n = 66), Combined (68), and Control (n = 64) groups at

baseline. All participants were included in analyses across conditions at baseline, as participants were randomly assigned to each condition and there had yet to be any treatment conducted.

Across conditions, 44 people missed their 1-month post-intervention session: 10 participants in the CAST group, 13 in the CBM-I group, 10 in the Combined group, and 11 in the Control group. Thus, measurements of AS were not conducted for these participants, and total participants for analyses at 1-month post treatment amounted to 219. Subsequent analyses that include M1-BL treatment change scores excluded these participants. Further, investigation into treatment effects focused on treatment groups, relative to the control group, leaving the sample size for this set of analyses to be 166 across the 3 treatment conditions.

## Procedures

### *Screening Appointment*

All study procedures were approved by the university's institutional review board. After meeting initial inclusionary criteria through a brief telephone interview, individuals were brought in to complete a screening appointment. The screening appointment was meant to be more intensive. Suicide risk was assessed at all timepoints (via interview and suicide-relevant self-report measures), and based on risk designated for an individual, actions were in place to provide appropriate, standard care (e.g., suicide hotline information, creating a safety plan, means restriction; Chu et al., 2015). During this screening appointment, along with the thorough suicide risk assessment, participants also underwent a diagnostic interview

(First et al., 2016) with a trained therapist (Joiner et al., 1999). Participants then completed self-report measures to help determine study eligibility and inform diagnostic decisions. If, for any reason, participants were deemed ineligible based on the screening appointment, they were thanked for their time and given relevant community referrals based on their needs.

#### *Baseline Appointment*

Participants completed a baseline neurophysiology assessment (EEG) and were provided with commensurate monetary compensation.

#### *Intervention Appointment (3 Sessions)*

Participants received the intervention at a rate of one 60-minute session per week for three weeks, with all sessions being completed in the clinic. During each session, participants completed their assigned intervention, as well as subsequent assessment measures. In the active treatment conditions, Session 1 included the relevant psychoeducation and CBM interventions. Sessions 2 and 3 included only CBM.

#### *Follow-up Appointment (Month 1)*

Participants completed study questionnaires in an individual testing room. Upon completion of the measures, participants were scheduled for their next follow-up appointment (1 month after baseline/post-treatment) and were awarded any monetary compensation they earned.

### *Randomization*

Eligible participants were randomized, using an online random number generator, to one of four possible study conditions.

### *Intervention Procedures*

#### *Overview*

The three treatment groups received a computer-based intervention that combined psychoeducation, brief exposure therapy (CAST), and Cognitive Bias Modification-Interpretation (CBM-I). The psychoeducation component lasted approximately 45 minutes in the first session and focused on the nature of stress and the effect it has on the body. Participants were taught that the physiological arousal associated with stress is not harmful to them, and they were instructed to participate in guided exercises to correct the fear response associated with said arousal. CAST functioned as the guided exercise. CAST was developed based on educational and behavioral techniques commonly employed in the treatment of individuals with anxiety disorders and was adapted from a similar intervention, called Anxiety Sensitivity Amelioration Training, or ASAT, used by Schmidt and colleagues (2007). During the CAST portion of the session, participants were first directed to complete a standardized assessment of their fear to different arousal sensations. Participants completed repeated exposure trials engaging in an arousing sensation, such as hyperventilation, and subsequently rated the level of arousal they experienced during the exercise (on a scale of 1-10). They were told they would repeat each exercise until their subjective rating of distress was rated as minimal (i.e., a rating of 0-1). They

were also instructed to complete one set of each of the exercises daily until none of the exercises generated any fear/distress.

CBM-I focuses on changing an individual's automatic or reflexive interpretation of incoming information by providing feedback to participants about whether this interpretation of stimuli was correct. During the task, participants were presented with a word (e.g., "excited") for 1 second, followed by the presentation of a sentence (e.g., "You notice your heart is beating faster"). They were subsequently asked to, by buttonpress, determine whether they thought the word was related to the sentence or not by pressing "yes" or "no." On half of the trials, the word and sentence combination created a benign meaning (aforementioned example), while the other half of trials created an anxious meaning (e.g., "stressful" followed by "Your mind is full of thoughts"). Participants were given feedback during training: "correct" feedback was defined as judging the anxious combinations to be "unrelated" and the benign combinations to be "related", while feedback was defined as "incorrect" if they judged the anxious combinations to be related and the benign combinations to be unrelated, they were given feedback that the response is "incorrect." For incorrect responses, the feedback was also accompanied by a horn blast (approximately 85 decibels). An interpretation bias is thus typically measured by the number of trials in which participants endorse benign relationships and reject anxious or depressed combinations. Participants completed 40 test trials with no reinforcement (incorrect or correct feedback), followed by 80 training trials in which each response was given feedback. After the test trials, participants then took a short 5-minute break, and during this break they completed a filler task (simple math problems), followed by

another 80 training trials. Finally, they were given 40 more test trials of novel words and sentences that they had not seen before.

### *Treatment Group*

#### *Anxiety Intervention Condition (ANX)/ CAST Group*

Participants who received the anxiety intervention completed CAST (Schmidt et al., 2014) and an AS-focused CBM program (CBM-I for AS) (Capron & Schmidt, 2016). As mentioned previously, CAST is a fully computerized, 45-minute intervention designed to model the techniques, both educational and behavioral, that are commonly used in anxiety treatments. The CBM-I component used in this intervention condition was programmed using E-Prime software (Schneider, Eschman, & Zuccolotto, 2002). The trial sequence for the CBM-I component is described in detail above in the *Overview* section.

#### *Mood Intervention Condition (MOOD)/ CBM-I Group*

The mood condition paralleled the anxiety condition in that it included a top-down psychoeducational portion as well as a bottom-up CBM portion. Participants who received the mood intervention completed a fully computerized, 50-minute intervention designed to model the educational and behavioral techniques that are commonly used in the treatment of mood disorders, which is the same tact delivered in the ANX condition, except there the techniques being modeled are those that treat anxiety disorders. In the mood intervention, participants were taught that negative beliefs about being isolated and burdensome are usually inaccurate. Following this mood intervention, behavioral activation techniques were introduced as a way to

decrease isolation and feelings of burdensomeness. The CBM-I component of the Mood Intervention Condition was developed by (Holmes et al., 2006). 100 scenarios were presented across five training blocks, containing 20 scenarios each. For more information regarding the CBM-I used, see Holmes et al. (2006).

*Combined Intervention Condition (COMBINED)*

Participants assigned to the combined condition completed both the anxiety and mood intervention conditions. Thus, while this meant that the Combined group intervention was not matched for length, it was still delivered over three sessions, consistent with the other treatment conditions. The order of the mood and anxiety interventions, as well as their respective CBM tasks, were counterbalanced across participants at each session.

*Repeated Contact Control Condition (RCC)*

A relatively simple repeated contact intervention has been suggested to be effective in reducing suicide (Fleischmann et al., 2008; Motto & Bostrom, 2001). Therefore, a repeated contact control condition, or RCC, represents an ethically justifiable control in studies like this proposed one, in which participants at risk for suicide and AS are used. At their baseline appointment, participants in this RCC condition were assigned a personal study coordinator. Participants met with their study coordinator once per week for three weeks (corresponding to the treatment session intervals for those in the active treatment conditions) for a brief check-in where suicide risk was evaluated and preventative measures were taken if needed (e.g., safety plan, lethal means counseling, resource recommendations).

### Diagnostic Interview

#### *Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV)*

The SCID-5-RV is a semi-structured clinical interview that assesses the presence of DSM-5 psychiatric diagnoses (First et al., 2015). The SCID-5-RV was administered by clinical psychology doctoral student therapists who underwent a systematic training procedure. Therapists only began conducting diagnostic interviews once they demonstrated high levels of reliability. All diagnostic decisions were reviewed by a licensed clinical psychologist to ensure high levels of diagnostic accuracy. Diagnostic raters were blind to experimental conditions.

