

ABSTRACT

Title of Dissertation: MEDIAL FRONTAL THETA NEGATIVITIES
(MFTN) AS PREDICTORS OF ANXIETY
SENSITIVITY TREATMENT RESPONSE

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Anxiety is one of the most prevalent mental health problems around the world. Despite a number of widely available interventions, it can take weeks or months to see effects, and nearly half of individuals may not respond. In an effort to better understand response rates, a large body of evidence indicates the most consistent predictor of treatment outcomes is activity in the anterior cingulate cortex (ACC). Although activity in ACC can be measured by medial frontal theta event related potentials (ERPs) at a finer temporal resolution, these neurophysiological components have not been evaluated as predictors of treatment response. There is also a lack of research on the functional networks associated with ACC treatment prediction, despite implications for prefrontal engagement of cognitive control processes. The present study aimed to examine these gaps in the literature by using task-based electroencephalography (EEG) and medial frontal theta negativities (MFTN) as

predictors of anxiety sensitivity treatment response. Using amplitude as well as functional connectivity measures (i.e., inter-channel phase synchrony), baseline MFTN (i.e., Theta-FN, Theta-N2) were assessed as predictors of treatment response at mid-treatment, 1-week post treatment, and 6 months post treatment. Subjects underwent a baseline EEG before completing three sessions of a computerized cognitive behavioral intervention. Contrary to the hypothesis, findings revealed MFTN amplitude did not predict treatment response. However, medial to lateral prefrontal theta phase synchrony demonstrated significant prediction effects, such that lower phase synchrony was associated with greater symptom improvement at mid-treatment, 1-week post treatment, and 6 months post treatment. This effect was specific to certain task conditions (i.e., gain feedback and go stimuli), as well as to the combined anxiety and depression treatment group. Results demonstrated accuracy and consistency of treatment prediction, as well as incremental validity after controlling for self-report measures. Finally, results provide additional support for a convergent medial frontal theta process, and suggest that low engagement of regulatory and proactive control mechanisms may be predictive of better response to cognitive behavioral interventions. This work represents a novel finding that may contribute to the improvement in treatment efficacy by serving as a target for future interventions and individualized treatment selection.

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ANXIETY SENSITIVITY TREATMENT RESPONSE

by

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Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park, in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2019

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Acknowledgements

I would like to express my deepest gratitude to my advisor, Ed Bernat, for his mentorship, training, feedback, and encouragement over the past 5 years. It was an honor to have worked with you.

Thank you to my committee, Tracy, Alex, Alec, and DJ, for teaching me and challenging me. Your guidance and suggestions were instrumental in the completion of this project.

A very special thank you to my mother and father, Debbie and Joe Brockmeyer. None of this would have been possible without your unwavering support and assistance in caring for little Mason. To my husband, Mason, thank you for your consistent encouragement, reassurance, and inspiration to always persist despite the challenge. You have been my rock and your love and encouragement kept me going in the toughest hours.

Finally, thank you to the individuals whose gracious participation in this study made this work possible. My hope is that this work may contribute to the ongoing efforts to improve the lives of individuals who suffer from mental illness.

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List of Abbreviations

ACC: Anterior Cingulate Cortex

CBT: Cognitive Behavioral Therapy

DLPFC: Dorsolateral Prefrontal Cortex

ECT: Electroconvulsive Therapy

EEG: Electroencephalography

ERN: Error Related Negativity

ERP: Event Related Potential

fMRI: functional Magnetic Resonance Imaging

FN: Feedback Negativity

GAD: Generalized Anxiety Disorder

ICPS: Inter-channel Phase Synchrony

MDD: Major Depressive Disorder

MFTN: Medial Frontal Theta Negativities

OCD: Obsessive Compulsive Disorder

OFC: Orbitofrontal Cortex

PET: Positron Emission Tomography

PFC: Prefrontal cortex

PTSD: Post-traumatic Stress Disorder

rTMS: repetitive Transcranial Magnetic Stimulation

SPECT: Single Photon Emission Computed Tomography

SSRI: Selective Serotonin Reuptake Inhibitor

Chapter 1: Introduction

Anxiety and its impact on society

Approximately 42 million American adults live with an anxiety disorder, making anxiety one of the most prevalent mental health problems in the United States and around the world (Collins et al., 2011; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). According to data provided in the National Comorbidity Survey, the most prevalent lifetime disorders are specific phobia (15.6%), major depressive disorder (MDD; 14.4%), and social phobia (10.7%), followed by post-traumatic stress disorder (PTSD; 5.7%) and generalized anxiety disorder (GAD; 4.3%). Of the above mentioned disorders, four of the five fall under the spectrum of anxiety psychopathology, underscoring its pervasiveness in society.

With such high prevalence rates, the effects of anxiety on the individual and society remain substantial. Using GAD as an example, in primary care settings it is estimated that 22% of those who complain of anxiety problems have a diagnosis of GAD, but fewer than 20% of sufferers will experience remission of symptoms (Wittchen, 2002). For the individual, GAD is a persistent and severe mental disorder characterized by six months or more of excessive worrying, hypervigilance, and somatic symptoms, along with subjective feelings of loss of control. Further, these symptoms often translate to social and work impairment. It has been suggested that the level of social disability associated with GAD is as severe as seen with chronic somatic diseases (Kessler et al., 2001), and approximately 34% of patients with GAD will show a reduction of work productivity of 10% or more in a month (Witcchen et

al., 2000). Additional evidence from an Australian study found the burden of mental illness (particularly GAD and depression) was third after the burden of heart disease and cancer (Andrews et al., 2000). In these epidemiological studies, 'burden' is defined as a conglomerate measure estimated in disability-adjusted life years (DALYs) lost, expressed as the cumulative number of years lost due to ill-health.

Economically, anxiety disorders contribute significantly to mental health costs. Some estimates suggest anxiety disorders cost \$46.6 billion in direct (i.e., patient visits, professional services, medication costs, etc.) and indirect costs (i.e., lost income, lost productivity, mortality etc.), accounting for 31.5% of the total cost of mental illness in America (DuPont et al., 1996).

Anxiety is also associated with higher rates of suicidal ideation and suicidal behavior. Based on information provided by the National Comorbidity Survey, it is estimated that 70% of individuals with a previous suicide attempt had at least one anxiety disorder (Sareen, J. et. al., 2005). Even after controlling for comorbidity and other risk factors for suicide, anxiety remains a significant predictor.

Taken together, the presence of anxiety psychopathology is a significant factor that leads to individual and societal burden in the form of debilitating symptoms, medical costs, and even high rates of suicide. As such, there is a need for more research in this domain, particularly studies that may offer insight into anxiety treatment outcomes.

Importance of predicting treatment response

As alluded to above, remission rates for anxiety remain minimal. Remarkably, four out of five individuals will still experience debilitating anxiety symptoms even

after treatment (Wittchen, 2002). Even with some of the most effective pharmacotherapy treatments for anxiety, response rates are estimated at approximately 60%, indicating that nearly half of the individuals undergoing treatment do not show any change in symptom severity (Nimatoudis et al., 2004; Pollack, 2001).

Because such a large number of individuals do not respond to currently available treatments for mood and anxiety disorders, there is a need for 1) more effective treatments, and 2) more informed and individualized treatment selection (Simon & Perlis, 2010). While the former includes pharmaceutical drug discovery and development, the latter is an emerging field of research focused on identifying pre-treatment measures that predict an individual's likelihood of response to an intervention. Identifying predictors of treatment response is critical since many treatments take weeks or months to see effects, resulting in prolonged suffering and potential for worsening of symptoms. Therefore, patients and clinicians would benefit from having objective pre-treatment measures that predict which patients will and will not respond to a given treatment.

The ability to predict treatment outcome before or shortly after a treatment is initiated could mean significant improvement in individualized treatment selection, and ultimately improvement in the efficacy of treatments. Indeed, several sociodemographic and clinical measures have been identified in this regard, including history of failed treatments (Ellis, Zarate, Luckenbaugh, & Furey, 2014), pre-treatment symptom severity (Connor, Hidalgo, Crockett, Malik, Katz, & Davidson, 2001; Doehrmann et al., 2013; Karatzias et al., 2007; Otto, Pollack, Gould, &

Worthington, 2000; Tükel, Bozkurt, Polat, Genc, & Atli, 2006), comorbidity with other disorders (Baer, Jenike, Black, Treece, Rosenfeld, & Greist, 1992), and avoidant personality traits (Chambless, Tran, & Glass, 1997). As a complementary and arguably more objective approach, biological predictors of treatment response may offer greater insight into the neurobiological substrates of the disorders and serve as potential targets for future interventions.

Neuroimaging predictors of treatment response: Depression

The majority of work identifying neuroimaging predictors of treatment response has been done in Major Depressive Disorder (MDD) after Mayberg and colleagues (1997) discovered that pre-treatment pregenual anterior cingulate glucose metabolism could differentiate responders from non-responders to antidepressant medication response. Following this finding, subsequent studies have replicated this effect using positron emission tomography (PET) as well as functional magnetic resonance imaging (fMRI) across a variety of tasks (Chen et al., 2007; Langenecker et al., 2007; Saxena et al., 2003; Victor, Furey, Fromm, Ohman, & Drevets, 2013). Similarly, studies examining ventral anterior cingulate have found greater activation corresponds to better antidepressant treatment response (Brockmann, et al., 2009; Keedwell et al., 2010). Moreover, a recent meta-analysis found that in nineteen out of twenty-three studies, including resting and task-based designs, responders to various antidepressant treatments (medication, ECT, rTMS) had increased pre-treatment rostral/ventral ACC activity which was found consistently across treatments (SSRIs, tricyclic antidepressants, ketamine, rTMS), imaging modalities (EEG-LORETA,

fMRI, and SPECT), and did not depend on medication status at baseline (Pizzagalli, 2010).

While the majority of work on predictors of depression treatment response has been done in pharmacological studies, research employing Cognitive Behavioral Therapy (CBT) as the intervention have typically found *less* pretreatment ACC and prefrontal cortex activation predicts better treatment outcome (Dichter, Felder, & Smoski, 2010; McGrath et al., 2014; Siegle et al., 2006, 2012). In this regard, it has been suggested that in depressed samples ACC activity may optimize treatment selection, such that individuals with lower pre-treatment ACC may respond better to CBT, while individuals with greater pre-treatment ACC may respond better to antidepressants.

Interestingly, the majority of depression treatment prediction research has been conducted using fMRI or PET modalities, with limited evidence employing electroencephalography (EEG). While *task-based* (event related potential) predictors of treatment response is sparse, *resting-state* EEG evidence is consistent with the neuroimaging literature and suggests increased frontal-midline theta with neural generators in the anterior cingulate (ACC) may predict favorable treatment outcome (Mulert et al., 2007; Pizzagalli, et al., 2001, Pizzagalli et al., 2003; Spronk et al., 2011). However, more research is needed to determine if this effect extends to event related potentials.

While the ACC has been the most consistent and robust predictor of antidepressant treatment outcome, it is important to point out that other regions have also been assessed as predictors, however these results are generally not consistent

across studies. In some studies using emotional processing tasks, greater prefrontal activity (dorsolateral and dorsomedial PFC) is associated with better outcomes to both medication and CBT (Ritchey et al., 2011; Samson et al., 2011). However, other studies using working memory tasks suggest less PFC activation is associated with better response (Walsh, et al., 2007). The amygdala, insula, hippocampus, and orbitofrontal cortex (OFC) have also been studied as predictors of treatment response, but have similarly generated mixed findings.

In summary, pre-treatment ACC activity has been shown to consistently predict treatment outcome in major depression, and may potentially be used to optimize treatment selection by differentiating between medication and psychotherapy response.

Neuroimaging predictors of treatment response: Anxiety

Because depression is often comorbid with anxiety, we might expect to see similar results for predicting anxiety treatment response. Even though research in this area is just beginning, emerging evidence shows a similar effect, indicating the ACC is the most consistent predictor for anxiety treatment outcomes as well. According to two review papers on neuroimaging predictors of treatment response in anxious populations, similar to the findings in depression, anxious patients with enhanced pre-treatment anterior cingulate activity generally have greater response to a variety of interventions (Ball, Stein, & Paulus, 2014; Shin et al., 2013).

In contrast to depression, anxiety psychopathology represents a heterogeneous group of disorders, which have traditionally included Generalized Anxiety Disorder (GAD), Panic Disorder, Social Phobia, Specific Phobia, Obsessive Compulsive

Disorder (OCD), and Posttraumatic stress disorder (PTSD). Of all the anxiety disorders, the most neuroimaging treatment prediction work has been done in OCD. Within this patient group, studies have consistently implicated the cingulate cortex (including anterior and posterior) and orbital frontal cortex (OFC), with a majority showing greater pretreatment activation in ventral anterior cingulate and posterior cingulate is associated with better medication response rates (Buchsbaum et al., 2006; Rauch et al., 2001; Rauch et al., 2002) as well as better response to an electrostimulation intervention (Van Laere et al., 2006). In contrast to the ventral ACC findings, some studies have found an inverse relationship between dorsal ACC and OCD treatment response, such that lower pre-treatment dorsal/caudal ACC predicts better response (Hendler et al., 2003; Swedo et al., 1989). Interestingly, there is a lack of studies assessing whether the same anterior and posterior cingulate predictors apply to cognitive behavioral therapy for OCD. As a result, although the majority of findings on treatment prediction in OCD suggest a role for the ACC, it is currently not clear whether this extends to psychotherapy, or whether subdivisions of the ACC may show different predictive directions in this population.

Additionally, much less work has been done examining predictors of treatment response in the other anxiety disorders. Of the few studies that have been conducted, the two regions of interest have been the ACC and the amygdala. While the amygdala has been robustly associated with fear based anxiety disorders (Davis, 1992) and is hyperactive broadly across anxious phenotypes (Etkin & Wagner, 2007), its role in predicting treatment response is less clear. In fact, several studies found no relation between pre-treatment amygdala and treatment outcome (Doehrmann et al.,

2013; Evans et al., 2009; Nitschke et al., 2009). In contrast to mostly null prediction findings in the amygdala, greater dorsal ACC has been consistently found to predict better CBT response in individuals with PTSD (Aupperle et al., 2013; Bryant et al., 2018), as well as social anxiety (Klumpp, Fitzgerald, & Phan, 2013), and better medication response in GAD (Nitschke et al., 2009). Ventral ACC has also shown predictive value, but the direction of prediction has been less consistent across types of interventions and disorders. In medication studies, for example, greater ventral ACC predicted better response in GAD (Whalen et al., 2008), but lower ventral ACC predicted better response in social anxiety disorder (Evans et al., 2009).

Regarding mechanisms of treatment prediction, several studies speculate that increased ACC may represent an adaptive response by calling upon cognitive control resources primarily located in dorsolateral PFC (Cavanagh, Cohen, & Allen, 2009; Cavanagh & Shackman, 2015; Miller & Cohen, 2001; Pizzagalli, 2010). The extent to which these two regions (and others) are integrated in processing various cognitive or affective challenges is considered an index of their functional connectivity. The functional connectivity (or synchronization) between regions can be assessed across a number of tasks, including during cognitive control (Cavanagh et al., 2009), perception of human faces (Rodriguez et al., 1999), working memory (Bluhm et al., 2011), and complex attention (Rosenberg et al., 2016). Functional connectivity can also be assessed by a number of imaging modalities, including EEG. Specifically, inter-channel phase synchrony between medial to lateral prefrontal regions has been shown during gambling feedback tasks (Watts et al., 2017), as well as during go/no-go response inhibition (Aviyente et al., 2017), and error monitoring (Bolanos et al.,

2013). Moreover, disrupted synchronization has been implicated in a variety of pathological conditions, including schizophrenia, epilepsy, autism, Alzheimer's, and Parkinson's (Uhlhaas & Singer, 2006).

Given the role for functional connectivity in understanding basic task processing, as well as its implication in pathological brain states, it may also be informative for predicting clinical treatment outcomes. Indeed, there is some evidence suggesting a role for dorsolateral PFC, in addition to ACC, as a predictor of treatment response in individuals with GAD and panic disorder (Ball, Stein, Ramsawh, Campbell-Sills, & Paulus, 2014), as well as OCD symptom reduction (Olatunji et al., 2014). Importantly however, these studies did not examine the functional relationship between ACC and DLPFC. In fact, very few studies have assessed functional connectivity between these regions as treatment predictors, despite several studies speculating that regulatory capacity or cognitive control capability may be a mechanism underlying treatment prediction findings. To our knowledge there has been only one study to examine ACC/DLPFC functional connectivity as a predictor of treatment outcomes. This study was conducted by Klumpp and colleagues (2016), hereafter referred to as 'the Klumpp study.' This study used fMRI to examine both the activation and functional connectivity between ACC and PFC in relation to treatment outcomes. Results indicate greater anxiety treatment response to CBT was predicted by more dorsal ACC activity and lower functional connectivity between dACC and DLPFC to negative stimuli during high cognitive demand (Klumpp et al., 2016). Based on these findings, the authors concluded that patients with overall less pre-treatment regulatory ability may benefit more from CBT. Although this work is

promising, more research is needed on the functional connectivity between ACC and DLPFC in relation to predicting treatment response.