### Self-Report Measures

#### *Anxiety Sensitivity Index-3*

The primary treatment outcome measure was the Anxiety Sensitivity Index (ASI-3; Taylor et al., 2007), which is an 18-item self-report measure designed to assess an individual's tendency to interpret anxiety-related sensations as potentially harmful or dangerous. These sensations may take the form of thoughts/cognitions, physiological experiences, or social situations. The ASI-3 has strong psychometric properties. In the present study, the ASI-3 cognitive concerns subscale demonstrated excellent internal consistency ( $\alpha = .94$ ) at baseline with scores ranging from 0-24 at baseline. Example items include: "When I have trouble thinking clearly, I worry that there is something wrong with me" (cognitive), "It scares me when my heart beats rapidly" (physical), and "It is important for me not to appear nervous" (social). Respondents use a 5-point Likert-type scale ranging from 0 (very little) to 4 (very much) to indicate the extent to which each item reflects their typical experience. In

the present study, ASI was tracked at baseline appointment (BL), as well as one-month post-treatment (M1).

### Experimental Procedures

#### *Overview*

Prior to treatment condition randomization, participants completed a structured clinical interview and self-report measures prior to being scheduled for the EEG session. The recording session consisted of several different tasks, including the emotional picture paradigm (presented second after a resting task), which was utilized for the current study. All data presented in the current study were collected prior to treatment randomization. After participants completed the baseline questionnaires and psychological assessments, they participated in baseline EEG measurements, as well. These measurements included the following tasks: Resting, Emotion Regulation, Fast Pictures, Go/No-go, Gambling, and Oddball.

#### *Psychophysiological Data Extraction*

All neurophysiological data was collected in a dimly lit sound attenuated room, where E-prime version 2.0 was used to present the computer tasks. Experimental stimuli was presented on a 21-inch Dell high definition CRT color monitor, centrally placed in front of participants at a viewing distance of 100 cm.

Neurophysiological data was recorded using a BrainVision 96-channel actiCap (sintered Ag-Ag/Cl; international 10-20 system; Jasper, 1958) as well as a 24-bit battery-supplied active channel amplifier. Horizontal electrooculogram activity was recorded from electrodes placed on the outer canthus of both eyes, while vertical

electrooculogram activity was recorded from electrodes placed above and below the left eye. Impedances were kept below 10 k $\Omega$ . EEG signals were vertex referenced (FCz) during recording. Recordings were collected using a 500Hz sampling rate, analog 0.05 to 100Hz bandpass filter, and digitized at 1000 Hz using BrainVision PyCorder (Brain Vision LLC).

### Data Processing

The EEG data was preprocessed using a toolbox developed by Dr. Spencer Fix and analyzed using a Psychophysiology Toolbox (PTB) developed by Dr. Edward Bernat. Both processes are done through MATLAB scripts.

The preprocessing steps are set up to clean and correct the EEG datafiles. In the end, there will be a set of preprocessed mat files that can then be analyzed through the PTB. Epochs of 3,000ms were taken from 1,000ms pre to 2,000ms post-stimulus with a 500ms pre-stimulus baseline correction, 150ms post-stimulus baseline correction, and were re-referenced to averaged mastoid sites. Data were corrected for ocular artifacts and downsampled to 256Hz using the Matlab resample function (Mathworks, Inc.), which applied an anti-aliasing filter during resampling. The respective triggers for each task were set in the respective task preprocessing script (e.g., loss and gain trials in the gambling task). The PTB will be used to identify principal component measures in each task across frequencies. For all tasks, the feedback data (i.e., the time period after stimulus presentation) will be analyzed. Time-frequency principal component analyses will be conducted to identify important ERP components.

### Emotional Picture-Viewing Paradigm

To closely replicate Jackson et al. (2000), we obtained and used their regulation instructions. The aim was to encourage participants to use cognitive reappraisal strategies as articulated by Gross (1998). In short, participants were told that before a picture was presented, they would be instructed to enhance, suppress, or view the emotion they felt toward the picture. To enhance the emotion, they were asked to increase the intensity of emotion they felt. To suppress the emotion, they were instructed to decrease the intensity of emotion they felt. Suppress, as operationalized here (and in Jackson et al., 2000), corresponds to a reappraisal strategy (Gross, 1998). In addition, it was explained that participants would sometimes be asked simply to view pictures, in which case they were not to attempt to manipulate their emotions. In all cases they were advised to stay focused on the picture and the induced emotion. Incorrect methods of regulation were described as generating unrelated emotions, thinking of things unrelated to the picture, looking away from the picture, or only focusing on parts of the picture.

The emotion regulation task is based on images from the International Affective Picture System (Lang, Bradley & Cuthbert 1997). Participants were shown 24 pleasant pictures (i.e., socially rewarding or erotic pictures) (Kanske, Schönfelder & Wessa 2013), 24 unpleasant pictures (i.e., threat/mutilation images), and 60 neutral images (i.e., non-affective people, places, or objects). Three instruction types were utilized for pleasant and unpleasant images: View (i.e., passively observe the image), increase (i.e., enhance emotional response), and decrease (i.e., reduce emotional response). On view trials, participants were instructed to allow their emotions to happen naturally, and to not manipulate their emotions in any way. For the increase

and decrease trials, participants were instructed not to focus on any specific part of the image or avert their gaze from the picture in order to regulate their emotional reaction and to instead use other emotional regulation strategies. For neutral images, only view trials were conducted, to avoid confusion in trying to regulate emotional responses to non-emotional images. In line with prior work (Moser, Hajcak, Bukay et al., 2006), each trial began with a regulation trial-type cue (i.e., Increase, Decrease, or View) lasting 2000ms, which was followed by the image presentation for 6000ms. Inter-trial intervals consisted of a blue fixation point presented for 2000ms.

Emotional images were divided into six blocks (AS, unpleasant, pleasant, thwarted belongingness, perceived burdensomeness, and suicide) which were further subdivided into five sub-blocks. All 24 trials for a specific emotional content type were presented within a single block, which was split up into 3 blocks of 8 trials for each specific instruction and content type (e.g., all 8 AS View trials were presented in a single block, all 8 Negative View trials were presented in a single block, etc.). Each of these blocks was then separated by a block of Neutral View trials (5 images). Thus, a block of AS trials would be composed of the following sub-blocks: AS View - Neutral View - AS Increase - Neutral View - AS Decrease. The order of the presentation of the instruction blocks (i.e., which instruction type was presented first, second, and third) was counterbalanced across participants. Individual images were also counterbalanced across instruction type, such that images were randomly chosen from a set of 24 images so that each instruction type was composed of 8 distinct images. Blocks and sub-blocks were counterbalanced across people. Regulation instruction and affective ratings were distributed across valence category and

proportionately across content category within each stimulus order. An exception to this was that the neutral images were only presented with the regulation instruction “View” to avoid confusion of trying to regulate emotional responses to a non-affective image. Analyses of reactivity in this study only included unpleasant (UP) imagery, in line with previous work (Jackson et al., 2000; Allan et al., 2019). AS focuses on exaggerated reactivity to negative/unpleasant stimuli (e.g., stress and anxiety symptoms), and the fear of anxious arousal due to a belief of negative incoming stimuli (physical, cognitive, and/or social consequences) (Schmidt et al., 2014; Allan et al., 2019). The LPP is increased for emotional stimuli relative to neutral, as literature concludes that it is a marker of motivated attention (Bradley et al., 2003; Lang et al., 1997). The P3 and LPP, emotional stimuli are automatically processed, as they are natural targets (Hajcak et al., 2010), and AS reflects an exaggerated negative response to unpleasant stimuli, this study featured unpleasant imagery exclusively.

#### *Electrophysiological Data Extraction*

The LPP was measured as the mean voltage from 350-1500ms after stimulus onset. Based on the scalp topography of the LPP in our data and the selection of centro-parietal electrodes in previous studies, the LPP was measured at CPz (Brown, van Steenbergen, Band, de Rover, & Nieuwenhuis, 2012; Gable, Adams, & Proudfit, 2015; Thiruchselvam, Blechert, Sheppes, Rydstrom, & Gross, 2011).

#### *Data Reduction*

The time-domain P3 ERP component was defined and used for analysis of early processing differences between groups. The P3 was defined as the positive

deflection ranging from about 281ms to 422ms (36 to 54 bins), as it is generally maximal around 350ms (Hajcak et al., 2010). Also explored was the late positive potential (LPP), a late slow wave ERP component ranging from 350ms to 1500ms, explored for more latent processing differences. P3 and LPP are similar in that they are both positivities heightened for emotional stimuli, and they are both evident by 300 milliseconds. Due to the similarities and overlap, it can be difficult to parse the P300 and LPP, but evidence of different timecourse and topographical distribution helps clarify the two ERP components. The P3 is evident predominantly at parietal sites and is generally maximal earlier in time, while the LPP is a later-peaking component that can be evident at frontal (or frontocentral) sites in EEG topographical distribution. Due to the fact that there is some overlap between the P3 and LPP, and that one of the most distinctive characteristics of the LPP that separates itself from the P3 is the longer duration, in their review, Hajcak and colleagues suggested to study and evaluate the P3/LPP in multiple windows at parietal sites and frontal/central sites. For this reason, The LPP window from approximately 350-1500 milliseconds is split into 3 waves: early wave (EW: 328-656 ms), middle wave (MW: 656-1000 ms), and late wave (LW: 1000-1500 ms) LPP. Further, we defined analyses across two clusters: a frontal cluster, and a parietal cluster. For frontal and parietal analyses, two clusters were utilized for analyses. The frontal cluster was a subset of 14 electrodes, centered around a frontocentral electrode (FCz). The parietal cluster was a subset of 13 electrodes, centered around a parietal electrode (Pz).

Next, a difference waveform approach was taken. For baseline analyses, the waveform approach was taken by subtracting average activity in individuals high in

baseline AS from average activity in individuals low in baseline AS. For analyses looking at post treatment AS change scores from baseline to month one, the approach was taken by subtracting average activity in individuals high in ASI change scores from average activity in individuals low in ASI change scores, within the Unpleasant stimuli condition, for each participant and for each electrode.

## Chapter 3: Data Analytic Plan

To assess the hypotheses, analyses will be conducted for both frontal and parietal clusters, either separately, or including frontal/parietal as a factor. Hypotheses are numbered to match the presentation in the *Current Study* section.

- 1) First, in order to validate the task operation, differences between increase, decrease and view conditions will be assessed. Replicating previous work, the first hypotheses are that “increase” instructions will result in increased P3 and LPP amplitude, while “decrease” instructions will result in decreased amplitudes, relative to viewing. These hypotheses will be assessed using an ANOVA. A one-way ANOVA will be conducted with each ERP measure (P3 and LPP, respectively) as the dependent variable, with emotion regulation task (increase, decrease, and view) as the independent variable.
- 2) Next, I will assess the second hypothesis, replicating previous work, of treatment-related reductions in AS, both across and within treatment groups. We’re predicting here that AS will decrease, as seen in lower AS scores posttreatment, as further replication and validation of the treatment efficacy in targeting AS. A t-test will be conducted to compare AS at baseline to AS at 1-month post-treatment.
- 3) Next, the baseline P3 and LPP measures will be correlated with baseline AS, to assess for prediction at intake. This will assess the third hypothesis that P3 and/or LPP amplitude can index a sensitivity to AS, as such that higher levels of AS are associated with higher P3

and LPP amplitude. Correlations will be conducted between baseline AS and each ERP measure to assess this hypothesis.

- 4) Then, the baseline P3 and LPP measures will be correlated with measures of change in AS between baseline and 1-month (change score), in order to assess for CAST-related treatment change between groups. This will assess the fourth hypothesis that there are differences in treatment-related effects between treatment groups; we will be assessing a sensitivity to change scores. The hypothesis here is that there exists differences among the means, we are not necessarily hypothesizing in a directional manner the nature of the differences. This will be done using an ANOVA with a continuous predictor (AS change score) and a categorical predictor (group: Anx, Mood, Combined), with the P3 and LPP measures as the dependent variable. This analysis will assess for any differences in treatment effects between groups across emotion regulation instructions.
- 5) Differences in treatment-related effects for the instruction condition will also be assessed (increase, decrease, and view). This, like the previous analysis, will also be testing the fifth hypothesis of a sensitivity to change score, but this time taking emotion regulation task instruction into account. Similarly, the hypothesis is not directional: I hypothesize that there exists differences in treatment-related effects among the different instruction conditions. An 2 (instruction: increase, decrease, view) x 3 (treatment group) ANOVA

will first be conducted to test for main effects instruction, group, and the interaction (to assess if effects varied by emotion regulation instruction). It is noteworthy that due to our study being underpowered (around ~225 individuals with month 1 AS scores due to attrition), the tests will be framed as an AS x group within each task instruction, with P3 and LPP measures as the dependent variable.

In summation, the analysis for this proposed work is very straightforward. The analyses consist mainly of correlations. There is much to be interpreted from any potential findings we come across in our statistical analyses. These analyses overall will allow for an examination of efficacy of treatment on AS by assessing potential modulations/reductions of AS one month after treatment, assess underlying mechanisms through a time-domain LPP approach that relates the ERP measures to treatment group and AS at baseline and 1-month post-treatment, and any differences within or across emotion regulation task instruction and treatment group for the proposed measures. This methodology ensures an ability to fulfill our aim of assessing CAST and brain mechanisms confidently.



## Chapter 4: Results

### Baseline ERP Measures and Baseline AS

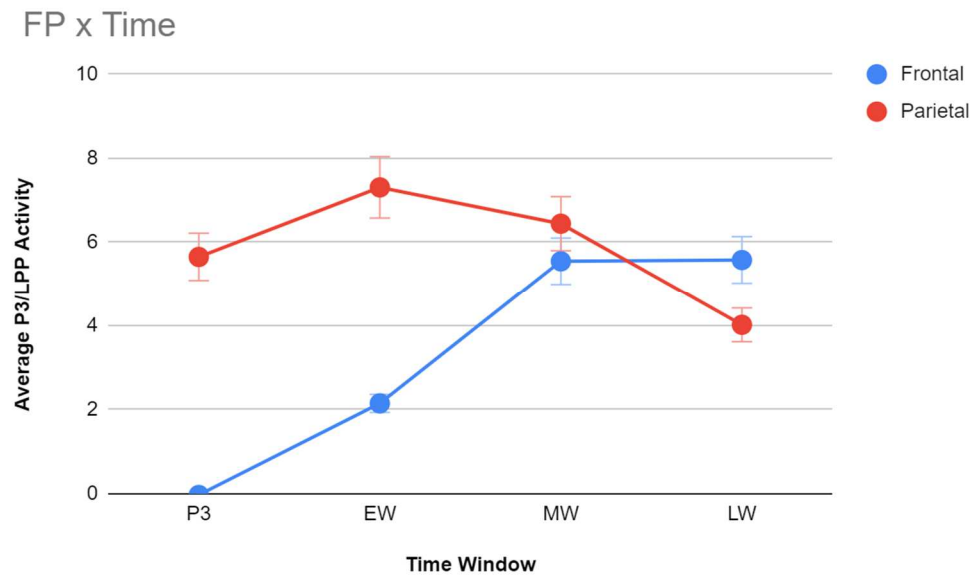
To assess for prediction at intake, in accordance with #3 of the Data Analysis Plan, baseline AS was correlated with baseline P3/LPP measures. An ANOVA was conducted to assess a relationship between the P3/LPP ERP and baseline AS. Pearson correlation coefficients were computed across all participants, and across task instruction, at baseline to assess the linear relationship between ERP and AS. All significant correlations reported are significant at the  $p < .05$  level. Analyses were conducted for reactivity to unpleasant images. Reactivity to pleasant images was not related to baseline AS ( $F(1, 261) = 2.44, p = 0.120, \eta^2 = .009$ ), nor was baseline AS related to neutral images ( $F(1, 261) = .750, p = 0.387, \eta^2 = .003$ )