Additionally, it's important to point out that the vast majority of treatment prediction work has been done using fMRI or PET paradigms, with very few studies examining EEG predictors. Of those studies using EEG, the early prediction work focused broadly on alpha or theta frequencies during sleep and resting state. While one study indicated resting EEG alpha asymmetry predicts better anxiety treatment response to Cognitive Behavioral Therapy (Moscovitch et al., 2011), other studies found greater resting frontal midline theta predicted better medication response (Pizzagalli, et al., 2001; Spronk et al., 2011). Only more recent work has begun to examine ERPs as potential predictors of treatment response. Of those studies, there is some evidence to suggest lower time-domain Reward Positivity (RewP; 200-250ms following reward feedback) predicts better treatment outcome to CBT in a sample with comorbid anxiety and depression (Burkhouse et al., 2016). Another study found larger pre-treatment late positive potential (LPP; 400-1000ms) to aversive pictures predicted better treatment outcomes to CBT, also in individuals with anxiety and depression (Stange et al., 2017). While informative, future EEG research would benefit from building upon the existing body of neuroimaging findings by directly focusing on medial and lateral prefrontal regions in treatment prediction.

In summary, examining predictors of treatment response in anxiety is an emerging field with relatively fewer studies compared to depression. Of the existing studies, converging evidence suggests greater dorsal ACC consistently predicts better treatment response. However, the mechanisms of this effect are still not clear (e.g.,

functional connectivity to DLPFC) and the direction of the effect may depend on the type of anxiety disorder (i.e., less activation for OCD, but greater activation for all other anxiety disorders). Moreover, a majority of previous work has been limited to fMRI or PET paradigms. While not surprising given the use of these methods during the inception of treatment prediction work, EEG may serve as a quicker and more cost effective method with potentially greater applicability in clinical/hospital settings. As such, more work is needed to clarify and expand upon the role of the ACC in anxiety treatment response.

Anterior Cingulate Cortex (ACC)

Given its relevance to treatment prediction, it is important to clarify the structure and function of the ACC, as well as why activation in this region may be adaptive. Regarding structure, the anterior cingulate cortex is located in the medial wall of each hemisphere, adjacent to the corpus callosum, and can be functionally divided into two distinct regions: the ventral or rostral anterior cingulate cortex (rACC) and the dorsal or medial cingulate cortex (MCC). Anatomical studies suggest further delineation of both the rACC and MCC, resulting in four sub-regions (Palomero-Gallagher et al., 2008; 2009; Stevens, Hurley, & Taber, 2011). These studies suggest the rACC can be divided into pregenual anterior cingulate (pACC) and subgenual anterior cingulate (sACC) with each involved in different but overlapping functions. Similarly, the MCC can be further divided into anterior (aMCC) and posterior (pMCC) regions, resulting in a total of four main subdivisions of the anterior cingulate cortex (Figure 1A). A detailed review of the literature

indicated the main reason for separating the ventral/anterior and dorsal/middle regions of the anterior cingulate is the evidence pointing to different structural and functional connections (Vogt, 2009). To summarize, the MCC has extensive structural connections to lateral prefrontal, motor, and thalamic nuclei, and has been primarily implicated in ‘cognitive’ functions, including conflict-monitoring, response-selection, and execution. In contrast, the rACC has been associated with ‘affective/emotional’ processing, as well as memory and reward-related functions, with primary connections to the amygdala, hippocampus, orbitofrontal cortex, and ventral striatum. Additionally, within the rACC, the pACC and sACC subdivisions have also shown evidence for differentiation such that pACC has more widespread connections to lateral prefrontal cortex and is functionally tied to emotion regulation, autonomic integration, and affect related to pain (Stevens, Hurley, & Taber, 2011). Compared to pACC, sACC has more connections to amygdala and ventral striatum, and is related to autonomic processes and conditioned learning (Haber & Knutson, 2007; Ghashghaei, Hilgetag, & Barbas, 2007). Similar differentiations occur within the MCC, such that aMCC is implicated in approach-avoidance decisions, conflict-monitoring, control of actions, and emotional appraisal, whereas pMCC has more connections to inferior parietal cortex, and is functionally related to body-orientation and movement-execution.

Despite previous evidence for different regions associated with cognitive and affective functions in the anterior cingulate, there is a growing consensus that the aMCC plays a unique role in the brain, with functional and structural connections to both ‘cognitive’ and ‘affective’ processes (Figure 1B; Botvinick, 2007; Cavanagh &

Shackman, 2015; Etkin et al., 2011; Pereira et al., 2010; Pessoa, 2008; Shackman et al., 2011). A meta-analysis performed across 192 studies and nearly 3,000 participants demonstrates that negative affect, pain, and cognitive control are anatomically and functionally integrated in the aMCC (Shackman et al., 2011). In these studies, negative affect was indicated by tasks that induced negative emotions such as fear, anger and disgust, while pain represented tasks delivering physically painful stimuli such as heat, cold, or shock. The cognitive domain included tasks that induced reallocation of attention or execution of actions such as a Go/No-go or Flanker task. In the meta-analysis, functional segregation between ventral ACC ('emotional') and dorsal MCC ('cognitive') was tested after identifying voxels within these regions corresponding to negative affect, pain, and cognitive control. Consistent with previous work, results indicated studies of cognitive control elicited greater activation in MCC compared to rACC. However, negative affect was equally likely to activate the MCC and rACC, and studies of pain were more likely to activate MCC compared to rACC. Contrary to earlier notions that cognitive and emotional processes are differentially represented in the anterior cingulate cortex, these functional data suggest all three domains converge in the aMCC. Anatomical evidence also reviewed in this meta-analysis supports this notion by demonstrating the aMCC has substantial connections to subcortical regions involved in affect and pain (e.g., periaqueductal gray, amygdala, ventral striatum), as well as with frontoparietal regions implicated in cognitive control. Given these findings, the authors claim the aMCC may represent a hub that synthesizes information about pain, punishment or otherwise negative feedback, and response conflict, which then operates to bias selective attention and

recruit other areas of the brain to modulate behavior. This theory is labeled The Adaptive Control Hypothesis (TACH) and claims that greater activation in aMCC serves an adaptive function by calling upon other regions to modulate behavior in a goal-directed manner (e.g., subcortical and cortical motor centers, amygdala, and prefrontal cortex). This theory may partially explain why greater ACC activation has been related to better treatment outcomes.

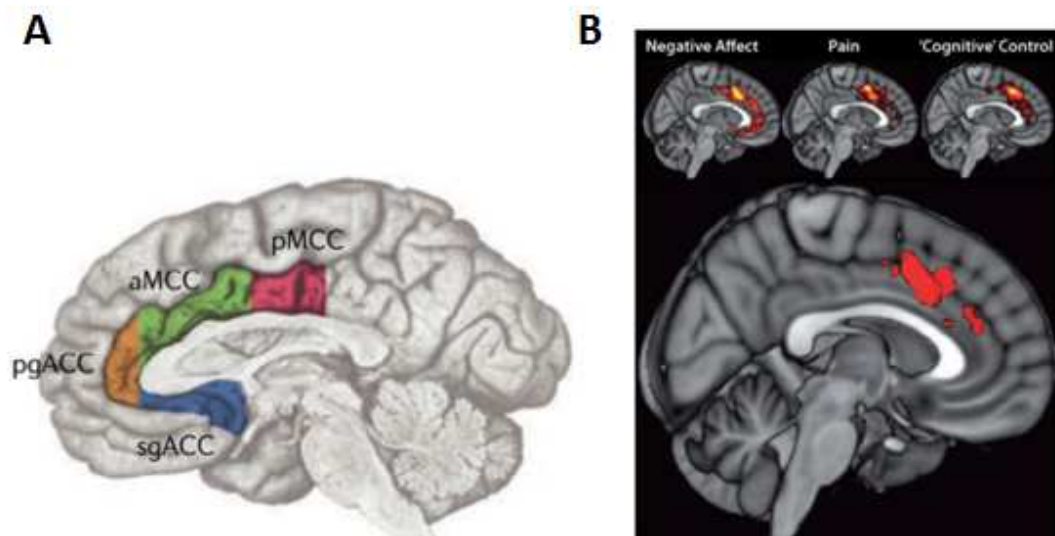


Figure 1 (A) The human cingulate cortex can be divided into four major sections, including the subgenual anterior (blue), pregenual anterior (yellow), anterior midcingulate (green), and posterior midcingulate (red). The anterior and posterior midcingulate are considered anatomical divisions of the dorsal midcingulate (MCC) which has been implicated in ‘cognitive’ functions, while the pregenual and subgenual anterior regions comprise the rostral or ventral cingulate (rACC) and have been tied to ‘emotional’ processes. (B) Despite previous evidence for the anatomical and functional divisions of the cingulate cortex, emerging research suggests the aMCC subdivision reflects both ‘cognitive’ and ‘affective’ processes, including greater activation during tasks associated with negative affect, pain, and cognitive control. Figure adapted from (Cavanagh & Shackman, 2015).

ACC as reflected by Medial Frontal Theta

An extensive body of literature has shown that activity in aMCC propagates to the scalp where it can be reliably measured by EEG and medial frontal ERPs at a finer temporal resolution (Cavanagh et al., 2012; Cavanagh & Shackman, 2015;

Gehring & Willoughby, 2002; Hauser et al., 2014; Holroyd & Coles, 2002; Holroyd et al., 2004; Miltner, Braun, & Coles, 1997; Potts, Martin, Burton, & Montague, 2006; Yeung, Botvinick, & Cohen, 2004). The three ERPs that have been consistently source localized to aMCC reflect feedback processing (Feedback Negativity, FN), error monitoring (Error Related Negativity, ERN), and response conflict ('control' N2). As a widely studied indicator of feedback and performance monitoring, the FN is a negative-going deflection which occurs approximately 250-400ms after performance/evaluative feedback (e.g., win or lose), and is typically more sensitive to negative versus positive feedback (Gehring & Willoughby, 2002; Miltner, Braun, & Coles, 1997). The ERN represents endogenous error monitoring (i.e., internal error signals) and is a negative-going ERP peaking approximately 50-100ms following erroneous responses (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). Finally, the N2 is a negative deflection in the ERP waveform peaking approximately 250 to 350ms after the presentation of a stimulus eliciting the potential for response inhibition (Eimer, 1993; Folstein & Van Petten, 2008). All three medial frontal ERPs are negative deflections primarily represented in the theta frequency band and collectively have been designated medial frontal theta negativities (MFTN, ~4-8Hz; Cavanagh et al., 2009; Cavanagh et al., 2012; Luu et al., 2004, 2003; Trujillo and Allen, 2007; Yordanova et al., 2004). While the neuronal sources for these components are not limited to just the aMCC (Bonini et al., 2014; Cohen et al., 2008; Emeric et al., 2010; Foti, Weinberg, Bernat, & Proudfit, 2014; Gehring & Willoughby, 2004), a number of studies using EEG source localization, simultaneous EEG/fMRI, and invasive recordings have

implicated the aMCC as a key generator (Becker et al., 2014; Cohen et al., 2008; Gehring et al., 2012; Hauser et al., 2014; Wang et al., 2005).

Medial Frontal Theta Negativities (MFTN) and anxiety

Extending this work to individual differences, Cavanagh & Shackman (2015) employed a series of meta-analyses, which showed MFTN (Theta-N2, Theta-FN, Theta-ERN) were not only reliable indicators of aMCC activity, but also correlated with greater dispositional anxiety and compensatory behavioral change. Specifically, all three medial frontal ERPs were enhanced (more negative) in relation to a number of self-report measures of anxiety (e.g., trait anxiety, behavioral inhibition, negative affect, general worry). Additionally, greater loss-related FN predicted greater avoidance of punishment on the subsequent trial, and greater ERN predicted slower reaction times following an error, consistent with the notion that aMCC, as indexed by medial frontal theta ERPs, contributes to the adaptive regulation of behavior.

Error Related Negativity (ERN)

The error-related negativity (ERN) is the medial frontal ERP that is most consistently associated with elevated levels of anxiety. Research has shown that the ERN is amplified in clinical populations, including individuals with obsessive-compulsive disorder (Gehring, Himle, & Nisenson, 2000; Hajcak & Simons, 2002; Johannes et al., 2001; Mathews, Perez, Delucchi, & Mathalon, 2012; Ruchow et al., 2005) and generalized anxiety disorder (Weinberg, Klein, & Hajcak, 2012; Weinberg, Olvet, & Hajcak, 2010). In addition to diagnostic categories, transdiagnostic measures of anxiety also demonstrate a robust relationship with ERN (Hajcak, McDonald, & Simons, 2004; Luu, Collins, & Tucker, 2000; Moser, Moran, Schroder, Donnellan, &

Yeung, 2013; Moser, Moran, & Jendrusina, 2012; Olvet & Hajcak, 2008). Interestingly however, different facets of anxiety (e.g., physiological arousal v. general worry) may show different sensitivities to the ERN amplitude. According to a meta-analysis conducted by Moser and colleagues (2013), studies utilizing continuous measures of anxious apprehension revealed a more robust relationship with the ERN ($r = -0.35$) than those using other measures of anxiety ($r = -0.09$). Specifically, results from one study indicated that anxious apprehension (i.e., general worry) but not anxious arousal (i.e., physiological symptoms of arousal) was associated with increased ERN amplitude (Moser, Moran, & Jendrusina, 2012). In these studies, ‘anxious apprehension’ is defined as worry and verbal rumination in relation to perceived future threats, whereas ‘anxious arousal’ is defined as somatic tension and physiological hyperarousal elicited by clear and present threats. Making a similar distinction, previous research has also shown that the ERN is sensitive to trait but not state measures of anxiety (see Olvet & Hajcak, 2008 for a review), including anxiety sensitivity (Beste et al., 2013), and negative affect/emotionality (Hajcak, McDonald, & Simons, 2004; Luu, Collins, & Tucker, 2000).

Taken together, medial frontal ERN is consistently enhanced in relation to anxiety disorders, particularly those with general worry symptoms. Importantly however, while the magnitude of the ERN has been shown to predict the longitudinal development of anxiety disorders in the subsequent three years (Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, 2015), it’s relation to predicting treatment response has not been assessed.

Feedback Negativity (FN)

Although not as well established as the ERN and anxiety, a similar relationship between the feedback negativity (FN) and anxiety is emerging. While the time-domain literature on FN and anxiety contains some mixed results, approximately half of the studies suggest medial frontal FN is enhanced in relation to anxiety. Specifically, across different feedback tasks, multiple studies found enhanced loss-related FN for individuals with greater behavioral inhibition (DePascalis et al., 2010; Balconi & Crivelli, 2010), a trait common in many anxiety disorders. Additional research focusing on negative affect/emotionality, commonly seen in anxiety disorders, found enhanced FN amplitude and ACC activity for individuals with greater negative emotionality (Santesso et al., 2012; Sato et al., 2005). Enhanced FN was also found in the context of ambiguous feedback for individuals with greater dispositional anxiety (Gu, Ge, Jiang, & Luo, 2010).

More importantly, several recent studies demonstrate a consistent link between enhanced frontal midline *theta*-FN and anxiety (Cavanagh & Shackman, 2015; Ellis, Watts, Schmidt, & Bernat, 2018; Mueller et al., 2014; Mueller et al., 2015; Osinsky et al., 2017). For example, Mueller and colleagues (2014) found increased frontal midline theta power for individuals with high neuroticism/anxiety. Additionally, among individuals with both depression and anxiety, enhanced processing of negative feedback was associated with greater medial frontal theta and aMCC activity (Mueller et al., 2015).

To help contextualize these results, a recent paper by our group points out that discrepancies in the time-domain FN and anxiety literature may be due to the overlapping but distinct contributions from different frequency bands (Ellis et al.,

2018). Specifically, while frontal midline theta-FN was enhanced for individuals with greater anxiety, delta-FN (<4Hz) was also significantly modulated by anxiety. Regression results revealed that blunted or non-significant time-domain FN may be due to suppression effects occurring from an increased positive-going delta, combined with an increased negative-going theta. As such, research focusing on the spectral properties of FN is important for generating an accurate depiction of its modulation with respect to individual differences. However, despite the evidence for theta-FN as a marker of anxiety, no studies have examined this component as a predictor of anxiety treatment response.