ANOVA results revealed a significant effect of baseline AS on P3/LPP ( $F(1, 261) = 9.12, p = 0.003, \eta^2 = .034$ ) (**Table 1**). Across all experimental conditions, there does exist a relationship between baseline AS and the P3 through LW-LPP. Baseline AS was not related to topographical clusters (frontal and parietal, or FP) (FP x AS:  $F(1,261) = .000, p = .989, \eta^2 = .000$ ), and AS was not related to time (Time x AS:  $F(1,261) = .563, p = .454, \eta^2 = .002$ ). ANOVA results indicate that distributed across topography, and across the time windows, a relationship between Anxiety Sensitivity and P3/LPP is present: higher P3/LPP amplitude is associated with higher baseline AS. There also existed an interaction between topography and time (FP x Time:  $F(1,261) = 119.04, p < .001, \eta^2 = .313$ ), indicating that activity differs within time windows between topographical cluster, such that parietal effects start earlier, around the P3, and frontal effects start later, around MW-LPP (see **Figure 1**).

**Table 1.** Omnibus ANOVA: Baseline AS and P3/LPP

	SS	MS	F(1,261)	p	$\eta^2$
Time	153.05	153.05	5.85	.016	.022
FP	623.51	623.51	27.83	< .001	.096
AS	715.91	715.91	9.12	.003*	.034
AS x Time	14.74	14.74	.563	.454	.002
AS x FP	.004	.004	.000	.989	.000
FP x Time	853.71	853.71	119.04	< .001*	.313
FP x Time x AS	3.33	3.33	2.65	.105	.010
Error	20497.24	78.53			

Note: \*  $p < .05$

**Figure 1.** Omnibus ANOVA Plot: FP x Time Interaction on P3/LPP Amplitude**Table 2.** Mean Activity at Each Time Window

	Frontal	Parietal
P3	-.029	5.65
EW	2.15	7.31
MW	5.55	6.44
LW	5.58	4.02

Frontally, a one-way ANOVA with P3/LPP windows revealed a significant effect of baseline AS on P3/LPP ( $F(1, 261) = 6.48, p = 0.012, \eta^2 = .024$ ). Baseline AS is significantly related to reactivity. There was also an effect of time on P3/LPP ( $F(1, 261) = 44.85, p < .001, \eta^2 = .147$ ). Post hoc comparisons of means suggested that amplitude is rising from P3 to LW, with no differences in activity from MW to LW (see **Table 2** for statistical means). These results indicate that at the different P3/LPP windows, frontal EEG activity was significantly different. Parietally, it was similarly revealed to be an effect of baseline AS on P3/LPP ( $F(1, 261) = 7.86, p = 0.006, \eta^2 = .029$ ), as well as an effect of time on P3/LPP ( $F(1, 261) = 71.11, p < .001, \eta^2 = .214$ ): activity rose from the P3, was strongest in the EW LPP, and declined in the MW and LW (**Figure 1**).

Correlation analyses confirmed the nature of the relationship between baseline AS and P3/LPP activity, such that higher amplitude (heightened emotional reactivity) is associated with higher AS at intake,  $r(261) = .184, p = .005$ . **Table 3** below shows the correlations, across clusters, within time windows, to show the effects are largely significant within the LPP: AS is correlated with MW-LPP,  $r(261) = .197, p = .001$ , and LW,  $r(261) = .182, p = .003$ . Further correlations conducted within clusters are presented below as well. Frontally, there was a positive correlation between MW-LPP and Anxiety Sensitivity,  $r(261) = .16, p = .011$ . There was also a positive correlation between LW-LPP and Anxiety Sensitivity,  $r(261) = .18, p = .004$ . The correlation between P3 amplitude and AS, while insignificant, was trend level,  $r(261) = .12, p = .063$ . In parietal correlation analyses, there was a positive correlation between MW-LPP and Anxiety Sensitivity,  $r(261) = .20, p < .001$ . There was also a positive

correlation between LW-LPP and Anxiety Sensitivity,  $r(261) = .19$ ,  $p = .002$ . The correlation between P3 amplitude and AS was insignificant,  $r(261) = .097$ ,  $p = .116$ . The correlation between EW-LPP and AS was insignificant, though at trend level,  $r(261) = .11$ ,  $p = .064$ .

**Table 3.** Correlation between and across P3/LPP time windows with Baseline AS.

	P3	EW	MW	LW	Overall
BL AS	.106	.088	.197*	.182*	.184*

Note: \*  $p < .05$

**Table 4.** Correlations between P3/LPP and Baseline AS within cluster

	Frontal				Parietal			
	P3	EW	MW	LW	P3	EW	MW	LW
BL AS	.115	.087	.157*	.178*	.097	.114	.204*	.189*

Note: \*  $p < .05$

Taken together, these results support the hypothesis that P3 or LPP amplitude can be used to index a sensitivity to AS, such that higher levels of AS were associated with higher LPP amplitude.

#### *Treatment-Related Reductions in AS*

To assess for treatment-related reductions in AS, both within and across treatment groups, paired samples t-tests were conducted to compare AS at baseline and AS 1-month after treatment (see **Table 5** for results).

Across treatment groups, there was a significant decrease in AS 1-month post treatment ( $M = 16.35$ ,  $SD = 12.97$ ) compared to baseline AS ( $M = 29.06$ ,  $SD = 14.08$ ),  $t(164) = 12.66$ ,  $p < .001$ , Cohen's  $d = .985$ . In the CAST group, there was a significant decrease in AS in the month after treatment ( $M = 16.44$ ,  $SD = 12.21$ ) compared to AS measured at baseline ( $M = 31.62$ ,  $SD = 14.83$ ),  $t(54) = 8.51$ ,  $p < .001$ .

.001, Cohen's  $d = 1.15$ . In the CBM-I group, there was a significant decrease from baseline ( $M = 25.58$ ,  $SD = 12.74$ ) to M1 ( $M = 17.77$ ,  $SD = 12.86$ ),  $t(52) = 5.50$ ,  $p < .001$ , Cohen's  $d = .755$ . Similarly, there was a decrease from baseline ( $M = 29.82$ ,  $SD = 14.11$ ) to M1 ( $M = 14.93$ ,  $SD = 13.84$ ) in the Combined group,  $t(56) = 8.24$ ,  $p < .001$ , Cohen's  $d = 1.092$ .