N2

Compared to the ERN and FN, fewer studies have assessed the N2 in relation to anxiety. Nevertheless, the results from those studies are consistent with the previous two ERPs and suggest that medial frontal N2 is similarly enhanced in relation to various measures of anxiety. For example, Sehlmeier and colleagues (2010) focused on anxiety personality traits in healthy undergraduate subjects and found evidence of enhanced no-go N2 amplitudes in individuals with greater trait anxiety. Using a different task and a smaller sample size, Righi and colleagues (2009) similarly found increased medial frontal N2 using trait and state measures of anxiety. Also within the context of anxiety traits, other research suggests behavioral inhibition is correlated with greater no-go N2 amplitudes over dorsal mid-cingulate (Armodio, Master, Yee, & Taylor, 2008). Finally, using a clinical population with obsessive compulsive disorder (OCD), Ruchow and colleagues (2007) found that patients with OCD had enhanced (more negative) no-go N2 amplitudes compared to healthy controls. However, topographically, this effect only occurred in mid-central regions,

not in medial frontal areas as expected. Similar to the ERN and FN, there is a lack of research on medial frontal theta-N2 as a predictor of anxiety treatment response, despite evidence for its association with anxiety and its neural correlates with aMCC.

To summarize, medial frontal theta ERPs (i.e., ERN, FN, & N2) are consistently shown to reflect activity in aMCC, and are generally enhanced in relation to various measures of anxiety. However, while extensive evidence consistently implicates aMCC in treatment prediction work, medial frontal theta ERPs have not been evaluated as predictors of treatment response. Consistent with the emerging interest in treatment prediction for anxiety, examining these components represents a novel and important contribution to this area. As such, the primary aim of the proposed research is to evaluate medial frontal theta ERPs as predictors of anxiety sensitivity treatment response.

Medial Frontal Theta Negativities as a shared process

Given that all three medial frontal theta ERPs have been shown to reflect activity in aMCC, and all three have demonstrated a similar association with anxiety, it has been suggested that they may represent a “lingua franca” or a shared process in relation to motivationally significant outcomes (Cavanagh et al., 2012; Cavanagh & Shackman, 2015). In fact, Holroyd & colleagues (2008) suggest the FN is simply an N2 that occurs to unexpected negative feedback. This view is also supported by Cavanagh & colleagues (2012) who suggest N2 and FN may both represent a form of expectation mismatch, even though they are elicited under different cognitive circumstances (e.g., feedback processing versus action selection). Similarities are also

drawn between the ERN and FN since both broadly reflect ‘performance monitoring,’ and according to the reinforcement learning theory, both are enhanced when the outcome is worse than expected (Holroyd & Coles, 2002). Additionally, evidence for performance monitoring and behavioral adjustment has been found for both ERPs. As a response-locked ERP, the ERN is most sensitive to errors of commission and has been linked to post-error slowing on subsequent trials, indicating an adjustment of performance. As a stimulus-locked ERP, the FN is most sensitive to negative feedback and is associated with post-punishment switching (for a meta-analytic review of ERN and FN behavioral change results, see Cavanagh & Shackman, 2015). Additionally, a number of studies point to the evidence from ERP source localization, fMRI, and simultaneous fMRI/EEG techniques which has suggested that all three components reflect activity in medial frontal regions including the anterior midcingulate cortex (aMCC; Cavanagh & Shackman, 2015; Gehring & Willoughby, 2002; Hauser et al., 2014; Holroyd et al., 2004; Miltner, Braun, & Coles, 1997; Potts, Martin, Burton, & Montague, 2006).

However, while the ERN and FN are both thought to reflect a performance monitoring system with primary activity over medial frontal regions, evidence for at least partially distinct processes underlying these components has been shown in terms of differing scalp distributions (Foti, Weinberg, Bernat, & Proudfit, 2014; Gehring & Willoughby, 2004) and differential sensitivity to externalizing psychopathology (Bernat, Nelson, Steele, Gehring, & Patrick, 2011), obsessive-compulsive traits (Simons, 2010), and schizophrenia (Horan, Foti, Hajcak, Wynn, & Green, 2012). Since the ERP components arise under different cognitive

circumstances, involve contributions from a diverse network of brain regions, and are differentially sensitive to some types of psychopathology, it has been suggested that these components reflect similar but distinct processes. Given the two contrasting views, additional research is needed to clarify the convergent or discriminant nature of these ERPs in a variety of contexts. One area that has not been assessed is whether these ERPs represent shared versus independent contributions to predicting treatment outcomes.

Summary and current aims

As outlined in detail above, a large body of evidence indicates the most consistent predictor of treatment outcomes is activity in the anterior cingulate cortex (ACC). Although activity in ACC can be measured by medial frontal theta event related potentials (ERPs), these neurophysiological components have not been evaluated as predictors of treatment response. There is also a lack of research on the functional networks associated with ACC treatment prediction, despite implications for prefrontal engagement of cognitive control processes. Therefore, the present study aimed to examine these gaps in the literature by using task-based electroencephalography (EEG) and medial frontal theta negativities (MFTN) as predictors of anxiety sensitivity treatment response.

Using amplitude as well as functional connectivity measures (i.e., inter-channel phase synchrony) allows for insight into possible mechanisms. Moreover, by assessing multiple ERPs, this work contributes to the existing literature on whether these components represent a shared or unique medial frontal process.

These objectives are represented by the following specific aims:

AIM 1: To assess the a) amplitude and b) inter-channel phase synchrony of MFTN (theta-FN, theta-N2) as predictors of anxiety sensitivity treatment response.

Hypothesis: Increased medial frontal theta-FN and theta-N2 amplitude is expected to predict greater treatment response. With respect to phase synchrony, the directionality of effects could not be predicted based on limited work in this area.

AIM 2: To determine if the MFTN components represent a shared or unique process in relation to treatment prediction.

Hypothesis: Theta-FN and theta-N2 are expected to have shared variance in predicting treatment response.

Significant impact: This work represents a novel contribution at the forefront of an emerging field, and may ultimately lead to the improvement in treatment efficacy and individualized treatment selection.

Chapter 2: Study Overview

Using an archival dataset, medial frontal theta negativities were examined as predictors of anxiety sensitivity treatment response. As a brief overview, this dataset included approximately 275 individuals recruited from the community and was designed to assess cognitive and affective risk factors related to anxiety and suicide. Study duration for each participant was approximately 6 months, at the beginning of which each participant was randomly assigned to one of four treatment conditions. Throughout the study, participants completed a battery of self-report measures at multiple time points, and all subjects completed a baseline EEG assessment before undergoing treatment.

Study design

All participants completed a baseline assessment that included answering self-report questionnaires related to anxiety and depression severity, as well as a baseline neurophysiological assessment that included EEG recordings during multiple tasks. Two of those tasks included gambling-feedback and go/no-go computer tasks, which were examined in the current study since those tasks elicited the medial frontal ERPs of interest.

After the baseline assessment, participants were then randomly assigned to one of four conditions: Anxiety Risk Reduction ('Anxiety-RR'), Depression Risk Reduction ('Depression-RR'), Anxiety and Depression Risk Reduction ('Combined-RR'), or the repeated-contact control condition. All treatment groups (Anxiety-RR, Depression-RR, and Combined-RR) underwent the same intervention procedures; the

only difference between groups was the type of stimuli that were shown in a subset of the intervention. Specifically, in the Anxiety-RR group individuals were presented with anxiety related stimuli in the Cognitive Bias Modification part of the treatment (described below), while the Depression-RR group was presented with depression-related stimuli. The Combined-RR group represents a direct combination of the Anxiety and Depression intervention groups, such that participants received both anxiety and depression-related stimuli and therefore spent more time in the intervention per session. Regardless of intervention group, participants completed three intervention sessions at a rate of 1 session per week for three weeks (Figure 2). For the Anxiety-RR and Depression-RR groups, each session lasted approximately 1 hour. For the Combined-RR group, sessions lasted approximately 1.5 hours due to the inclusion of both anxiety and depression-related intervention materials. Session 1 of treatment focused on psychoeducation and brief exposure therapy in the form of ‘Cognitive Anxiety Sensitivity Treatment’ (CAST; described in more detail below). Session 2 and 3 incorporated Cognitive Bias Modification (CBM) for the majority of the session, and allowed a small portion of time for review of psychoeducational materials. In addition to the three treatment sessions, participants were instructed to practice the CAST exposure exercises (learned in session 1) daily as ‘homework’ until none of the exercises generated any fear/distress.

The control group represented a repeated contact condition, where each participant was assigned a personal study coordinator and asked to check-in with that coordinator at various intervals. During each check-in, the coordinator asked about their symptoms and severity status, and administered some brief measures. Each

check-in occurred once per week over the phone and suicide risk was also evaluated. The purpose of the repeated contact design was to control for any effects of personal interaction that may mitigate anxiety and mood disorder symptoms, as well as to control for symptom improvement over time. This is an important component of the existing dataset because many clinical trials involving psychotherapy typically do not include a control condition, so it is unclear if predictors of treatment response identified in those studies are specific to the intervention or simply to symptom alleviation over time.

Treatment	Control
Week 1: Baseline assessment	Week 1: Baseline assessment
Week 2: Session 1 – 45min of Psychoeducation, 45 min of CAST	Week 2: Session 1: study coordinator check in
Week 3: Session 2 – 45min of CBM-I (mood), 45min of CBM-I (anxiety)* Mid-tx assessment	Week 3: Session 2: study coordinator check in Mid-tx assessment
Week 4: Session 3 – 45min of CBM-I (mood) 45min of CBM-I (anxiety)*	Week 4: Session 3: study coordinator check in
1 week post-treatment assessment	1 week post-treatment assessment
6 months post-treatment assessment	--Offered Treatment condition--

Figure 2. Timeline of procedures for the Combined treatment (left) and control (right) groups. Note: * indicates the order of mood and anxiety components was counterbalanced across participants.

In addition to the baseline assessment and the intervention procedures, the study design also incorporated post-treatment EEG sessions for a small subset of subjects randomly selected from the Combined-RR and Control groups (Combined-RR N=25, Control N=25). These individuals underwent intensive neurophysiological evaluation, consisting of additional EEG evaluations at multiple time points. These

included 1) mid-treatment (after session 2), 2) post-treatment (1 week post-treatment), and 3) 6 months post-treatment. Unfortunately however, due to attrition there were only 15 subjects with post-treatment data in the treatment group, and 14 subjects with post-treatment data in the control group. Given the low number of subjects in each group and the low power to detect a between group effect (Power=.08; two tailed independent samples t-test with estimated Cohen's $d=.2$, alpha level=.05, Group 1 $N=15$, Group2 $N=14$), the pre/post change in neurophysiological data was not analyzed.

Additionally, unfortunately the ERN could not be assessed using this dataset due to the limited number of subjects with erroneous responses. Methodological studies demonstrate that at least six error trials/epochs are needed to reliably elicit an ERN (Olvet & Hajcak, 2009; Pontifex et al., 2010; Steele et al., 2016). In this dataset, only four subjects made 6 or more errors during the Go/No-go task, indicating this particular task cannot be used to assess the ERN. Three out of the other four tasks collected in this dataset did not involve response data (i.e., picture viewing and resting tasks), and therefore are not viable candidates for eliciting an ERN. The only other task in this dataset that elicits correct and incorrect responses is the three-stimulus visual Oddball task. However, this task generated even fewer error counts, with only two subjects making six or more errors. As such, the existing dataset does not contain sufficient ERN data, and therefore the current analyses focus on the FN and N2 as the medial frontal theta ERPs of interest.

Chapter 3: Methods

Participants

A total of 275 subjects participated in the study at Florida State University that assessed neurophysiological markers and psychological risk factors related to anxiety and depression. Thirty-four participants were excluded due to an excessive number of EEG artifacts (>50% of trials rejected using methods described in *Data Preprocessing*), two participants did not have useable data due to equipment malfunctions while recording, and six subjects failed to complete the baseline self-report measures. This left a total of 233 participants for analysis (129 females; M age= 35.03 years, SD= 15.91 years). All participants were 18 years of age or older and were screened for neurological conditions, visual impairments, and/or traumatic brain injuries.

Eligibility for the study was based on an assessment of risk factors for anxiety and depression, as determined by elevated scores on the 18-item self-report Anxiety Sensitivity Index-3 (ASI-3; Taylor et al., 2007) or elevated scores on the 15-item self-report Interpersonal Needs Questionnaire (INQ-15; Hill & Petit, 2013; Van Orden, Cukrowicz, Witte, & Joiner, 2012). The ASI-3 measures an individual's tendency to interpret anxiety-related sensations as potentially harmful or fear inducing, and has been shown to be a risk factor associated with development of anxiety disorders and suicidal behavior (Taylor, Koch, & McNally, 1992; Schmidt, Zvolensky, & Maner, 2006). The INQ-15 assesses an individual's level of perceived burdensomeness and thwarted belongingness, which are two constructs shown to be associated with

development of mood disorders and suicidal behavior (Baumeister & Leary, 1995). To have continuous measures of anxiety severity across a range of anxiety disorder categories, the inclusion criteria was purposefully inclusive of those with and without a diagnosis. Individuals were excluded from participation if they met any of the following criteria: significant medical illness, current substance dependence, current or past psychotic spectrum disorder, uncontrollable bipolar disorder, or serious suicidal intent. Participants were provided informed consent before starting the study.

Upon entering the study, all participants were assessed for psychiatric diagnoses as determined using the Structured Clinical Interview for DSM-V, Research Version (SCID-5-RV; First, Williams, Karg, & Spitzer, 2015). The SCID-5-RV was administered by trained doctoral level therapists with substantial training in SCID-5-RV administration and scoring. All SCID-5-RV results were reviewed by a licensed clinical psychologist to ensure accurate diagnoses. Previous studies conducted using this method of training and scoring have demonstrated high inter-rater reliability (e.g., over 80% with a kappa of .77; Timpano & Schmidt, 2012).

Intervention procedures

The three treatment groups received a computer-based intervention that combined psychoeducation, brief exposure therapy in the form of Cognitive Anxiety Sensitivity Treatment (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 its effect on the body. Participants were taught that the physiological arousal associated with stress is not harmful to

them and were instructed to participate in guided exercises to correct the fear response associated with bodily sensations. The guided exercises took the form of a brief exposure therapy, labeled CAST. 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 used by Schmidt and colleagues (2007). CAST was specifically designed to reduce anxiety sensitivity (AS) symptoms, which are associated with the etiology and maintenance of multiple types of psychopathology. Additionally, proof of concept effects in ongoing pilot studies suggest immediate post-intervention anxiety reduction, as measured by the ASI-3. During the CAST portion of the session, participants were first directed to complete a standardized assessment of their fear to different arousal sensations. With the program's direction and assistance, participants completed repeated exposure trials of engaging in an arousing sensation (i.e., hyperventilation) followed by rating the level of arousal they experienced during the exercise (scale of 1 to 10, with 10 being the highest). They were told that they would repeat each exercise until their subjective rating of distress was rated as minimal (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.

As the third component of the intervention, CBM-I focuses on changing an individual's automatic interpretation of incoming information. This was done by providing feedback to participants about whether their 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 then asked to determine if the word was related to the sentence by pressing “yes” if they thought they were related, and “no” if they thought they were not related. On half of the trials, the combination of word and sentence created a benign meaning (previous 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 such that “correct” feedback was elicited by judging the anxious combinations to be “unrelated” and the benign combinations to be “related”. 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” and they heard a horn blast (approximately 85 decibels). An interpretation bias is 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/reinforced. Participants then took a short 5-minute break during which they completed a filler task (simple math problems), followed by another 80 training trials. At the end, they were given 40 test trials of novel words and sentences that they had not seen before. Unfortunately, response data were not collected in this dataset, so the effectiveness of each individual component of the treatment (CBM-I v. CAST v. psychoeducation) is unknown. However, the cumulative effectiveness of the intervention can be measured by examining change in symptom severity compared to the control group.

Measures and tasks

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. 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. Early work investigating AS demonstrated contributions to the etiology and maintenance of panic disorder (PD; Schmidt, Lerew, & Jackson, 1997; 1999). Recently, AS has also been implicated in the development of several other affective disorders (Schmidt, Zvolensky, & Maner, 2006), including depression and generalized anxiety disorder (Allan, Capron, Raines, & Schmidt, 2014), obsessive-compulsive disorder (OCD; Raines, Oglesby, Capron, & Schmidt, 2014), posttraumatic stress disorder (PTSD; Lang, Kennedy, & Stein, 2002), substance use disorders (McCaul, Hutton, Stephens, Xu, & Wand, 2017; Paulus, Hogan, & Zvolensky, 2018), and externalizing disorders (Bilgic et al., 2017). Further, empirical evidence suggests AS can be treated through brief interventions, ultimately resulting in reduced symptom severity across psychopathologies (Schmidt et al., 2007; Schmidt, Capron, Raines, & Allan, 2014; Smits et al., 2008). There has also been some evidence pointing to the neural processes specifically associated with AS

severity. Results from these fMRI studies show a positive association between self-reported AS and activity in the insula and ACC during emotional processing tasks (Poletti et al., 2015; Stein et al., 2007).