**Table 5.** T-tests for Baseline and M1 AS within group and across treatment groups

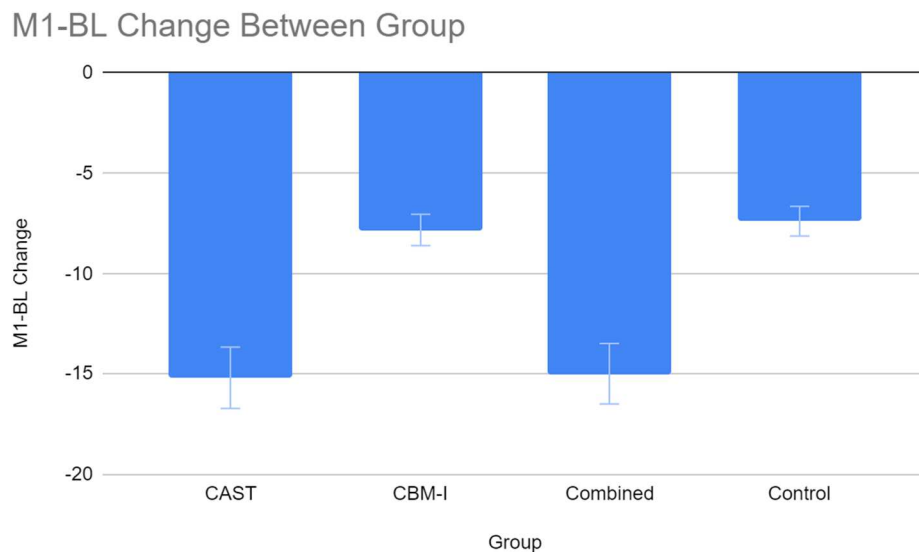
Group	Baseline		1-Month		$t$	$p$	Cohen's $d$
	$M$	$SD$	$M$	$SD$			
CAST	31.62	14.83	16.44	12.21	8.51	< .001*	1.15
CBM-I	25.58	12.74	17.77	12.86	5.50	< .001*	0.755
Combined	29.82	14.41	14.93	13.82	8.24	< .001*	1.09
Across Tx Group	29.06	14.08	16.35	12.97	12.66	< .001*	.985
Control	30.02	14.28	22.72	15.10	4.14	< .001*	.564

Note: \*  $p < .05$

Interestingly, there was also a significant difference in the Control group, in that there was a significant decrease in AS from baseline ( $M = 30.02$ ,  $SD = 14.28$ ) to M1 ( $M = 22.72$ ,  $SD = 15.10$ ),  $t(53) = 4.14$ ,  $p < .001$ , Cohen's  $d = .564$ . To assess differences in treatment effects, a one-way between subjects ANOVA was conducted to compare the treatment effects in the 4 treatment groups. There was a significant effect of Condition on AS M1-BL change scores at the  $p < .05$  level for the 4 treatment groups ( $F(3, 215) = 6.52$ ,  $p < .001$ ,  $\eta^2 = .083$ ). Post hoc comparisons using the Tukey HSD test indicated that relative to the Control group, treatment effects were larger in the CAST group. The mean treatment change score (M1-BL) for the CAST group ( $M = -15.2$ ,  $SD = 1.69$ ) was significantly larger than the Control

group ( $M = -7.38$ ,  $SD = 1.73$ ). The Combined group's treatment effects were also larger relative to the Control group, as the Combined group's mean change score ( $M = -15.00$ ,  $SD = 13.30$ ) was larger than the Control's. The CBM-I group ( $M = -7.81$ ,  $SD = 1.73$ ) did not significantly differ from the Control group in terms of treatment effects. Further, no significant differences were found between the CAST group and the Combined group. The effects in the CAST group were however larger than the effects of the CBM-I group, as indicated by higher treatment change in CAST. Further, the Combined group ( $M = -15.00$ ,  $SD = 1.65$ ) also showed significant differences with the CBMI group. These results indicate that the CAST and the Combined treatment groups showed the highest effect on treatment-related change in AS scores from M1 to BL. More specifically, CAST and Combined groups led to greater reductions in AS relative to the CBM-I and Control groups, while the CBM-I and Control groups did not differ in their treatment related AS reductions. See **Figure 2** for a visual depiction of AS change from baseline to M1.

**Figure 2.** Change in AS from Baseline to M1 within Each Treatment Group and Control



#### AS Treatment Change Predicted by Baseline P3/LPP Measures

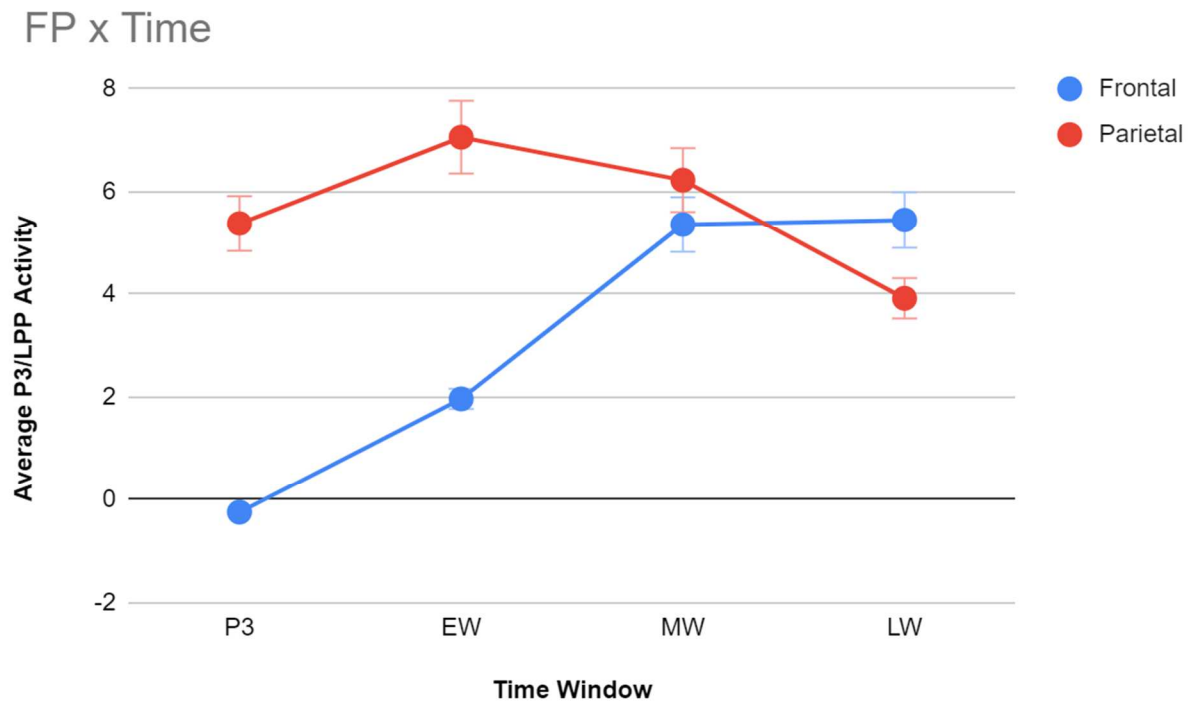
In accordance with #4 of the Data Analysis Plan, analyses were conducted to correlate baseline P3 and LPP measures with measures of change in AS between baseline and 1-month (change score). Results from ANOVAs with AS Change Score and treatment group as predictors (see Figure 8), as well as correlation coefficients, are explained below.

Similar to results for the relationship between P3/LPP and baseline AS, omnibus testing revealed a significant relationship between AS change scores 1-month post treatment and baseline P3/LPP measures ( $F(1,164) = 9.23$ ,  $p = .003$ ,  $\eta^2 = .053$ ) (**Table 6**). This result indicates that across topography, and across the time windows, a relationship between baseline P3/LPP and change scores from baseline to one month is present. Across treatment groups, treatment-related effects are associated with baseline P3/LPP ERP measures. ASI change scores are not related to time ( $F(1,164) = .017$ ,  $p = .897$ ,  $\eta^2 = .000$ ), nor are they related to frontal and parietal topography differently ( $F(1,164) = .019$ ,  $p = .891$ ,  $\eta^2 = .000$ ). Further, there exists an interaction between topography and time (FP x Time:  $F(1,261) = 184.78$ ,  $p < .001$ ,  $\eta^2 = .530$ ), stated earlier that parietal effects start earlier in time, at the P3, and frontal effects start later, during the LPP (Figure 3). The omnibus revealed that there were no significant differences between the 3 treatment groups on P3/LPP activity ( $F(1,164) = .670$ ,  $p = .513$ ,  $\eta^2 = .008$ ). Regression analysis revealed that the relationship between P3/LPP activity and ASI change scores was not significant between treatment groups (Beta = .256,  $t = 1.11$ ,  $p = .269$ ).