Participants also completed the 16-item Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990), as well as the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). The PSWQ is a self-report measure designed to assess trait worry and apprehension using a Likert scale ranging from 1 (not at all typical of me) to 5 (very typical of me). It is a widely used tool for assessing Generalized Anxiety Disorder specifically, and has been shown to have high internal consistency and test-retest reliability. Total scores can range from 16 to 80 with higher scores indicating greater severity. The BDI-II is another widely used self-report measure for depression symptom severity. This measure includes 21 items scored from 0 to 3 where higher numbers indicate greater severity and/or frequency. All items are summed to generate a total score with higher scores indicative of greater depression symptom severity.

Participants also completed a series of tasks designed to assess cognitive and affective processes (e.g., emotional picture viewing tasks, visual oddball task, gambling feedback, go/no-go, resting state). The current analyses focused on the gambling and go/no-go tasks since these are reliably used in generating the FN (gambling feedback) and N2 (go/no-go) ERPs.

The gambling task was a modified version used by Gehring and Willoughby (2002) in which the participant chose between two monetary options on each trial and then received feedback indicating whether the choice resulted in winning or losing

money on that trial (Figure 3). Target stimuli consisted of two squares side-by-side, each containing a number (5 or 25) representing a monetary value (in cents). After subjects made a choice by pressing the left or right button, feedback was presented 1000 ms after the button press. The feedback stimulus indicated the outcome of the participant's decision. That is, the chosen box turned either red or green to signify either a win or a loss (with red or green as the winning color counterbalanced across participants), and the box that was not chosen turned the other color (either green or red) to indicate what the outcome of the trial would have been had that box been chosen. The feedback stimulus appeared for 1000 ms, followed by a blank screen for 1500 ms preceding the onset of the next trial. Based on the design used by Gehring and Willoughby (2002), all four possible combinations of 5 and 25 (i.e., 5-5, 5-25, 25-5, and 25-25) were evenly crossed with the four possible win/loss outcomes (win-win, win-loss, loss-win, loss-loss), resulting in 16 trial types. Stimulus combinations and win/loss feedback on all trials were randomly determined, such that future trials were not predictable from outcomes associated with prior choices. Two sets of these 16 trial types, ordered randomly, were included in each block. Upon completion of a block, participants received feedback about their win/loss ratio within that block. Participants completed 7 blocks of 32 trials each.

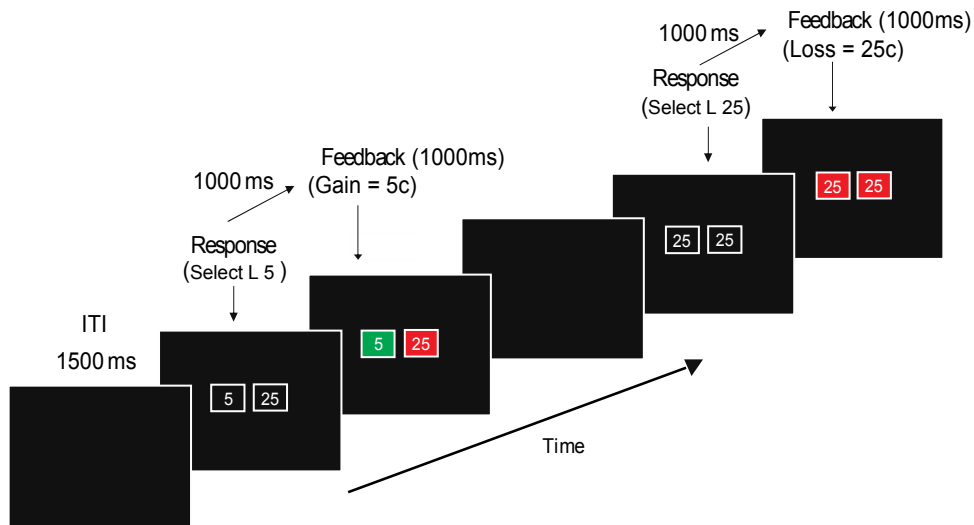


Figure 3. Sequence of stimuli and feedback events in the gambling task.

The Go/No-go task is a stimulus-response selection task where participants decide whether to execute or inhibit a response (Figure 4). Participants were presented with two different white letters (e.g., S-F) displayed sequentially on a black background, and instructed to press the right or left button corresponding to the letter that appeared (go trials; e.g., S=left, F=right). However, when the stimulus repeated itself participants were asked to withhold their response (no-go trials; e.g., the third letter in the string S-F-F-S-F). No-go trials were pseudo-randomly interspersed throughout the task such that one, three, or five go trials always preceded a no-go trial. Seven blocks of twenty-four trials each were completed, with eighteen go trials (75%) and six no-go trials (25%) in each block. Stimulus duration was 296 ms, the response window was 1150 ms, and the inter-trial-interval was 900 ms. Participants also completed a practice version of the task consisting of 20 practice trials with different letters, but no electrophysiology data was recorded during the practice. Participants were provided with their overall accuracy after each block, and

associations between the letter (e.g., S or F) and right/left button presses were counterbalanced across participants.

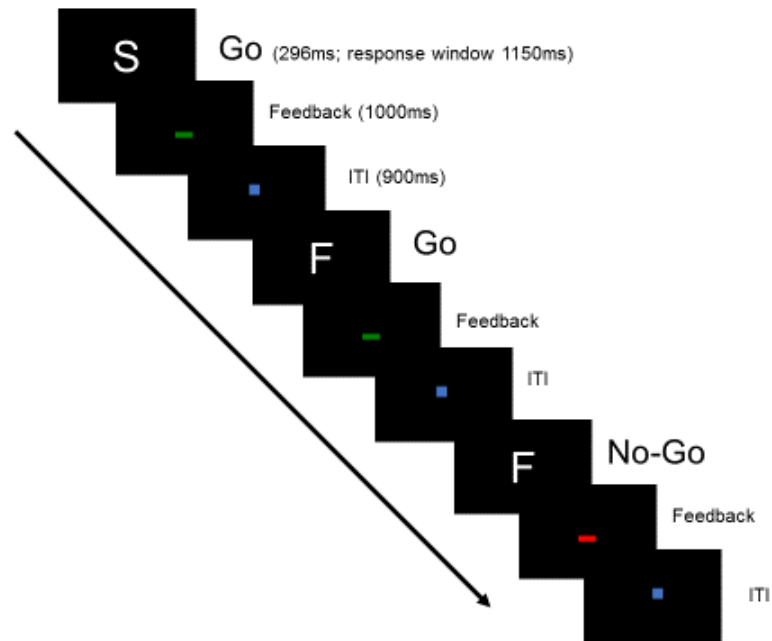


Figure 4. Sequence and timing of events in the Go/No-go task.

Psychophysiological data acquisition & processing

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) 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 Ω . EEG signals were vertex referenced during recording, and referenced to average mastoid signals offline (electrodes TP9 and TP10). 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).

Epochs of three seconds were taken from 1000 ms pre to 2000 ms post stimulus with a 150 ms to 10 ms pre-stimulus baseline, and re-referenced to averaged mastoid sites. Data was corrected for ocular artifacts using an algorithm developed by Semlitsch and colleagues (1986) in the Neuroscan Edit 4.5 software (Neuroscan, Inc.), and downsampled to 128 Hz using the Matlab resample function (Mathworks, Inc.), which applies an anti-aliasing filter during resampling. Then, two methods of data cleaning were used. In the first method, trials were rejected if activity at frontal electrodes (F3 or F4) exceeded $\pm 100 \mu\text{V}$ in either the pre-stimulus period of -1000 to -1 ms, or the post stimulus period of 1 to 2000ms. Within-trial individual electrodes were rejected if activity exceeded $\pm 100 \mu\text{V}$ during the same pre- and post-stimulus time periods. This removed 14.9% of all trials from the gambling task, and 13.8% of all trials from the Go/No-go task. Additionally, visual analysis of the averaged waveforms indicated that 94 electrodes out of 25,850 (0.4%) were disconnected during recording in the gambling task, and 135 (0.5%) were disconnected during recording in the Go/No-go task. These electrodes were replaced with the mean of the three nearest neighbors. After preprocessing, the data were averaged according to each stimulus category for N2 (i.e., go, no-go) or feedback category for FN (i.e., gain, loss).

Time-frequency amplitude

Time-frequency (TF) analysis is a technique that can be used to disentangle overlapping frequency band effects in several common ERP signals, including the FN and N2 components (Bernat, Williams, & Gehring, 2005; Bernat, Malone, Patrick, & Iacono, 2007; Bernat, Nelson, & Baskin-Sommers, 2015; Harper, Malone, & Bernat, 2014). As suggested by previous work (Bernat et al., 2005), time-frequency principal components analysis (TF-PCA) can be used to parse overlapping spatial and temporal activity related to both ERP components. To separate theta activity relevant to each component, the data were pre-filtered using a 2 Hz high-pass and 7 Hz low-pass filter before applying the TF-PCA, to isolate theta-band activity. Next, the theta-filtered signals were transformed into time-frequency energy representations using the binomial reduced interference distribution (RID) variant of Cohen's class of time-frequency transforms. Generally, the binomial RID transformation computes a complex time-frequency distribution with uniform time-frequency resolution, avoiding the trade-off between time and frequency resolution inherent to other transforms, including wavelet analysis (Bernat et al., 2005). Although either transform can be applied, wavelets have non-uniform time-frequency resolution, producing reduced temporal resolution at low frequencies and reduced frequency resolution at high frequencies (for additional details, see Aviyente et al., 2011; Bernat et al., 2005). Since RID does not suffer from this trade-off, it is arguably the more desirable transform and was therefore employed here. Following this, PCA with Varimax rotation was applied to the TF transforms separately for theta-FN and theta-N2 filtered distributions, using a 0-14 Hz frequency window and 0-1000ms post-

feedback (for FN) and post-stimulus (for N2) time window. The resolution of the time-frequency transforms was 32 bins/second in the time domain, and 2 bins/Hz in the frequency domain, consistent with previous reports using these approaches.

Figure 5 displays the grand average TF-PCA decomposition for theta in the Gambling (left) and Go/No-go (right) tasks. For the Gambling task, two components were extracted based on the scree plot and ability to distinguish the FN component, where both PCs accounted for a total of 43.59% of the variance. The first principal component (PC1) occurred earlier in the N1/P2 window (approximately 100-200ms) and accounted for 30.85% of the variance, while PC2 occurred during the FN window (approximately 225-400ms) and accounted for 12.74% of the variance. The variance accounted for by the first two principal components (PCs) far exceeded that accounted for by the next PC (e.g., PC3= 6.52% and PC4= 5.79%), indicating that retention of two PCs was justifiable. Similarly for the Go/No-go task, two components were extracted using the same criteria, where both PCs accounted for 51.47% of the variance. The first PC (PC1) occurred in the N1/P2 time window (100-250ms) and accounted for 34.65% of the variance. The second PC (PC2) occurred during the N2 window (approximately 200-400ms), and accounted for 16.81% of the variance. Again, the variance accounted for by the first two PCs exceeded that accounted for by the next PC (e.g., PC3= 8.31% and PC4= 5.68%), indicating that two components were justifiable. PCs during the FN window (Gambling- PC2) and N2 window (Go/No-go- PC2) served as the primary variables of interest. Electrode FCZ was most proximal topographically to the center of activation for theta-FN during gain and loss conditions as well as theta-N2 during go and no-go conditions.

Therefore, the average of three electrodes in medial frontal (FCZ, FC1, FC2) areas will be included in analyses.

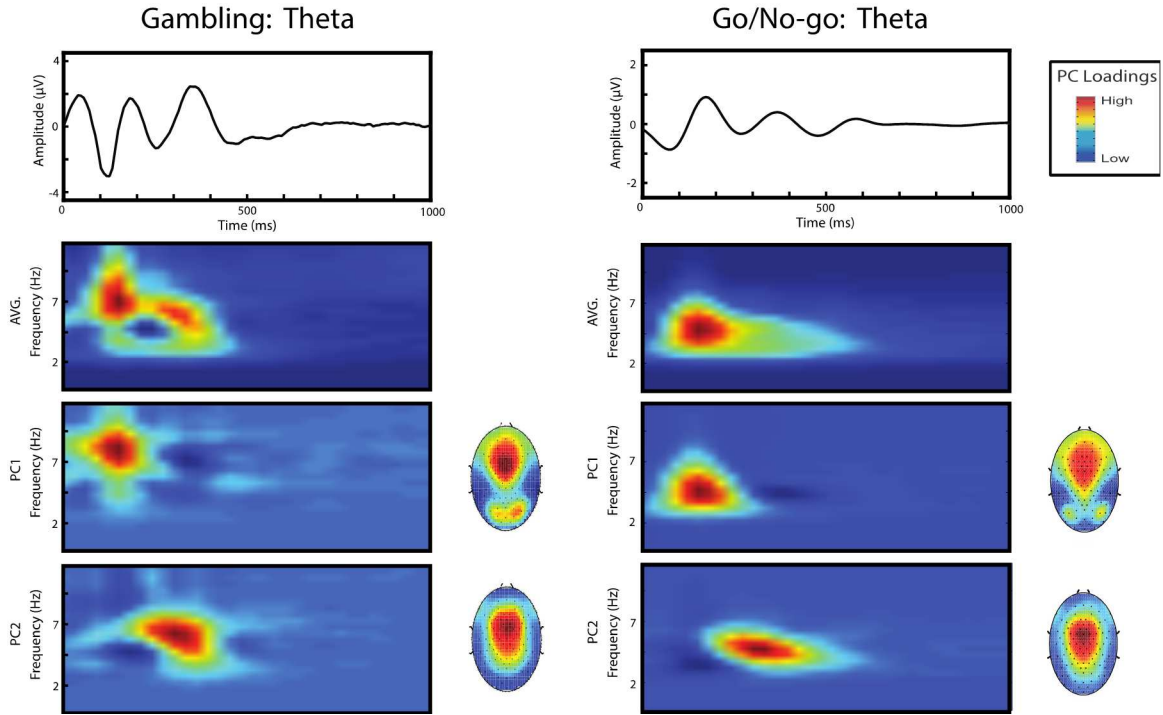


Figure 5. Grand average time-frequency (TF) decomposition of theta during the Gambling task (left) and the Go/No-go task (right) using principal components analysis (PCA) across all trial types (i.e., gain and loss trials in Gambling, & go and no-go trials in Go/No-go). *Waveform plots, top level:* Average time-domain ERPs across all trials, theta frequency-filtered. *Color surface plots, second level:* grand average time-frequency effects, with principal components depicted beneath. *Colored topographical head maps:* scalp topography distributions for the mean of the respective principal components. Gambling theta effects are best captured by two principle components, where PC1 represents theta-N1/P2, and PC2 represents theta-FN and is maximal at FCZ regions. Go/No-go theta effects are also indicated by two principal components, where PC1 represents N1/P2, while PC2 represents N2 and is maximal at FCZ regions.

Time-frequency inter-channel phase synchrony (ICPS)

Inter-channel phase synchrony (ICPS) indexes the degree of phase alignment between two electrode sites, and can be considered an index of functional

connectivity between regions (Cavanagh et al., 2009; Cohen, 2011). Specifically in the theta band, ICPS between medial and lateral prefrontal regions has been widely studied in the context of tasks requiring cognitive and affective control. These studies show that during trials that elicit more surprise, conflict, or punishment, as well as those that are particularly valuable tend to show increased ICPS between the ACC and lateral prefrontal cortex, in addition to other brain regions (Aviyente et al., 2017; Bolanos, Bernat, He, & Aviyente, 2013; Hanslmayr et al., 2007; Luft, 2014; Smith et al., 2015; Watts, Tootell, Fix, Aviyente, & Bernat, 2018). Taken together with the treatment prediction work suggesting a role for regulatory ability and prefrontal control networks, medial frontal theta components will be assessed for phase synchrony with lateral prefrontal electrodes (Figure 6) over the FN and N2 windows. To avoid spurious phase synchrony between scalp electrodes due to volume conduction (Srinivasan et al., 2007), all EEG epochs will first be transformed using current source density (CSD), which minimizes volume conduction by source localizing activity toward the cortical surface (Tenke and Kayser, 2012). Subsequently, phase-synchrony will be computed as a phase locking value (PLV; Aviyente et al., 2011; Lachaux et al., 1999) which represents the average difference in phase-synchrony between a pair of electrodes across epochs. PLV values range from 0 to 1, where 1 indicates highly consistent phase synchrony between electrodes, and values near 0 indicate almost entirely unrelated phase between electrodes. As such, PLV will be used to quantify the synchrony between medial frontal and bilateral frontal theta EEG signals, separately for the FN and N2 windows. To do so, the mean of each bilateral electrode pair will be used (i.e., mean of FCZ – F3 and FCZ – F4

PLVs). The PLV values, representing phase synchrony between medial and lateral prefrontal regions, will be used to predict magnitude of treatment response at mid-treatment, 1-week post treatment, and 6 months post treatment.