**Table 6.** Omnibus ANOVA: M1-BL Change Score and P3/LPP

	SS	MS	F(1,164)	p	$\eta^2$
Time	503.36	503.36	17.47	< .001	.022
FP	1018.03	1018.03	43.79	< .001	.211
M1-BL AS	718.20	718.20	9.23	.003*	.053
M1-BL x Time	.488	.488	.017	.897	.000
M1-BL x FP	.436	.436	.019	.891	.000
FP x Time	1417.91	1417.91	184.78	< .001*	.530
FP x Time x M1-BL	.785	.785	.598	.440	.004
Error	12763.65	77.83			

Note: \*  $p < .05$

**Figure 3.** Omnibus ANOVA Plot: FP x Time Interaction on P3/LPP Amplitude

Correlation analyses reveal the nature of the relationship between treatment change scores and baseline P3/LPP activity. Across treatment groups, time windows, and clusters, ASI treatment change scores are correlated with treatment change, such

that higher baseline reactivity is associated with greater AS reductions across treatment groups,  $r(164) = -.247$ ,  $p = .001$ . Within each P3/LPP window, the correlation was also significant (see **Table 7** below). The control group did not show significant correlations between treatment change and EEG activity,  $r(51) = -.027$ ,  $p = .846$ . Although there appears to be no between-group differences, a one-tailed Fisher's Z transformation was marginally significant between treatment groups and the control group ( $z = 1.393$ ,  $p = .082$ ), indicating overall treatment-related effects on the relationship between P3/LPP and ASI change scores.

**Table 7.** Correlations between P3/LPP and M1-BL Scores

	P3	EW	MW	LW	Overall
M1-BL	-.164*	-.163*	-.242*	-.200*	-.247*

Note:  $p < .05$

*Regression to Assess Relationship between Baseline Measures and Treatment Change*

A regression analysis was conducted to see if baseline AS and P3/LPP ERP measures predicted the total M1-BL treatment change score. Due to the omnibus showing no difference in time windows and topographical clusters on Anxiety Sensitivity, the analysis was conducted across P3/LPP time windows and clusters.

**Table 8.** Regression Model: M1-BL Change Predicted by ERP and BL AS

Effect	Estimate	<i>t</i>	95% CI		<i>p</i>
			<i>LL</i>	<i>UL</i>	
Predictors					
BL AS	-.514	-7.75	-.588	-.348	< .001*
ERP	-.132	-1.99	-1.05	-.005	< .048*

Note: \*  $p < .05$ .

A regression model with our ERP measures and baseline AS explained a significant amount of variance in treatment change ( $F(2,163) = 36.29, p < .001$ ,  $R^2 = .31$ , Adjusted  $R^2 = .30$ ). Additionally, both baseline AS (Beta  $-.514, t = -7.75, p < .001$ ) and P3/LPP (Beta  $-.132, t = -1.99, p < .05$ ) activity were significant predictors (**Table 8**). Negative directions of both estimates indicate that higher P3/LPP reactivity and higher AS at baseline predicts greater AS reduction from baseline to M1.

#### Assessment of Emotion Regulation Task Instruction

To validate the emotion regulation task (data analysis #1), differences between increase, decrease and view conditions were assessed. A one-way within-subjects ANOVA was conducted to compare the effect of task instruction on P3 and LPP amplitudes, respectively (**Table 9**).

**Table 9.** Task Validation ANOVAs.

	Frontal				Parietal			
	SS	F(1,265)	Sig	$\eta^2$	SS	F(1,265)	Sig	$\eta^2$
P3	19.01	.852	.357	.003	120.32	11.11	< .001*	.040
EW	35.92	2.35	.126	.009	90.13	8.77	.003*	.032
MW	49.41	2.29	.131	.009	59.15	4.14	.043*	.015
LW	.568	.022	.883	.000	17.32	.935	.334	.004

Note: \*  $p < .05$

In parietal analyses, there was a significant effect of task instruction on P3( $F(1,265) = 11.11, p < .001, \eta^2 = .040$ ), EW ( $F(1,265) = 8.77, p = 0.003, \eta^2 = .032$ ), and MW-LPP ( $F(1,265) = 4.14, p = 0.043, \eta^2 = .015$ ) amplitude. In the P3 window, post hoc comparisons of means (see **Table 10**) indicated that the mean

amplitude for the Enhance/increase condition ( $M = 6.19$ ,  $SD = .336$ ) was significantly higher than both the mean amplitude for the Suppress/decrease condition ( $M = 5.47$ ,  $SD = .302$ ) and the View condition ( $M = 5.26$ ,  $SD = .308$ ). The mean difference between the decrease and view conditions was not significantly different. In the early wave LPP window the mean amplitude for the increase condition ( $M = 7.77$ ,  $SD = .315$ ) was significantly higher than the mean amplitude for decrease ( $M = 6.95$ ,  $SD = .296$ ) and view ( $7.16$ ,  $SD = .313$ ) conditions, respectively; decrease and view conditions were not significantly different ( $p = .430$ ). In the MW-LPP, the mean amplitude in the Enhance condition ( $M = 6.81$ ,  $SD = 4.77$ ) was significantly higher than in the Suppress condition ( $M = 6.18$ ,  $SD = 4.41$ ). These results are in support of the hypothesis that increase instructions led to increased P3 and LPP amplitudes relative to the viewing condition, but the results are not in support of the hypothesis that decrease instructions lead to decreased amplitude relative to viewing. The ANOVA in the LW-LPP ( $F(1,265) = .935$ ,  $p = 0.334$ ,  $\eta^2 = .004$ ) showed no significant differences in effects of task instruction on P3 and LPP amplitude.

**Table 10.** Parietal means in each instruction condition.

	View		Enhance		Suppress	
	Mean	SD	Mean	SD	Mean	SD
P3	5.26	5.02	6.19	5.49	5.47	4.93
EW	7.16	5.11	7.77	5.13	6.95	4.83
MW	6.27	4.79	6.81	4.77	6.18	4.41
LW	3.77	4.68	4.19	5.17	4.00	4.45

In frontal analyses, there was not a significant effect of task instruction on amplitude at the  $p < .05$  level for the 3 conditions in neither the P3 nor the LPP time

windows. Separate ANOVAs were conducted for the P3 ( $F(1,265) = .852$ ,  $p = 0.357$ ,  $\eta^2 = .003$ ), EW-LPP ( $F(1,265) = 2.35$ ,  $p = 0.126$ ,  $\eta^2 = .009$ ), MW-LPP ( $F(1,265) = 2.29$ ,  $p = 0.131$ ,  $\eta^2 = .009$ ), and LW-LPP ( $F(1,265) = .022$ ,  $p = 0.883$ ,  $\eta^2 = .000$ ) components, and all tests had significance levels above  $p = .05$ . These results are not in line with our hypothesis that increase and decrease instructions will result in increased and decreased P3/LPP amplitudes, respectively. Taken together, these results indicate that frontally, there was no effect of task instruction on amplitude, while parietally, an effect was indeed present.

**Table 11.** Frontal means in each instruction condition

	View		Enhance		Suppress	
	Mean	SD	Mean	SD	Mean	SD
P3	-.27	5.84	.19	5.92	-.003	5.42
EW	1.99	5.99	2.43	5.89	1.98	5.79
MW	4.15	5.14	5.86	5.79	5.51	5.20
LW	5.21	5.14	5.50	6.31	5.91	5.11

In accordance with #5 of the Data Analysis Plan, to assess a sensitivity to change scores, this time taking into account task instruction, an ANOVA was conducted to correlate instruction to change scores. The omnibus ANOVA revealed that, across treatment groups, time window, and topography, task instruction was not significantly related to M1-BL change scores in terms of P3/LPP amplitude ( $F(1,164) = .191$ ,  $p = .662$ ,  $\eta^2 = .001$ ) (**Table 12**). Across clusters, instruction was not related to amplitude ( $F(1,164) = 2.79$ ,  $p = .097$ ,  $\eta^2 = .017$ ).

**Table 12.** ANOVA: Relationship between Instruction and Change Scores on LPP Amplitude

	SS	MS	F	p	$\eta^2$
Instruction	27.80	27.80	2.79	.097	.017
Instr. x M1-BL	1.91	1.91	.191	.662	.001
Error	1634.12	9.96			

## Chapter 5: Discussion

### Key Effects

In this study, we found evidence of treatment related reductions in Anxiety Sensitivity, as seen by significant declines in AS measures from baseline to one month after baseline in all treatment groups. Our findings of reduced AS in treatment groups from baseline to month 1 are consistent with a number of studies that validates CAST as efficacious in reducing AS (Schmidt 2014; Schmidt et al., 2006; Schmidt et al., 2017; Schiele et al., 2021). Along with this finding of reductions in AS across treatment groups relative to the control group, we found that baseline AS was significantly related to baseline P3 and LPP measures. Distributed across topography, conditions, and across the time windows, a relationship between Anxiety Sensitivity and P3/LPP is present, such that higher amplitude (heightened emotional reactivity) is associated with higher AS at intake.

Importantly, a relationship was observed between P3/LPP ERP measures and treatment-related change in AS, in addition to the baseline relationships. Treatment-related reductions in AS were associated with higher baseline reactivity. Heightened emotional response was predictive of better treatment outcomes. Thus, not only was baseline amplitude correlated with baseline AS measures, but it was also related to treatment outcome: greater AS reductions at month one were associated with higher baseline P3 and LPP activity. These findings suggest a sensitivity to AS, and further suggest that the P3/LPP time windows can be used as neurophysiological correlates that assess for prediction at intake. The LPP is a validated measure of motivational salience, and it is influenced by the emotional intensity of a stimulus (Hajcak et al., 2010; Lang et al., 1997; Palomba et al., 1997). AS represents a predisposition to

general fearfulness, and a higher tendency to misinterpret signs of arousal as real, impending danger (Shiele, 2020; Reiss, 1986). Further, it is one of the earliest transdiagnostic constructs, as it is associated with the maintenance of several internalizing problems (anxiety and mood disorders) (Sturges et al., 1997). Identifying a relationship between LPP and AS at baseline and with treatment outcome provides the benefit of developing a more accurate representation of underlying neural systems. AS reductions have been linked to reductions in a variety of internalizing symptoms, such as anxiety, PTSD, depression, insomnia, and suicidality (Mitchell et al., 2014; Raines et al., 2015; Short et al., 2015; Stanley et al., 2018). A neurophysiological correlate to current status and treatment outcome will aid in interventions targeting reductions in AS, which will have subsequent benefits in alleviation of several internalizing problems.

Another key finding of this paper is from the task validation. In the emotion regulation paradigm, previous literature has indicated that enhanced instructions have led to heightened activity relative to passive viewing, while the suppress instructions have led to decreased reactivity relative to passive viewing (Jackson et al., 2000; Moser et al., 2006; Hajcak & Nieuwenhuis, 2006). In the current study the decrease instruction did not lead to decreased amplitude relative to viewing. Difficulty downregulating responses is in line with findings that individuals with elevated AS have exaggerated responses to benign experiences/sensations they perceive as negative (such as heart palpitations being indicative of a heart attack), and exaggerated reactivity to stress and anxiety symptoms more broadly (Schmidt et al., 2014; Zvolensky, et al., 2005). The elevated anxiety in this sample showed no issue in

increased P3/LPP to increase conditions, a more common finding (Moser et al., 2006), but the ability to downregulate and show decreased amplitude to suppress conditions was disrupted, showing a dysfunction of mental control associated with elevated AS.

### *LPP Related to AS*

In the current study, the LPP elicited from unpleasant images was related to AS. LPP was significantly correlated to AS at baseline, such that higher amplitude was associated with higher baseline Anxiety Sensitivity scores; LPP was also related to treatment effects, as across treatment groups, higher LPP amplitude was related to greater reductions in AS one month after treatment. The comparison of reactivity in treatment groups to control was only marginally significant, but it does suggest that treatment interacts with P3/LPP activity to affect AS reduction. While neurophysiological correlates of AS are underexplored in the literature, at least two studies have reported a relationship between AS and LPP. based on a subset of the current data, Allan and colleagues (2019) found an association between LPP amplitude and AS. Saulnier and colleagues (2021) found a similar association in independent data. Thus, the LPP appears to be an emerging as an index of AS.

Importantly, in our analyses for both baseline AS and M1-BL AS change scores, results indicate that this relationship is across task conditions, e.g. not different for the primary instruction task manipulation in the emotion regulation task. The significant interaction between topography and time indicated that parietal effects start earlier, around the P3, and frontal effects start later, around MW-LPP. These findings replicate effects reported by Hajcak and colleagues (2010) of an earlier,

parietal P3, and later LPP windows seen frontally. EEG activity is differential across time, as the P3 and LPP, while overlapping, are two separate ERP components. However, while topography and time interacted with each other in the expected manner: prominent modulation of the P3 earlier in parietal regions, with later emotional modulation of the LPP at frontal/central recording sites (Hajcak et al., 2010; Foti, Hajcak, & Dien, 2009), topography and time windows were not significantly related to AS. The relationship between AS and P3/LPP activity is significant across clusters, and across time windows. Thus, it is not this widely observed finding of frontal/parietal topography and time interacting that is driving the processes involved in our findings that relate AS to LPP activity.

#### *Indexing LPP and AS: Why a Connection Matters*

The LPP is widely observed to be increased for emotional stimuli (Hajcak et al., 2010; Cuthbert et al., 2000), and these effects are understood to be driven by motivational salience, as opposed to things such as stimulus novelty, or low-level perceptual differences. Broadly, LPP activity is reflective of salience (appetitive or aversive). The LPP may be particularly useful in studying emotional disruptions (Albanese et al., 2019): it provides a measure of reactivity to specific emotional images, and can be increased or decreased when participants are up-regulating and down-regulating their emotional responses (Hajcak and Nieuwenhuis, 2006; Moser et al., 2006). Hajcak and Nieuwenhuis (2006) found that the LPP, a marker of stimulus detection and categorization, is highly sensitive to the emotional intensity of stimuli, thus making it an ideal candidate to study the time course of emotion regulation. Anxiety Sensitivity, a causal risk factor for both anxiety and mood pathology

(Narragon-Gainey, 2010), reflects the tendency to misinterpret anxiety-related sensations as indicators of impending physical, psychological, or social consequences. Exaggerated reactivity to stress and anxiety symptoms augments numerous internalizing problems (Stanley et al., 2018; Capron et al., 2013; Schmidt et al., 2014). In the context of this study's findings, the relationship between LPP and AS can be understood as such: individuals with higher levels of AS have impairments in attributing appropriate levels of significance to incoming stimuli, and a larger LPP, an ERP that can be elicited based on individual differences in preference for stimuli (Hajcak et al. 2010), is reflective of this difficulty.