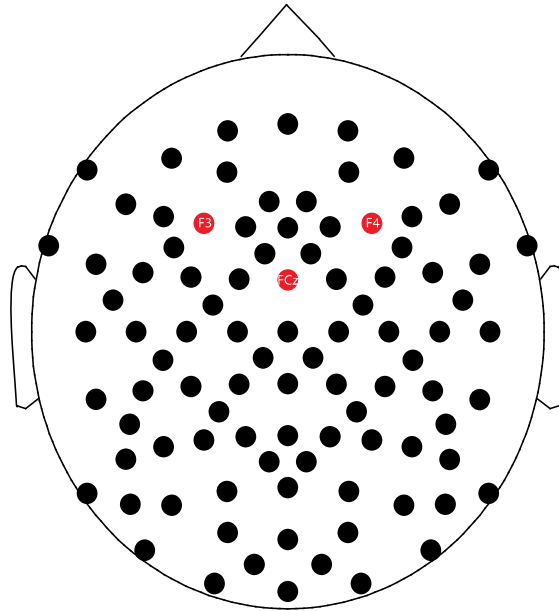


Figure 6. Topographical representation of electrodes in the 96-channel EEG cap. Red indicates medial frontal (FCZ) and lateral frontal (F3 & F4) electrodes included in ICPS analyses for theta-FN and theta-N2.

Data analytic methods

Analyses of behavioral, demographic, and treatment outcome data are reported first, followed by analyses of neurophysiological data as predictors of treatment outcome. Amplitude and inter-channel phase synchrony for theta-FN and theta-N2 are separately assessed as pre-treatment predictors of anxiety sensitivity response. Treatment response was defined at three time points by the percent change in anxiety sensitivity symptoms on the ASI self-report measure.

Primary treatment prediction analyses were conducted in two steps. Step 1 represented a comprehensive approach with all four treatment groups and time points

to determine if any significant effects were present. The purpose of this first step was to reduce the number of bivariate comparisons and to represent an ‘omnibus’ model where all variables of interest were considered simultaneously. To do this, a treatment group by time by MFTN fixed effects linear mixed model (LMM) was performed on symptom severity (i.e., mean ASI scores).

Linear Mixed Models were run separately for each neurophysiological predictor (theta-FN gain, theta-FN loss, theta-N2 go, theta-N2 no-go) for both amplitude and inter-channel phase synchrony, resulting in a total of 8 models. In all models, separate terms were included for each of the treatment groups and dummy coded relative to the control. For simplicity, groups were labeled as Group1 (combined treatment), Group2 (anxiety treatment), and Group3 (depression treatment), with the intercept as the control group. The ‘time’ variable in each model included four levels, quantified as weeks into the study (i.e., baseline=0, mid-treatment=2, 1-week post treatment=4, and 6 months post-treatment=26). The dependent variable in each model was the primary outcome measure (i.e., average anxiety sensitivity scores). Terms of interest within each model included the three Group x MFTN interactions (e.g., Group1 x Theta-FN gain amplitude; Group2 x Theta-FN gain amplitude; Group3 x Theta-FN gain amplitude), as well as the three Group x MFTN x Time interactions. Within each model, the two-way interactions tested whether the MFTN variable differentially predicts treatment response based on treatment group (e.g., does Theta-FN gain amplitude predict treatment response in any of the three treatment groups relative to the control?). The three-way interactions with time tested whether this prediction effect differs as a function of time. For

example, if a significant two-way interaction was identified, but the three-way interaction was non-significant, this would indicate that the treatment prediction effect did not differ as a function of time (i.e., it was consistent across time points). An unstructured covariance matrix with restricted maximum likelihood estimation was used. Due to the number of models being tested, Bonferroni p-value correction was applied such that significance in the models is based on $p < .0125$ (.05/4 for amplitude and .05/4 for ICPS).

Step 2 of the analyses involved specific effects testing with the purpose of assessing the specificity, sensitivity, and incremental validity of any significant effects identified in step 1. To do this, significant interactions from the linear mixed models were further assessed with nonparametric spearman correlations. Nonparametric methods were used due to their robustness against violations of normality. Specificity is indicated here by effects that are present for one group and not the other/s. Sensitivity is demonstrated by reliability (i.e., consistency across time) and accuracy (i.e., percent of individuals classified as responders versus non-responders). To test for incremental validity, partial spearman correlation coefficients are reported after controlling for baseline symptom severity, and other self-report measures (including anxiety and depression) that may be quicker and more cost-effective predictors. Age and gender were also assessed in relation to treatment response. Multiple comparison correction was applied based on the number of correlations performed.

Finally, theta-FN and theta-N2 were assessed for unique versus shared effects in relation to treatment outcome by entering both into a regression model predicting treatment response.

Given the extensive literature showing enhanced ACC activity as a predictor of treatment outcomes, increased medial frontal theta-FN and theta-N2 amplitude is expected to predict greater treatment response. With respect to phase synchrony, the directionality of effects could not be predicted based on limited work in this area.

For demographic purposes and to further illustrate treatment effectiveness, subjects will be characterized as achieving (1) a full response ($\geq 50\%$ improvement in ASI scores from baseline), (2) a partial response ($< 50\%$ but $\geq 25\%$ improvement), or (3) no response ($< 25\%$ improvement), based on thresholds used in other treatment prediction studies (Nierenberg & DeCecco, 2001). Chi-square tests and Fisher's Exact Tests will be used to compare response rates between treatment and control groups, and between 'responders' ($\geq 50\%$ improvement) versus 'non-responders' ($< 50\%$ improvement).

Chapter 4: Results

Behavioral results

Reaction times and accuracies were computed for the Go and No-go trial types. Correct responses to Go stimuli had a mean reaction time (RT) of 586.57 ms (SD= 138.93), and incorrect responses to No-go stimuli (false alarms) had a mean RT of 1969.08 ms (SD= 239.27). Mean accuracy rates for Go trials was 94.94% (SD= 9.10), while the mean accuracy for No-go trials was 83.47% (SD= 14.58). The four treatment groups did not differ on mean RT to Go ($p=.802$) or No-go ($p=.672$). There were also no significant differences between groups on accuracy for Go trials ($p=.355$) or No-go trials ($p=.708$), indicating the four treatment groups did not differ in their behavioral performance. Reaction time and accuracy was not applicable in the gambling feedback task.

Demographics & treatment efficacy

Demographic characteristics for all four groups of subjects as well as their baseline severity scores (i.e., ASI) and response rates are shown in Table 1. The four groups do not significantly differ on age ($p=.449$), gender ($p=.536$), race ($p=.292$), or psychopathology ($p=.356$), indicating these factors were reasonably balanced across groups.

Importantly, however, the treatment and control groups do show significant differences in response rates (Table 1, $\chi^2 =29.13$, $df=6$, $p<.001$). As shown in Figure 7, by one week post-treatment the combined treatment group had the highest percent

improvement (M=63.77, SE=3.97), which was significantly greater than the anxiety group (M=45.43, SE=5.78; $t=2.58$, $p=.011$), the depression group (M=27.23, SE=6.46; $t=4.82$, $p<.001$), and the control group (M=15.50, SE=9.74; $t=4.59$, $p<.001$). The anxiety group had the second highest percent improvement, which was significantly greater than the depression group ($t=2.1$, $p=.038$) and the control group ($t=2.7$, $p=.008$). The depression and control groups did not differ in treatment response magnitudes ($t=1.0$, $p=.318$).

The combined treatment group also had a significantly greater proportion of individuals achieving full response (>50% improvement) compared to the control group ($\chi^2 =13.85$, $p<.001$). Specifically, 38 of 55 individuals (69.1%) in the treatment group achieved full response (Table 1), compared to 18 of 54 (33.3%) in the control group. Additionally, only 7 individuals in the combined treatment group (12.7%) experienced no response, while almost half of the control group (24/54; 44.4%) failed to show a response. This difference was also statistically significant ($\chi^2 =13.34$, $p<.001$), indicating the combined treatment was the most effective method of reducing anxiety sensitivity, compared to a repeated contact control condition.

Table 1. Demographics and outcome indices for individuals in the treatment and control groups.

	Combined (N=60)	Anxiety (N=60)	Depression (N=57)	Control (N=56)
Age (mean years, SD)	35.2(15.04)	34.2(16.76)	34.1(15.58)	36.7(16.49)
Gender (N female)	29(48%)	37(62%)	32(56%)	31(55%)
Race (N)				
white	37(61%)	38(63%)	35(61%)	31(55%)
black	14(23%)	12(20%)	13(23%)	20(35%)
other	9(15%)	10(17%)	9(16%)	5(9%)
Psychopathology (N)				
Anxiety disorders	20(33.3%)	29(48.3%)	19(33.3%)	24(42.8%)
Depressive disorders	13(21.7%)	12(20%)	16(28.1%)	9(16.1%)
Bipolar disorders	1(1.7%)	2(3.3%)	1(1.7%)	2(3.6%)
Trauma disorders	10(16.7%)	9(15%)	13(22.8%)	6(10.7%)
Obsessive compulsive disorders	2(3.3%)	2(3.3%)	1(1.7%)	4(7.1%)
Substance use disorders	4(6.7%)	0(0%)	1(1.7%)	1(1.8%)
Other (Axis II, somatic)	2(3.3%)	1(1.6%)	2(3.5%)	3(5.4%)
No diagnosis	8(13.3%)	5(8.3%)	4(7%)	7(12.5%)
Baseline severity (mean ASI, SD)	32.7 (16.8)	32.3 (17.4)	28.3 (16.0)	32.5 (17.7)
Post-Treatment response rates				
Responder ($\geq 50\%$ reduction)	38/55 (69.1%)	32/59 (54.2%)	16/54 (29.6%)	18/54 (33.3%)
Partial Response (25-49% reduction)	10/55 (18.2%)	17/59 (28.8%)	17/54 (31.5%)	12/54 (22.2%)
No Response ($< 25\%$ reduction)	7/55 (12.7%)	10/59 (16.9%)	21/54 (38.9%)	24/54 (44.4%)

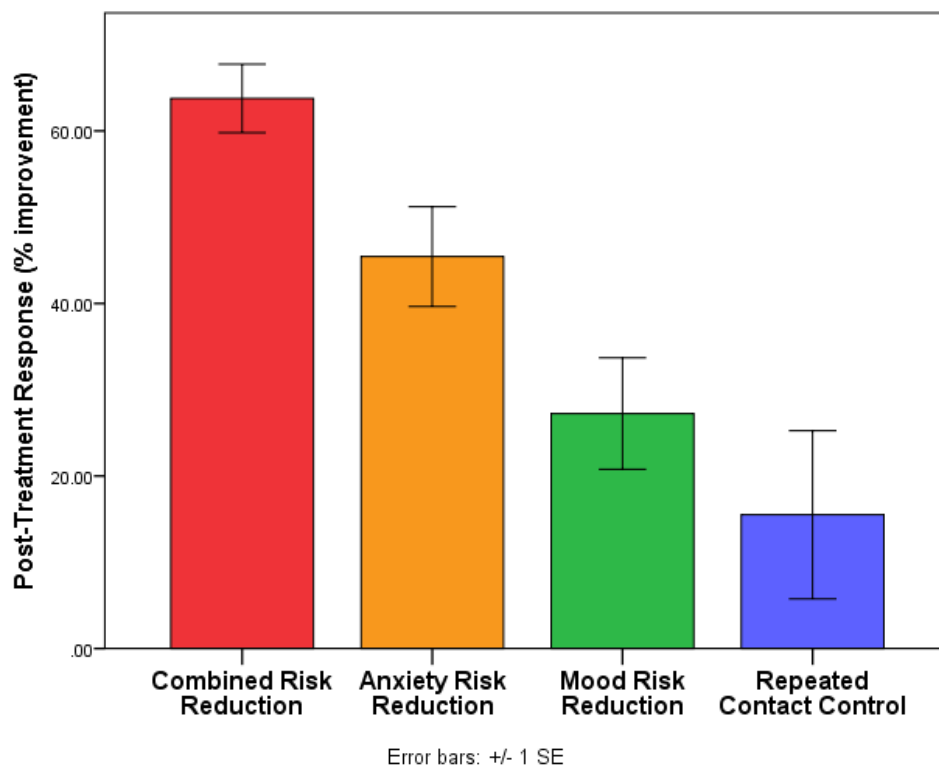


Figure 7. Post-treatment (1 week post) response rates according to intervention group. Individuals in the Combined-RR group had significantly greater improvement in anxiety sensitivity symptoms compared to all other groups. The Mood/Depression-RR group did not significantly differ from the control group.

In addition to 1 week post-treatment, treatment effects are also apparent at the mid-treatment time point as well as 6 months post-treatment (Figure 8). As shown in Figure 8, the combined treatment group had significantly lower anxiety sensitivity scores at mid-treatment and 1-week post treatment compared to the control group ($p's < .001$). This difference in symptom severity continued at trend level by 6 months post-treatment. Importantly, the groups did not differ in baseline severity, indicating the symptom reduction is not driven by pre-treatment severity differences. Overall, these results suggest the treatment is effective in reducing anxiety sensitivity symptoms, and generates significantly greater improvement compared to a control

group. Comparable to other interventions, approximately 30% of individuals did not show full response, warranting further investigation of what predicts treatment response.

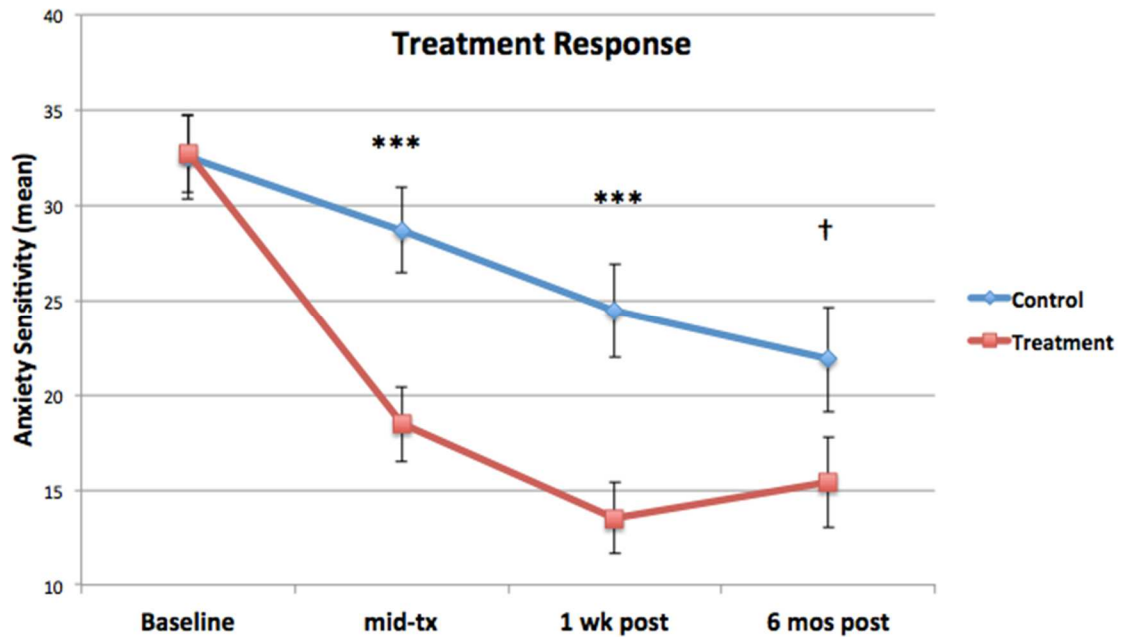


Figure 8. Change in symptom severity over time between the control (blue) and Combined treatment (red) groups. Symptom severity was defined by mean scores on a continuous measure of anxiety sensitivity (AS). Improvement in symptoms is indicated here by a reduction in mean AS scores. Statistical comparisons indicate significant differences in symptom reduction between the control and treatment groups at mid-treatment and 1 week post-treatment, with a trend level difference at 6 months post-treatment. The groups did not differ at baseline. Note: *** $p < .001$, † $p < .10$

Neurophysiological data

To demonstrate the gambling and go/no-go tasks reliably generate an FN and N2, the grand average for each component was assessed for basic condition differences. Consistent with previous findings, a one-sample t-test indicated the loss – gain difference for FN to be significantly less than zero ($M = -1.72$, $SD = 2.36 \mu V$; $t = -$

11.27, $p < .0001$), indicating that the gambling task used in the present study reliably elicited an FN, and consistent with previous work, FN amplitude was maximal during processing monetary loss feedback compared to gain. Additionally, the loss-gain FN difference in theta was significantly greater than zero ($M = .10$, $SD = .157$; $t = 10.02$, $p < .0001$), consistent with previous work showing greater theta-FN amplitude to loss feedback compared to gain (Bernat et al., 2015; Bernat et al., 2011). Similarly for the N2, no-go – go differences in theta were significantly greater than zero ($M = .05$, $SD = .08$; $t = 9.45$, $p < .0001$), consistent with previous work indicating theta-N2 is maximal for no-go compared to go stimuli (Harper et al., 2014; 2016). These results demonstrate that the medial frontal theta ERPs of interest were reliably elicited in the gambling and go/no-go tasks, and sufficiently captured by time-frequency principal components analysis, justifying their use in further analyses.