The LPP has potential to be explored as a neurophysiological correlate of Anxiety Sensitivity, as it is sensitive to incoming status for individuals in terms of self-report AS levels. Identifying connections between neurophysiological processes and behavioral expression of AS has immense utility in terms of identifying this reactivity as a treatment target. AS is related to a number of different mental health disorders, and our findings of a relationship between AS and the LPP provides a stronger empirical basis for intervention target development. This ERP measure has the ability to offer unique information regarding a sensitivity to AS. Assessment can then be conducted to demonstrate change in the treatment target (AS), and then whether change in the transdiagnostic target (e.g. INT) produces change in the outcome symptoms (e.g. anxiety or depression symptoms). Identifying empirically-validated referents in the brain to serve as treatment targets allows a more precise and parsimonious understanding of underlying systems (Sha et al., 2019; McTeague et al.,

2020), thus advancing a neuroscience-informed intervention for anxiety and mood pathology.

### *Broader Impact and Utility of Current Findings*

The lack of literature on underlying neural mechanisms regarding the LPP and AS treatment leaves interpretation open-ended as to exactly what these findings could suggest. Studies exist where AS is significantly related to the Nogo P3, and the error-related negativity (ERN), but as Allan (2019) points out, these ERPs are not directly associated with AS, and these ERPs have been associated with broader cognitive-affective processing constructs in similar contexts (e.g. externalizing psychopathology such as impulse control, executive control, substance use) (Beste et al., 2013; Sehlmeier et al., 2010). Less work exists on the relationship between the LPP and AS, and as the LPP is a direct reflection of emotional stimuli, it positions itself to have more validity and direct association with AS, a causal risk factor for anxiety and mood pathology that prospectively predicts clinical diagnosis of related psychopathology (e.g. anxiety, depression, panic, posttraumatic stress symptoms) (Sturges et al., 1998; Schmidt et al., 1997; Schmidt et al., 2007). The interventions in the study here broadly target maladaptive cognitions and attempt to teach strategies of emotion regulation (Schmidt et al., 2007; Capron & Schmidt, 2016; Gross, 2014; Fernandez et al., 2016). Thus, participants' higher reactivity potentially relates to better treatment outcome in the sense that they are better able to successfully engage in reappraisal.

AS is one of the most well-studied, validated transdiagnostic constructs related to internalizing problems. AS is associated with the etiology and maintenance

of a number of mental health disorders, such as panic disorder, depression, anxiety, and more (Fernandez et al., 2016; Narragon-Gainey, 2010; Sturges et al., 1998; Schmidt et al., 1997; Schmidt et al., 2007). Treatment outcome studies have reflected that changes in AS result in changes in internalizing symptoms (Schmidt & Eggleston, et al., 2007; Shiele et al., 2020; Mitchell et al., 2014; Raines et al., 2015; Short et al., 2015). Reductions in AS can have broad positive outcomes by way of reductions in a number of internalizing problems (Forsyth et al., 2000; Schmidt et al., 2014; Capron et al., 2017). Tying this to underlying neural mechanisms provides opportunities for using neuroscience measures to index separable mechanisms as well as treatment success. This study's results represent a rather novel finding in that the LPP is related to treatment outcome for an intervention targeting AS. That we found baseline ERP measures are related to treatment outcome underscores a need for deeper understanding of the neural processes associated with constructs such as AS, and this study's findings help propel us to a deeper understanding: locating neurophysiological correlates helps in identifying overlapping neural networks, and more broadly, cognitive affective processes related to other constructs and disorders. Demonstrating a direct correlate of AS, an internalizing construct validated to be driven by exaggerated emotional reactivity/stimulus misinterpretation (Schmidt et al., 2014; Zvolensky et al., 2005), with the LPP, a positivity directly associated with motivational salience and emotional intensity of stimuli (Hajcak et al., 2010; Schupp et al., 2000), can provide a deeper understanding of the construct, which can provide important advancements by way of strong and accurate intervention development/treatment target development.

### Task Validation

Analyses revealed that while the usual increased LPP amplitude was observed for increase instructions, decrease instructions did not produce decreased amplitude relative to view, as is generally observed in the literature (Moser et al., 2006). This suggests that while this sample did not have difficulty in amplifying emotion, as evidenced by heightened activity associated with higher AS, they were ineffective at modulating or downregulating their response to unpleasant images. This is consistent, for example, with Moser (2013), who suggests that anxiety involves heightened reactivity to salient stimuli, but decreased ability to implement cognitive control relative to those same stimuli. Thus, the lack of this replication may represent important sample-specific characteristics.

### Power in the Current Study

Low power for group effects in the current study is an important factor to consider relative to the nonsignificant group effects. This is despite some potentially interesting looking nominal mean and correlation patterns, with notable effect sizes. Further research must be conducted with larger samples, as we hypothesized group differences in amplitude in relation to AS and treatment outcome, and thus to confidently support or reject a hypothesis, further work exploring the LPP's role in relation to intervention group must be conducted.

### Exploratory Directions for Future Work

While we did not observe statistically significant between-group effects for the relationship between P3/LPP and treatment outcome. It may be worth speculating about some patterns in the data nonetheless, in order to inform better powered future. In our study, we found that P3 amplitude evidenced nominally larger treatment

effects in both the CAST and CBM-I groups, relative to the Combined group, where the combined group showed stronger effects later during the LPP. Interestingly, in the CAST group, treatment effects in the P3 occurred parietally, whereas in the CBM-I group, nominally larger treatment effects were observed in the P3 occurred frontally. During the LPP, there were no treatment effects within the CAST and CBM-I groups. The Combined group, however, did evidence larger treatment effects during the LPP, and these effects were seen frontally and parietally. These results offer a suggestion that while the CAST and CBM-I groups differ early, they function relatively the same during the LPP, and the combination of the two treatments shows both frontal and parietal contributions.

Further exploration showed nominally (but not statistically) differential effects within task instruction conditions. That is, the effects seen in each group for the relationship between amplitude and treatment-related AS reductions could be parsed into effects within different instruction conditions. Frontally, within the CBM-I group, ASI change scores and P3/LPP amplitude were only related in the View and Suppress conditions. Similarly, the early parietal effects were only present in the enhance and suppress conditions. The LPP window effects frontally and parietally in the Combined group were solely seen within the View condition.

These described nominal effects were not significant, so we reserve substantive inferences for effects across treatment groups described. P3/LPP activity was associated with AS reductions from baseline to month 1, but if future research finds differential modulation of this relationship based on treatment type, these findings could have high utility in comparing treatment efficacy in order to reduce AS

and address related disorders. The potential for a treatment group-specific sensitivity to treatment outcome could have major implications for emotion regulation, intervention targets, and interventions broadly.

### Conclusion

In this study, results indicate first that AS is reduced from baseline to 1 month after the first intervention session, and that across treatment groups, this reduction is predicted by baseline P3 and LPP measures elicited by unpleasant images. Further research should seek to explore P3 and LPP as neurophysiological correlates and predictors of Anxiety Sensitivity, as well as their relationship with treatment outcome in different treatment types, in combination with the emotion regulation task paradigm. Although the study is underpowered, its findings still identify P3/LPP's ability to identify AS status, as well as be indicative of treatment outcome for AS. There is a scarcity of equivalent research in the literature right now, so these findings advance understanding in this area. New research should explore these findings in larger samples, a broader array of populations, and examine individual differences in reactivity in order to have a broader impact on psychopathology overall. This set of findings is novel and potentially very informative in terms of shaping future prevention and intervention approaches to anxiety and mood psychopathology.

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