Predictors of treatment response: Step 1, Linear Mixed Models

Using a comprehensive model with all four treatment groups and time points entered simultaneously, a series of Linear Mixed Models were conducted to determine if any significant effects were present. Terms of interest within each model include the three Group x MFTN interactions, as well as the three Group x MFTN x Time interactions. Within each model, the two-way interactions test whether the MFTN variable differentially predicts treatment response based on treatment group. The three-way interactions with time test whether this prediction effect differs as a function of time.

Amplitude

Each of the theta amplitude variables (theta-FN gain, theta-FN loss, theta-N2 go, theta-N2 no-go) were tested independently, resulting in four linear mixed models presented below. Groups are labeled as Group1 (combined treatment), Group2 (anxiety treatment), and Group3 (depression treatment), with the intercept as the control group. The dependent variable in each model is the primary outcome measure (i.e., average anxiety sensitivity scores).

Model 1: Theta-FN Gain

Results from the first linear mixed model show a non-significant Group1 x Theta-FN Gain interaction on anxiety sensitivity severity ($F=.378$, $df=283.41$, $p=.539$), indicating that Theta-FN amplitude to gains did not differentiate the combined treatment and control groups on treatment response. Within the same model, there was a non-significant Group2 x Theta-FN Gain interaction ($F=.852$, $df=282.12$, $p=.357$), as well as a non-significant Group3 x Theta-FN Gain interaction ($F=.196$, $df=284.15$, $p=.659$). These results show that Theta-FN Gain amplitude did not predict treatment response in the combined, depression, or anxiety treatment groups relative to the control group.

These relationships were also tested in a three-way interaction with time in the model. All three tests were non-significant, including Group1 x Theta-FN Gain x Time ($F=.093$, $df=418.03$, $p=.760$), Group2 x Theta-FN Gain x Time ($F=.671$, $df=411.37$, $p=.413$), as well as Group3 x Theta-FN Gain x Time ($F=1.72$, $df=422.48$, $p=.190$).

Model 2: Theta-FN Loss

Similarly for Theta-FN Loss amplitude, there was a non-significant Group1 x Theta-FN Loss interaction on anxiety sensitivity severity ($F=2.32$, $df=284.39$, $p=.128$), as well as non-significant interactions for Group2 x Theta-FN Loss ($F=.032$, $df=282.35$, $p=.858$), and Group3 x Theta-FN Loss ($F=.015$, $df=284.45$, $p=.901$). These results indicate that Theta-FN Loss amplitude does not significantly predict treatment response to the combined, anxiety, or depression groups, relative to control.

These effects were also not modulated by time as shown by non-significant three-way interactions for Group1 x Theta-FN Loss x Time ($F=.403$, $df=421.59$, $p=.526$), as well as Group2 x Theta-FN Loss x Time ($F=.011$, $df=410.56$, $p=.916$), and Group3 x Theta-FN Loss x Time ($F=2.51$, $df=421.90$, $p=.114$).

Model 3: Theta-N2 Go

Results indicate non-significant two-way interactions for Group1 x Theta-N2 Go ($F=1.48$, $df=270.74$, $p=.224$), as well as Group2 x Theta-N2 Go ($F=.114$, $df=270.17$, $p=.736$), and Group3 x Theta-N2 Go ($F=.593$, $df=270.23$, $p=.442$). Similar to the above models, these results indicate that Theta-N2 Go amplitude does not significantly predict treatment response to the Combined, Anxiety, or Depression groups relative to control.

The three-way interactions with time were also non-significant for each of these terms, including Group1 x Theta-N2 Go x Time ($F=.917$, $df=405.16$, $p=.339$), Group2 x Theta-N2 Go x Time ($F=.204$, $df=402.49$, $p=.652$), and Group3 x Theta-N2 Go x Time ($F=.080$, $df=402.88$, $p=.777$).

Model 4: Theta-N2 No-go

Similarly for Theta-N2 No-go amplitude, results show a non-significant two-way interaction for Group1 x Theta-N2 No-go ($F=.278$, $df=270.15$, $p=.598$), as well as Group2 x Theta-N2 No-go ($F=.133$, $df=269.89$, $p=.715$), and Group3 x Theta-N2 No-go ($F=.533$, $df=269.63$, $p=.466$). These results show that Theta-N2 No-go amplitude does not significantly predict treatment response in the combined, anxiety, or depression groups, relative to the control.

These effects were also not modulated by time, as shown by non-significant three-way interactions for Group1 x Theta-N2 No-go x Time ($F=.003$, $df=405.34$, $p=.955$), as well as Group2 x Theta-N2 No-go x Time ($F=.487$, $df=403.81$, $p=.486$), and Group3 x Theta-N2 No-go x Time ($F=.848$, $df=402.72$, $p=.358$).

Inter-channel Phase Synchrony (ICPS)

Each of the theta ICPS variables (theta-FN gain, theta-FN loss, theta-N2 go, theta-N2 no-go) were tested independently, resulting in four linear mixed models presented below. Similar to the above models, groups are labeled as Group1 (combined treatment), Group2 (anxiety treatment), and Group3 (depression treatment), with the intercept as the control group. The dependent variable in each model is the primary outcome measure (i.e., average anxiety sensitivity scores).

Model 1: ICPS Theta-FN Gain

Results from the first model indicate a significant two-way interaction for Group1 x ICPS Theta-FN Gain ($F=6.98$, $df=285.99$, $p=.009$), indicating that Theta-FN phase synchrony significantly predicts treatment response to the combined group

relative to the control. The three-way interaction for Group1 x ICPS Theta-FN Gain x Time was non-significant ($F=2.07$, $df=425.92$, $p=.150$), indicating that the above treatment prediction effect does not differ as a function of time.

The other treatment groups showed non-significant two-way interactions for Group2 x ICPS Theta-FN Gain ($F=1.56$, $df=286.33$, $p=.213$), as well as Group3 x ICPS Theta-FN Gain ($F=2.71$, $df=290.29$, $p=.101$), indicating that ICPS Theta-FN Gain does not predict treatment response to the anxiety or depression treatment groups relative to the control group. Finally, there were no significant three-way interactions for Group2 x ICPS Theta-FN Gain x Time ($F=.006$, $df=417.34$, $p=.941$) or Group3 x ICPS Theta-FN Gain x Time ($F=2.09$, $df=466.19$, $p=.148$).

Model 2: ICPS Theta-FN Loss

Similarly for ICPS Theta-FN Loss, there was a significant two-way interaction for Group1 x ICPS Theta-FN Loss on treatment response ($F=10.82$, $df=286.39$, $p=.001$), indicating that Theta-FN Loss phase synchrony predicts treatment response to the combined group relative to the control group. This effect was not modulated by time as shown by a non-significant three-way interaction between Group1 x ICPS Theta-FN Loss x Time ($F=.165$, $df=413.88$, $p=.685$).

ICPS Theta-FN Loss did not predict treatment response to the anxiety or depression groups relative to control, as shown by a non-significant Group2 x ICPS Theta-FN Loss ($F=1.89$, $df=286.26$, $p=.170$) and Group3 x ICPS Theta-FN Loss ($F=3.29$, $df=291.39$, $p=.071$) interactions. Three-way interactions for these terms were also non-significant (Group2 x ICPS Theta-FN Loss x Time: $F=.916$, $df=413.13$, $p=.339$; Group3 x ICPS Theta-FN Loss x Time: $F=1.637$, $df=453.17$, $p=.201$).

Model 3: ICPS Theta-N2 Go

Results show a significant Group1 x ICPS Theta-N2 Go interaction ($F=12.37$, $df=279.47$, $p=.001$), indicating that Theta-N2 Go phase synchrony significantly predicts treatment response to the combined group relative to the control. This effect was not modulated by time, as shown by a non-significant three-way interaction (Group1 x ICPS Theta-N2 Go x Time: $F=.422$, $df=411.83$, $p=.516$).

Similar to the previous models, ICPS Theta-N2 Go did not predict treatment response to the anxiety or depression groups relative to the control (Group2 x ICPS Theta-N2 Go: $F=.319$, $df=278.93$, $p=.573$; Group3 x ICPS Theta-N2 Go: $F=.110$, $df=283.62$, $p=.741$). The three-way interaction for these terms was also not significant (Group2 x ICPS Theta-N2 Go x Time: $F=.036$, $df=409.91$, $p=.851$; Group3 x ICPS Theta-N2 Go x Time: $F=2.80$, $df=432.07$, $p=.095$).

Model 4: ICPS Theta-N2 No-go

Unlike the previous models, ICPS Theta-N2 No-go did not predict treatment response to the combined group (Group1 x ICPS Theta-N2 No-go: $F=2.05$, $df=275.55$, $p=.153$). It was also non-significant in predicting treatment response for the anxiety and depression groups relative to the control (Group2 x ICPS Theta-N2 No-go: $F=.001$, $df=275.22$, $p=.971$; Group3 x ICPS Theta-N2 No-go: $F=.378$, $df=278.81$, $p=.539$). Finally, similar to the above models, the three-way interactions for these terms did not reach threshold for significance (Group1 x ICPS Theta-N2 No-go x Time: $F=.041$, $df=408.16$, $p=.840$; Group2 x ICPS Theta-N2 No-go x Time: $F=.868$, $df=407.15$, $p=.352$; Group3 x ICPS Theta-N2 No-go x Time: $F=4.69$, $df=425.67$, $p=.031$).

Summary of Linear Mixed Model results

Medial frontal theta amplitude did not predict treatment outcomes for any of the treatment groups relative to the control. However, medial to lateral prefrontal phase synchrony for Theta-FN (Gains and losses) and Theta-N2 (Go's) significantly predicted treatment outcomes for the combined treatment relative to the control group. Results suggest this effect is specific to the combined group and does not differ as a function of time. These three variables will be further analyzed for specificity, sensitivity, and incremental validity in step 2 reported below.

Predictors of treatment response: Step 2, Correlations

Spearman correlation coefficients were computed for the three ICPS variables (Theta-FN gain, Theta-FN loss, Theta-N2 Go) and treatment groups (Combined treatment v. control group) that demonstrated a significant relationship to predicting treatment outcomes. Based on the number of tests, multiple comparison corrected was applied such that significance is based on $p < .0055$ (.05/9). As shown in Table 2, lower pre-treatment ICPS Theta-FN to gains is significantly correlated with better treatment outcomes. This effect was significant at the mid-treatment assessment ($p = .001$), as well as 1 week post-treatment ($p = .003$), and in a similar direction, though not significant, at 6 months post-treatment ($p = .120$). A similar finding occurred for ICPS Theta-N2 to Go stimuli, such that lower pre-treatment phase synchrony is correlated with better treatment response at mid-treatment ($p = .001$), and 1 week post-treatment ($p = .004$), and is in a similar direction, though not significant, 6 months after treatment ($p = .235$). Scatterplots for these findings are depicted in Figure

9 with the corresponding spearman rho effects. Finally, although lower ICPS Theta-FN to loss was also associated with better treatment outcomes, the effect was only trend level at mid-treatment ($p=.051$), and did not reach significance 1 week post-treatment ($p=.134$), or 6 months post-treatment ($p=.265$).

Specificity of treatment prediction

In contrast to the significant prediction effects for the combined treatment group, ICPS did not predict treatment outcomes to the control group (Table 2), thus demonstrating specificity of the treatment prediction effect. With the exception of ICPS Theta-FN to loss at trend level ($p=.075$), all other relationships did not approach significance in the control group ($p>.10$).

Table 2. Spearman correlations for pre-treatment ICPS with treatment response in the combined treatment group (top) and control (bottom).

		Treatment response: Combined group		
		Mid-tx (N=55)	1 week post (N=49)	6 mos post (N=39)
ICPS Theta-FN	Gain	-.43***	-.41***	-.26
	Loss	-.27 [†]	-.22	-.18
ICPS Theta-N2	Go	-.44***	-.41***	-.19
		Treatment response: Control group		
		Mid-tx (N=52)	1 week post (N=47)	6 mos post (N=34)
ICPS Theta-FN	Gain	.22	.16	-.01
	Loss	.25 [†]	.11	.07
ICPS Theta-N2	Go	.01	.03	.03

Note: *** $p<.005$, [†] $p<.10$

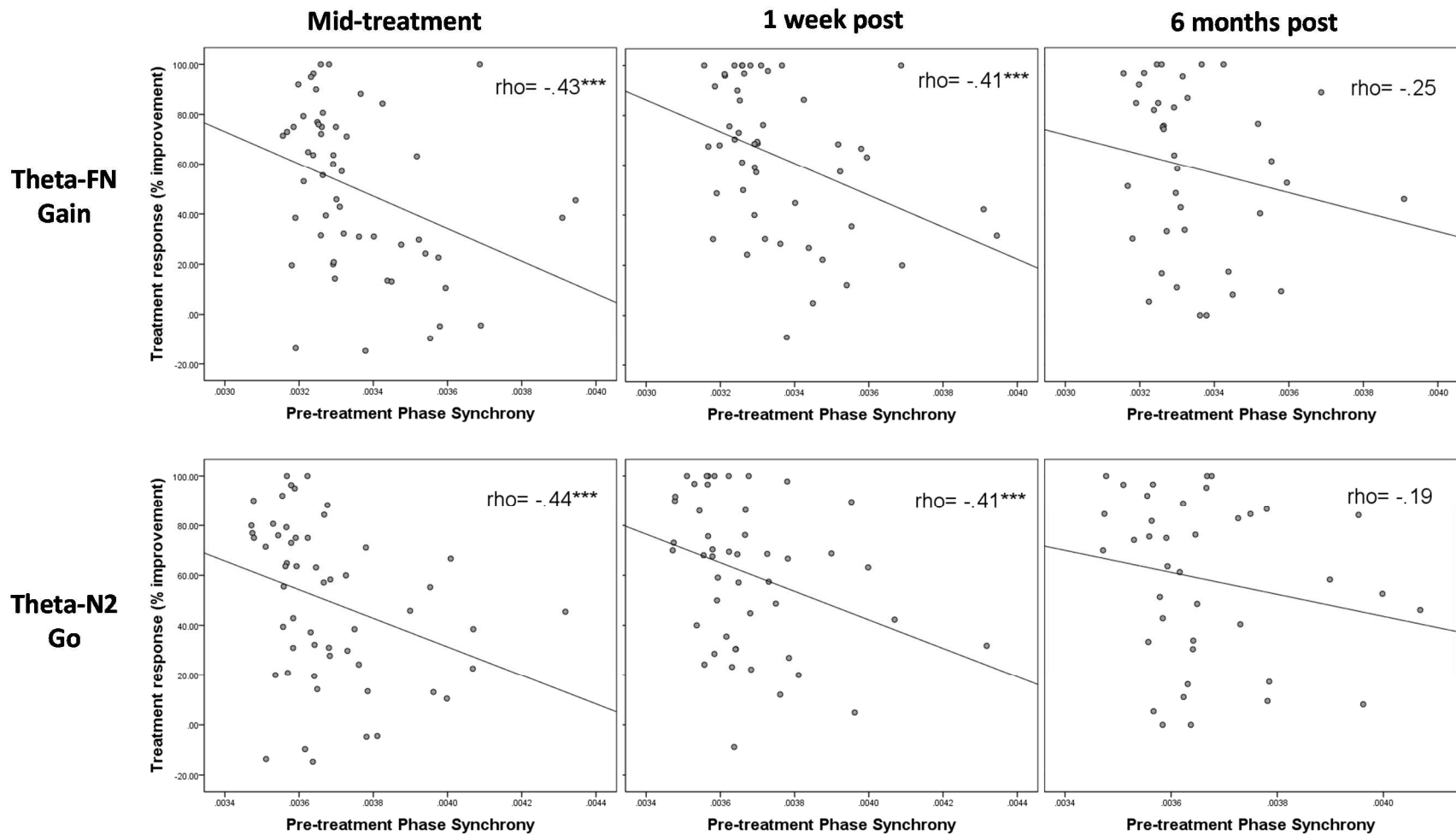


Figure 9. Scatterplots depicting relationships between pre-treatment phase synchrony for Theta-FN Gain and Theta-N2 Go with treatment response in the combined group at mid-treatment, 1 week post, and 6 months post-treatment.

Incremental validity: Examining potential covariates

Baseline symptom severity (i.e., mean ASI) as well as baseline depression and anxiety self-report measures were assessed as potential covariates. Baseline ASI significantly predicted treatment response at mid-treatment ($p=.010$), 1 week post-treatment ($p=.021$), as well as 6 months post-treatment ($p=.010$; Table 3). Baseline depression severity (BDI2) also demonstrated a significant relationship with treatment response at mid-treatment ($p=.001$), and 1 week post-treatment ($p=.041$), but was not significant at 6 months post treatment ($p=.281$; Table 3). Finally, baseline general worry (PSWQ) significantly predicted treatment response at all three assessment points (mid-treatment: $p=.004$, 1 week post: $p=.002$, 6 months post: $p=.019$; Table 3). As such, these variables were included as covariates in the analyses.

Age was not associated with treatment response at any of the assessment time points (mid-treatment: $p=.791$, 1 week post: $p=.604$, 6 months post: $p=.835$; Table 3). Gender was also not a significant predictor of treatment response at any of the assessments (mid-treatment: $p=.733$, 1 week post: $p=.105$, 6 months post: $p=.908$; Table 3).

Table 3. Correlation table for all dependent, independent, and covariate variables

	1	2	3	4	5	6	7	8	9	10	11
<i>Dependent Variables</i>											
1. ASI Mid-treatment response											
2. ASI 1 week post response	.68***										
3. ASI 6 months post response	.59***	.70***									
<i>Independent Variables</i>											
4. ICPS Theta-FN Gain	-.43**	-.41**	-.26								
5. ICPS Theta-FN Loss	-.27 [†]	-.22	-.18	.59***							
6. ICPS Theta-N2 Go	-.44**	-.41**	-.19	.69***	.63***						
<i>Potential Covariates</i>											
7. Baseline ASI severity	-.32*	-.31*	-.38*	.14	.32*	.45**					
8. Depression (BDI2)	-.42**	-.28*	-.17	.12	.15	.31*	.50**				
9. General worry (PSWQ)	-.36**	-.41**	-.35*	-.01	.20	.29*	.66***	.57***			
10. Age	-.04	-.08	-.03	.23 [†]	.01	.13	.06	.13	-.17		
11. Gender	-.05	-.23	-.02	-.12	-.03	-.05	.20	.33**	.40**	-.22 [†]	

Note: ***p<.001, **p<.01, *p<.05, [†]p<.10

Incremental validity: Partial correlations

Partial spearman correlations were computed after adding baseline ASI severity, depression, and general worry as covariates. As shown in Table 4, results indicate ICPS Theta-FN to gains remains significant as a predictor of treatment response at mid-treatment ($p=.001$), 1 week post-treatment ($p=.002$), as well as 6 months after treatment has completed ($p=.038$). ICPS Theta-N2 to go's also remains significant as a predictor of mid-treatment response ($p=.030$), but becomes non-significant at the 1 week post-treatment ($p=.247$) and 6 months post-treatment assessments ($p=.801$). Finally, ICPS Theta-FN to losses remains non-significant at all three assessment time points (mid-treatment: $p=.158$, 1 week post: $p=.375$, 6 months post: $p=.708$).

Table 4. Partial spearman correlations after including baseline severity, depression, and general worry as covariates

		Treatment Response (% improvement)		
		mid-tx (N=55)	1 week post (N=49)	6 mos post (N=39)
ICPS Theta-FN	Gain	-.45**	-.44**	-.35*
	Loss	-.20	-.13	-.07
ICPS Theta-N2	Go	-.30*	-.18	-.04

Note: ** $p<.01$, * $p<.05$

Sensitivity of treatment prediction: Accuracy

Given the findings above that low pre-treatment theta phase synchrony during gain and go trials predicts better treatment outcomes, post-hoc sensitivity estimates were calculated. Using the median split, subjects were classified as ‘high’ or ‘low’ on ICPS Theta-FN Gain and ICPS Theta-N2 Go. Treatment response was also dichotomized into ‘Responder’ ($\geq 50\%$ improvement) and ‘Non-responder’ ($< 50\%$ improvement) at 1 week post-treatment. As shown in Figure 10, 85% of individuals with low pre-treatment Theta-FN Gain phase synchrony were classified as responders, compared to 48% of individuals with high pre-treatment phase synchrony, a difference that was statistically significant ($p=.013$, Fisher’s Exact Test). A similar effect was found for pre-treatment Theta-N2 Go phase synchrony, where 85% of individuals with low phase synchrony were classified as responders, compared to 50% of individuals with high phase synchrony ($p=.016$, Fisher’s Exact Test).

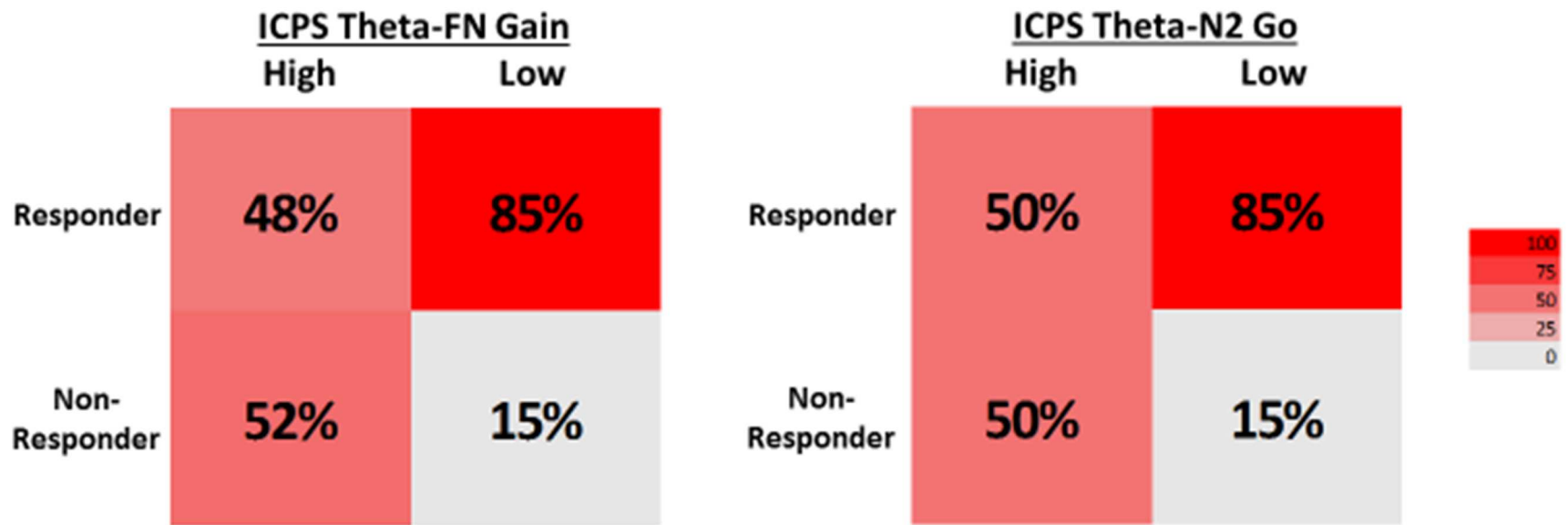


Figure 10. Percentage of individuals who are classified as a treatment responder versus non-responder at 1 week post-treatment, based on their high and low pre-treatment theta phase synchrony during gains (left) and go's (right). Low theta phase synchrony at baseline differentiates responders from non-responders.

Shared versus unique MFTN effects

Given that ICPS Theta-FN Gain and ICPS Theta-N2 Go were both significant predictors of anxiety sensitivity treatment response, regressions were conducted to assess the unique versus shared contributions of each measure at all three assessment time points. As shown in Table 5, when both measures are entered into a multiple regression model, they each become non-significant in predicting treatment response, suggesting they have shared variance in relation to treatment outcomes. This shared variance effect was demonstrated at mid-treatment (Theta-FN Gain: $p=.401$, Theta-N2 Go: $p=.317$), as well as 1 week post-treatment (Theta-FN Gain: $p=.530$, Theta-N2 Go: $p=.206$), and 6 months post-treatment (Theta-FN Gain: $p=.839$, Theta-N2 Go: $p=.292$).

Table 5. Multiple regressions with ICPS predictors of treatment response

	<i>B</i>	<i>t</i>	<i>p</i>	partial <i>r</i>	<i>R</i> ²
1. Mid-treatment response					.14
ICPS theta-FN Gain	-.18	-0.8	.401	-.12	
ICPS theta-N2 Go	-.22	-1.0	.317	-.15	
2. 1 week post-treatment					.16
ICPS theta-FN Gain	-.14	-0.6	.530	-.10	
ICPS theta-N2 Go	-.28	-1.3	.206	-.19	
3. 6 months post-treatment					.07
ICPS theta-FN Gain	-.04	-0.2	.839	-.04	
ICPS theta-N2 Go	-.23	-1.1	.292	-.18	

Chapter 5: Discussion

Previous research has demonstrated that the anterior cingulate cortex is a consistent and robust predictor of treatment response. While this effect has been shown across multiple interventions, clinical populations, and imaging modalities (Pizzagali, 2010), it has not been assessed using task-based EEG paradigms. As a scalp recorded measure of underlying electrical impulses from populations of neurons, EEG has greater temporal resolution and represents a more portable and cost effective method of measuring brain activity compared to other imaging modalities. Despite these advantages and the ability to detect anterior cingulate activity through medial frontal theta ERPs (Cavanagh et al., 2012; Gehring & Willoughby, 2002; Hauser et al., 2014), these components have not been evaluated as predictors of treatment response. Further, there is a lack of research on the functional relationship between medial and lateral prefrontal regions, despite claims that these functional networks are implicated in treatment response. The current study therefore represents the first study to assess task-based medial frontal theta amplitude and medial to lateral prefrontal theta phase synchrony as predictors of treatment response.

Amplitude

Regarding amplitude, results indicated that contrary to the hypothesis, MFTN amplitude did not predict treatment response for any of the treatment groups relative to the control group. The effects were non-significant for both Theta-FN and Theta-N2 under each task condition (gains and losses, go's and no-go's).

Regarding the lack of significant medial frontal theta amplitude effects, there are a number of possible explanations and interpretations, including the sample characteristics as well as the method of measurement. First, non-significant amplitude effects could be attributed to timing differences between imaging modalities. Although MFTN reflects activity over dorsal ACC, the timescale of activation is in milliseconds (approximately 200-450 ms) after stimulus or feedback onset, compared to 5-7 seconds, which is the typical Blood Oxygen Level Dependent (BOLD) signal delay during fMRI studies. Based on these differences in methodologies, it is possible that the effects of ACC on predicting treatment outcomes cannot be well detected at high temporal resolutions. Future research would benefit from the use of simultaneous EEG/fMRI to examine possible timing effects for ACC treatment prediction.

Second, the lack of significant effects could be attributed to a suppression effect based on the heterogeneity of the sample. Contrary to most treatment studies which recruit individuals from one diagnostic category, the current study included individuals across a variety of diagnoses including Major Depressive Disorder, Generalized Anxiety Disorder, Social Phobia, Specific Phobia, Obsessive Compulsive Disorder, Post-traumatic Stress Disorder, and Substance use Disorder, among others. Although greater ACC generally predicts better treatment outcomes across populations, there are some caveats that require further attention. First, most of the treatment prediction literature has been done in depressed samples using medication studies, with a much smaller proportion conducted for psychotherapy interventions. Within the category of predicting psychotherapy response, some

studies suggest *lower* ACC activity predicted better psychotherapy response in depressed populations (Dichter, Felder, & Smoski, 2010; McGrath et al., 2014; Siegle et al., 2006, 2012). Since the current study utilizes a behavioral intervention similar to psychotherapy, it is possible that in the subset of individuals with depression, lower amplitude may have predicted better treatment response.

Similarly for some anxiety disorders, the direction of effects may depend on the type of intervention (medication v. behavioral), as well as the sub-region of the ACC (dorsal v. ventral ACC). In the context of anxiety disorders, the majority of treatment prediction work has been done in Obsessive Compulsive Disorder (OCD). Since all of the studies in OCD have utilized a pharmacological intervention, as opposed to psychotherapy or behavioral treatments, it is unclear if the medication study results will translate to behavioral interventions. Second, within these medication studies, it has been suggested that different sub-regions of the ACC may predict treatment response in different directions (Hendler et al., 2003; Swedo et al., 1989), such that lower *dorsal* ACC, but greater *ventral* ACC, predicts better medication outcomes in OCD. Given that MFTN primarily reflect dorsal ACC, it is possible that for the subset of subjects with OCD in the current sample, lower MFTN could have predicted better treatment response.

Since the current study included individuals with depression and OCD, as well as other anxiety disorders, it is possible that low MFTN amplitude may predict treatment response for those with OCD or depression, while high MFTN amplitude may predict treatment response for those with other anxiety disorders (GAD, Social phobia, Panic disorder), resulting in a suppression effect. Unfortunately however,

given the low sample sizes within each diagnostic category and treatment condition, additional tests could not be conducted to confirm or refute these potential explanations.

Regarding diagnostic categories, it is also important to point out that with the publication of DSM-V in 2013, several modifications were made to the classification of disorders including separating anxiety disorders into the following categories: classical anxiety disorders, trauma and stressor related disorders, and obsessive compulsive related disorders. This classification change has effectively resulted in the removal of OCD and PTSD as ‘anxiety disorders’ and has now placed them in separate categories. This is relevant to the interpretation of non-significant amplitude effects because it suggests two things. First, there may be important qualitative distinctions between the categorization of PTSD, OCD, and anxiety, which may partially explain different ACC effects in treatment prediction. Second, with the removal of OCD under the umbrella of ‘anxiety disorders’, there are far fewer treatment prediction studies in this domain, which underscores the need for more research and suggests that directional hypotheses for this category may not be possible at this time. This theory is also partially supported by the present study, which found non-significant amplitude effects using a heterogeneous clinical sample. Taken together, the direction of ACC treatment prediction effects may be diagnostic specific. Future studies are needed to further test this potential explanation.

Inter-channel Phase Synchrony (ICPS)

Contrary to the non-significant MFTN amplitude results, phase synchrony demonstrated significant prediction effects. ICPS Theta-FN Gain and ICPS Theta-N2 Go both significantly predicted treatment response, such that lower baseline medial to lateral prefrontal phase synchrony was associated with greater symptom improvement. This effect was specific to the gain and go conditions, as well as to the combined treatment group, relative to the anxiety-only, depression-only, and control treatment groups. As predictors, both ICPS variables demonstrated specificity, sensitivity, and incremental validity.

Regarding specificity (i.e., prediction to one group versus the other/s), treatment prediction was demonstrated for the combined treatment group only. Because theta phase synchrony did not predict response in the control group, this indicates the prediction effect is specific to the intervention and not symptom alleviation over time. MFTN phase synchrony also did not predict to the anxiety or depression only treatment groups, although the effect was in the same direction. One explanation is that this could be due to differences in treatment efficacy across the groups. Since the combined treatment was the most effective, there may be more variance in symptom improvement to detect a prediction effect. Similarly, differences in the groups could be due to the amount of time spent in the intervention. Since the combined group spent approximately 50% more time undergoing the intervention components, this may be a factor contributing to the sensitivity of predicting outcomes. In addition, it could be related to the nature of the intervention and the combination of anxiety and depression treatment components, relative to undergoing each component separately or not at all. Since there are a number of treatment group

differences, causal explanations for the group-specific prediction effect are not feasible. Future research would benefit from modifying the design of the treatment groups such that the groups have comparable treatment efficacy, similar time spent in the intervention, and similar treatment components.

In addition to showing specificity of treatment prediction, MFTN phase synchrony demonstrated *sensitivity* in the form of reliability/consistency (e.g., similar effects across multiple time points) and accuracy (e.g., percent of individuals classified as responder versus non-responder). Consistency of treatment prediction was first demonstrated by a non-significant interaction with time in the linear mixed models. This suggests that the significant prediction effect from the two-way interaction was not differentially modulated by time. The consistency of treatment prediction across time was also corroborated by the correlations, which were significant or trend level at all three assessments. Consistency of treatment prediction is important because it not only suggests stability and reliability of the predictor, but it also demonstrates clinical utility by representing a marker of sustained symptom improvement. Sensitivity is also reflected by the accuracy of the predictor, or the extent to which it can differentiate responders versus non-responders. In this case, low MFTN phase synchrony demonstrated 85% accuracy in differentiating responders versus non-responders at the 1-week post treatment assessment. This level of accuracy is similar to other prediction estimates in the literature (85%; Furey et al., 2012), and suggests MFTN phase synchrony is a viable predictor of anxiety treatment outcomes. Finally, this effect maintained significance even after controlling for baseline severity and other self-report measures of depression and anxiety, thereby

demonstrating incremental validity and suggesting phase synchrony offers a unique approach above and beyond self-report measures.

Interpretation: Direction and condition-specific effects

Based on demonstrating the specificity, sensitivity, and incremental validity of medial frontal theta phase synchrony as a predictor of treatment outcomes, it is clear that this measure represents a promising predictor. However, further information is needed to understand what the effects represent and why they may predict better outcomes. As such, the first question to ask is ‘what does it mean to have *low* medial to lateral prefrontal phase synchrony?’ The second question for discussion is ‘what do the condition-specific effects (gain and go) represent?’ Regarding the former, evidence from basic science, individual difference research, and treatment prediction work points to a plausible interpretation: relative engagement of regulatory or cognitive control processes.

What does it mean to have low medial to lateral prefrontal phase synchrony?

Evidence from basic science research

Evidence for the interpretation of low medial to lateral prefrontal phase synchrony is largely consistent across a number of cognitive control theories, starting with some of the earliest work by Miller and Cohen (2001). According to their seminal publication, the prefrontal cortex is the primary means by which cognitive control is executed. Further, the allocation of control often depends on signals from the anterior cingulate cortex, among other regions. Using a very simple train track analogy, the authors claim that activation in the ACC represents the detection of competing resources or the identification of conflicting information, illustrated by

two trains headed for collision. The prefrontal cortex, on the other hand, represents a ‘switch operator’ by which adjustments are made to the train tracks such that a collision may be avoided. These adjustments represent the implementation of cognitive control and may be globally represented as a ‘biasing influence’. The specific control response depends on the sensory, attention, and/or behavioral resources needed to achieve the intended outcome. Although overly simplistic and missing the influence of several other subcortical structures, the purpose of the analogy is to demonstrate an important coupling between medial and lateral prefrontal regions, whose functional co-activation represents the allocation of cognitive control resources.

This work was extended in subsequent theories with a push toward more comprehensive models of cognitive control, taking into account outcome probability (Predicted Response Outcome model), cost-benefit analysis (Foraging Value Theory of task performance), and costs of effortful control (Expected Value of Control theory). Although these models differ in their level of complexity, they all claim a fundamental coupling between ACC and lateral prefrontal cortex in the detection and implementation of control.

More recent empirical findings corroborate these theories and further demonstrate a ‘functional loop’ between medial and lateral PFC, suggesting that their co-activation represents cognitive control through the integration of reward expectations, learned rules, and strategy selection (Duverne & Koechlin, 2017). In coordination with the pre-supplementary motor area (pre-SMA), the ACC has been shown to regulate the engagement of the lateral PFC in both rule-based cognitive

control paradigms (Botvinick et al., 2001; Holroyd & Coles, 2002), as well as during reward/motivational incentives (Kouneiher, Charron, & Koechlin, 2009). In both paradigms, medial to lateral PFC functional connectivity was enhanced during components of the task requiring increased control or regulation of responses.

The functional integration of medial and lateral PFC during cognitive control is also demonstrated using EEG phase synchrony measures. During trials which are conflicting, surprising, or represent a motivational incentive, studies show increased medial to lateral PFC theta phase synchrony (Hanslmayr et al., 2007; Luft, 2014; Smith et al., 2015). Similar results have been found during performance feedback tasks (Aviyente et al., 2017; Watts et al., 2018), as well as time estimation tasks (Van de Vijver et al., 2011), consistent with the notion that enhanced medial to lateral PFC theta phase synchrony indexes increased cognitive control or regulatory engagement. Applying these results to the current findings, it stands to reason that low phase synchrony would indicate less engagement of cognitive control resources. Indeed this relationship between low phase synchrony and reduced cognitive control has been shown in individual difference research as well as the Klumpp and colleagues (2016) treatment prediction study, as described in more detail below.

Evidence from individual differences & treatment prediction work

In the context of individual differences, Moran and colleagues found that anxiety was associated with cognitive control abnormalities, as reflected by low medial to lateral PFC theta phase synchrony following the commission of an error (Moran et al., 2014). Despite showing enhanced ERN amplitude, anxious individuals had low medial to lateral PFC phase synchrony and poorer post-error reaction times and accuracies. The authors claim that while the initial ACC/medial PFC processes

are enhanced in the context of anxiety, this ‘alarm signal’ is not being effectively transmitted to lateral PFC, and therefore does not translate into improved behavioral performance. Similar anxiety-related aberrations were found by Fitzgerald and colleagues (2013) who demonstrated that clinically anxious children had lower recruitment of cognitive control resources in lateral PFC during error processing. Another study using an emotional conflict task found that greater trait anxiety in adults was associated with lower functional connectivity between dorsal ACC and DLPFC, representing inefficient higher-order control (Comte et al., 2015). Taken together, these results suggest there are anxiety-related deficits in cognitive control, and that this may be partially reflected by lower medial to lateral PFC connectivity or phase synchrony.

Extending these findings to treatment prediction work, we refer back to the Klumpp et al., 2016 study which is the only other study to assess functional connectivity between medial and lateral prefrontal regions as a predictor of treatment response. Using fMRI, they examined predictors of CBT response in individuals with social anxiety disorder and, similar to the current study, they found low functional connectivity predicted better outcomes. Specifically, results show that low functional connectivity between dorsal ACC and DLPFC during high cognitive load on a target detection task predicted significantly better treatment response. The authors concluded that low functional connectivity between medial and lateral PFC regions reflected poor regulatory ability, and suggested that these individuals may benefit the most from a treatment targeting the engagement of cognitive control processes.

As the only study to directly assess functional connectivity as a predictor of anxiety treatment response, the Klumpp study lends support to the current findings and offers a potential explanation regarding why low functional connectivity is associated with better treatment outcomes. The authors claim that individuals with low pre-frontal functional connectivity benefitted more from the intervention because the cognitive behavioral treatment targeted the engagement of executive control processes. Specifically, CBT focuses on cognitive restructuring with an emphasis on altering maladaptive thoughts and behavior patterns by disputing negative beliefs and generating alternative responses. As such, it has been suggested that CBT draws upon executive functioning skills in a top-down manner (Mohlman & Gorman, 2005). Therefore, patients who have a deficit in this area may benefit more from the type of intervention that targets these cognitive processes. Although the current study does not employ CBT, it utilizes similar cognitive behavioral techniques such as challenging existing beliefs about anxiety through exposure exercises (e.g., CAST portion of the intervention), disputing maladaptive thoughts through education on the nature of stress and its effects on the body (e.g., psychoeducation portion), and practicing alternative responses/associations (e.g., CBM portion). Therefore, it is possible that individuals with low phase synchrony between medial and lateral PFC are benefiting more from this particular treatment because components of the intervention engage cognitive control and regulatory processes in an effort to reduce anxiety.

What do the condition-specific effects (gain and go) represent?

One additional area that requires further interpretation is why the ICPS treatment prediction effects were strongest for the gain and go conditions, as opposed

to the loss and no-go conditions. This is an important question because traditionally the FN and N2 medial frontal theta components show exaggerated amplitudes under ‘negative’ task conditions that may require an adjustment in behavior, such as punishment, loss, response inhibition, or conflict. However, given that previous studies have not evaluated these components in relation to predicting treatment outcomes, it is unclear if similar condition effects should be expected. Nevertheless, interpreting the condition specific results is important to generate additional insight into why certain individuals respond better to the treatment.

As alluded to above, a growing body of evidence suggests that increased theta power and synchronization between medial to lateral PFC occurs when the performance monitoring system detects stimuli important for learning or behavioral change (e.g., loss feedback or no-go response inhibition; Cavanagh et al., 2009; Cohen & Cavanagh, 2011; Marco-Pallares et al., 2008; Watts et al., 2018). Although the magnitude of synchronization may depend on some individual differences, it is a relatively universal phenomenon to show co-activation between ACC and DLPFC during the most salient task conditions that require engagement of cognitive control mechanisms. As such, it is possible that a saturation effect may have occurred during processing loss and no-go stimuli, such that phase synchrony was universally enhanced across all subjects. As a result, there may not have been sufficient variance in the loss and no-go conditions to detect a treatment prediction effect.

Additionally, treatment prediction effects may depend on 1) the context of the stimulus and 2) individual differences in stimuli processing. Regarding the former, we refer back to the Klumpp study which used functional connectivity as a predictor

and found that treatment outcomes were predicted by low medial to lateral PFC connectivity, but only under high cognitive load conditions (Klumpp et al., 2017). In the task, participants were asked to press a button to indicate when a specific letter (e.g., 'X' or 'N') appeared on the screen. In the low load condition, the string of letters was comprised entirely of target letters (e.g., 'XXXXXX'). In the high load condition, the string of letters included a single target letter and five non-target letters (e.g., 'MXHKZW'). In both conditions, the string of letters was superimposed on a task-irrelevant face distractor. Interestingly, the low load condition did not show any predictive functional connectivity effects. However, under the high load condition, low functional connectivity between ACC and DLPFC predicted better outcomes. Although the Go/No-go task in the current study is not the same as the one described here, an argument can be made that the two task conditions (i.e., Go and No-go) bear some resemblance to the high and low load conditions. In the Go/No-go task in the current study, participants are presented briefly with a letter on the screen and must decide whether to press a button if it is a 'Go' trial (i.e., not the same letter as the previous trial), or to withhold a response if it is a 'No-go' trial (e.g., the same letter repeated). In addition, during the 'Go' trials, participants must decide whether the letter presented corresponds to a right or left button press. Therefore, two decisions must be made during 'Go' trials: 1) to make a response or not, and 2) which button is the correct response. During 'No-go' trials however, participants do not engage in the second decision since the correct choice is to withhold a response. In this way, an argument can be made that the 'Go' trials may represent a relatively higher cognitive load condition because participants must maintain two pieces of information during

these trials. This type of interpretation would suggest the current results are in line with previous findings, and may further suggest that the complexity of the task and/or the level of cognitive effort needed to engage with a stimulus is predictive of treatment outcomes. Future studies could directly test this theory by utilizing an N-back working memory task with various levels of complexity. If the above theory is true, lower phase synchrony during greater cognitive task demands (e.g., three-back) should predict better treatment outcomes to a similar cognitive behavioral intervention.

Although the above explanation is plausible for understanding the Go relative to No-go effects, it does not explain the Gain specific effects during the Gambling feedback task. For this effect, an additional interpretation is needed that focuses on individual differences in processing negative versus positive feedback. One of the most common underlying traits across anxiety and depressive disorders is a tendency to experience a negativity bias, in which there is a strong proclivity to ruminate and focus attention on negatively-valenced stimuli and experiences (Hansen & Hansen, 1988; Ito et al., 1998). Negativity bias has also been associated with decreased activation of cortical regions such as DLPFC (Mayberg et al., 1999) and ACC (Drevets et al., 1997), but increased activation of limbic regions such as medial thalamus and amygdala (Siegle et al., 2002). Individuals with a negativity bias are further characterized by a vulnerability to psychological feedback, reflected by an increased responsiveness to aversive events, and a decreased sensitivity to anticipated (McFarland & Klein, 2009) or actual (Pizzagalli et al., 2008) rewards. Because DLPFC is involved in the appraisal of both positive and negative information (Golkar

et al., 2012), lower phase synchrony with this region during gain feedback may represent a disrupted regulatory ability for rewards. Therefore, by targeting and modifying negative cognitive biases toward a more positive or benign interpretation of information (i.e., CBM portion of the intervention), perhaps the current intervention is the most effective for individuals who have a negativity bias and deficit in reward-specific regulatory processes.

Shared variance among MFTN Gain and Go conditions

Finally, regarding the secondary aim of the study, results show that medial frontal theta phase synchrony during the Gain and Go conditions demonstrates shared variance in predicting treatment outcomes. Although these components are elicited in different tasks, their shared variance suggests a similar mechanism through which treatment outcomes are informed. That is, lower synchronization between medial to lateral prefrontal regions is common across both conditions and is similarly associated with better treatment outcomes. While there is some evidence for context specific effects (gain and go conditions relative to loss and no-go), the shared variance across these conditions may represent a task-independent function of medial to lateral PFC phase synchrony. This result is consistent with other studies in the literature that suggest MFTN represent a shared process in relation to motivationally significant outcomes (Cavanagh et al., 2012; Cavanagh & Shackman, 2015).

To better understand the nature of the shared variance across gain and go phase synchrony in treatment prediction, we may refer to relevant theories of cognitive control. Although there are a number of cognitive control theories (e.g., Predicted Response Outcome; Foraging Value Theory; Expected Value of Control),

they largely focus on an integrative and context independent function of ACC/PFC engagement. While necessary for understanding general mechanisms behind the *recruitment of control*, they do not differentiate *types of control* based on specific conditions (i.e., similarities between gain and go versus loss and no-go). For these purposes, we turn to the Dual Mechanisms of Control (DMC) theory (Braver, 2012; Braver, Gray, & Burgess, 2007), which could be viewed as consistent with and complimentary to the Expected Value of Control theory (EVC; Shenhav, Botvinick, & Cohen, 2013). The DMC theory postulates that cognitive control is supported by at least two mechanisms: proactive control and reactive control. Proactive control represents sustained and anticipatory *maintenance* of goal-relevant information, including support for task relevant goals and optimizing performance. This type of control is resource intensive and reflects reward processing (e.g., gain feedback) as well as active maintenance of task goals (e.g., press the button for a Go stimulus) and is particularly suitable to tasks that elicit high cognitive demand (Braver et al., 2012). Reactive control, on the other hand, reflects the *triggering* of control mechanisms, such as retrieval of task sets or goals when conflict or adverse outcomes are identified (e.g., no-go and loss stimuli). Both types of control call upon activation in DLPFC (Jimura et al., 2010), among other regions such as ventrolateral PFC and parietal cortex (Locke & Braver, 2008). In relation to other prominent theories of cognitive control, these two types of control are consistent with the ‘signal’ and ‘state’ variables described in the Expected Value of Control theory (EVC; Shenhav, Botvinick, & Cohen, 2013). In the EVC theory, the ‘signal’ is a control process that maintains mechanisms responsible for regulation of control, while the ‘state’ refers to a change

in the current situation (e.g., motivation, task difficulty, declining performance, etc.) that indicates a new control signal is needed (Shenhav, Botvinick, & Cohen, 2013).

Directly relevant to the current findings, previous research shows the two types of control (proactive v. reactive) are differentially utilized in individuals with anxiety. Using a working memory N-back task, Fales and colleagues (2008) found that anxiety was associated with a neural signature of increased reactive control and reduced proactive control (i.e., high transient activity and low sustained activity in cognitive control networks), particularly on high interference trials. In other words, anxiety was associated with a reduction in the capacity to actively maintain task goals, presumably because more cognitive resources are taken up with internal attentional focus toward unrelated thoughts (i.e., worry and rumination). Taken together with the results from the present study, it is possible that low phase synchrony in the gain and go conditions reflects less engagement of proactive control mechanisms. Since the current intervention works to reduce anxiety, a reduction in anxious symptoms may translate to increased availability of cognitive resources needed to implement proactive control. Therefore individuals with lower pre-treatment engagement of *proactive* control may have more room to benefit from the current intervention.

Limitations and future directions

There are several limitations that should be acknowledged when interpreting the results from the current study. First, the ERN could not be assessed due to an insufficient number of errors committed in the tasks. As an event-related potential

that has been strongly associated with anxiety and specifically tied to endogenous/internal sensitivities to performance monitoring, the ERN may have been particularly related to symptom improvement in the anxiety sensitivity treatment outcome measure. As such, evaluating the ERN as a predictor of treatment response represents an untapped area of research that future studies will need to examine. Additionally, testing modulation in MFTN before and after the intervention was not possible due to a limited sample size. Therefore, it is unknown if changes in amplitude or phase synchrony occur as a result of the intervention. This is an important area to build upon for future research because if the significant predictors of treatment response demonstrate change after the intervention, this would provide additional evidence that the treatment works for certain individuals as a function of targeting specific neural networks and cognitive processes. Moreover, it is unclear if the non-significant amplitude results represent a lack of treatment prediction potential, or if they are the result of a suppression effect from a heterogeneous sample. Finally, the intervention includes multiple treatment components and a lack of behavioral data to prove the efficacy of each individual component in relation to the others. There was also a lack of a standardized treatment comparison group, such as Cognitive Behavioral Therapy or a proven pharmacological intervention. As such it is unknown if the current predictors are specific to this particular type of treatment, or if they would predict outcomes to other classes of interventions as well. Future research should expand upon the current study by testing medial frontal theta ERPs and phase synchrony measures across multiple evidence-based interventions.

Despite the above limitations, results of the current study represent a promising avenue for future treatment prediction research. As the first study to examine task-based medial frontal theta components as predictors of treatment response, the current findings reflect a novel contribution at the forefront of an emerging field. The results also provide additional support for a convergent medial frontal theta process, and suggest that low engagement of regulatory and proactive control mechanisms is predictive of better response to cognitive behavioral interventions. As such, this work may ultimately lead to the improvement in treatment efficacy by serving as a target for future interventions and a method of improving individualized treatment selection.

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