Treatment Response in Depression:

Predictors and Moderators of Outcome

by

Ryan Cardinale

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Psychology)
in University of Michigan
2018

Doctoral Committee
Professor Patricia Deldin (Chair)
Research Fellow Jinsoo Chun
Professor Nestor Lopez-Duran
Professor Melvin McInnis

Ryan C. Cardinale

rcardina@umich.edu

ORCID iD: 0000-0002-3932-5959

Dedication

To my brother Taylor,

who's love, courage, and wisdom inspires me

Acknowledgments

While this dissertation has my name listed as the primary author, there so many individuals that allowed me to be able to write this, and, without them, this dissertation would not have come to fruition.

First, and foremost, is my advisor Dr. Patricia Deldin, Ph.D. Patty has tirelessly challenged me to go as far as I can, supported me along the way, and cheered me on at the finish line. Patty taught me to think like a true clinical scientist by helping me to pursue interdisciplinary research, helping me to identify angles I had not considered, and teaching me how to think outside of the box through projects such as Mood Lifters and PRIZM. Patty was always there late at night or on the weekends to help me "get unstuck" or to help me initiate new collaborations. I am proud to be joining the ranks of graduates from the Deldin Lab.

Next, I would like to thank the members of the EMBARC team, without whom these studies would not have been possible. More specifically, I would like to thank Dr. Melvin McInnis, M.D. Melvin's support initiating of the ancillary study that led to study number 2, encouragement and advice while applying for the STAR Award, and mentorship through the doctoral committee has challenged me to grow into a reflective academic. Further, I would be remiss if I did not include Chris Brucksch, Chris Brucksch went out of her way to make sure the collection of the data presented here was possible, often taking extra time out of her day to speak to participants and follow-up with me. I feel honored to be able to share the findings of this dissertation with her as she put in so much effort to make them possible. I would also like to

thank Dr. Diego Pizzagalli, Ph.D. and Dr. Gerald Bruder, Ph.D. for their support and advice while working on the Placebo study.

I would like to thank the members of the ERP team. First, I would like to thank Dr. Jinsoo Chun, Ph.D. I have been fortunate enough to know Jinsoo since early on in grad school, when I began working on the Bipolar ERP study. During my early years, when we would discuss the Bipolar data, Jinsoo made sure to check in on how I was doing during grad school and offer advice. As I finished up my Master's thesis and went through the process of attempting to have it published, Jinsoo provided me with useful feedback that helped shape it, encouraged me to keep re-submitting it, and was quick to congratulate me when it was published. As I moved on into later years, she helped me to implement the ERP task that was the basis of the third study, and she offered time and support throughout the dissertation phase. I would also like to thank Dr. Lisa O'Donnell Ph.D. and Dr. Masoud Kamali, M.D., who helped introduce me to the world of ERP research through the Bipolar ERP Study. I would like to think Nathan Shen, Stephanie Beaton, and Katy Michon for the hours of effort they put into collecting the data for the Defusion study.

I would like to thank my mentors and colleagues here at the University of Michigan who helped shape me into a Clinical Scientist. I would like to thank Dr. Nestor Lopez-Duran, Ph.D. for his advice and support on this dissertation as a member of my dissertation committee. Starting early on when he led one of the first courses I took here at Michigan through the time he spent on my dissertation committee, Nestor taught me how to think like a critical clinical scientist when. Throughout my time here, Nestor's door was always open to talk about a recent finding, or to chat about new ideas for a tiny house. I would also like to thank the UM Clinical Science Faculty, and the UM Clinical Science graduate students and alumni for their mentorship,

collegiality, advice, and support during my time here at Michigan. I would like to thank all my mentors at the UM Counseling and Psychological Services, UM Sleep Disorders Center, and the UM Psychological Clinic for teaching me how to think like a clinician, and for helping me navigate balancing my clinical work with my academic work.

I would like to thank my close friends for supporting me, encouraging me, and generally helping me feel grounded throughout graduate school, both during the times that were difficult and to celebrate with me during the good times. In particular, I want to acknowledge Cari Carson, Zarina Kraal, Justin Hutchens, Dr. Rachel Burrage, Ph.D., Kyle Moored, Cecilia Votta, Ariana Stickel, Mary Ann Trainor, and Christopher Hallett.

Table of Contents

List of Figures

List of Tables

List of Acronyms

MDD: Major Depressive Disorder

EMBARC: Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care

rACC: rostral anterior cingulate cortex

EEG: electroencephalography

Abstract

Major Depressive Disorder (MDD) is a highly prevalent psychological disorder that affects an estimated 20.6% of adults in the United States. Despite significant research efforts, treatment response rates remain unacceptably low. The Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study aimed to address this problem through the search for "biosignatures" that include clinical, contextual, and biological measures to identify a more personalized approach to identifying appropriate treatment recommendations. Through three distinct investigations, this dissertation aims to utilize prior research to study “biosignatures" that may be relevant for predicting antidepressant treatment response. Results from this dissertation may inform future personalized approaches to depression care that may reduce the time to receiving adequate treatment.

Chapter 1: Introduction to the Three-Paper Project

Overview

Major Depressive Disorder (MDD) is a highly prevalent psychological disorder that affects an estimated 20.6% of adults in the United States, with up to 50% being considered severe (Hasin, 2018). Globally, it is estimated that MDD contributes to a worldwide disease burden of up to 11% (Greden, 2001). For individuals with MDD and their family members, symptoms of depression can contribute to significant impairment in daily functioning.

MDD is characterized by 1) a history of a period of two weeks or longer where an individual experiences depressed mood or a loss of interest or pleasure in things they used to enjoy, and 2) at least four other symptoms reflective of impaired functioning including: difficulties sleeping, changes in appetite, decreased energy or concentration, feeling worthless or inappropriate guilt, or recurrent thoughts of death or suicide (American Psychiatric Association, 2013).

The prevalence rate of MDD has been increasing in recent years. It is expected that depression will be the second leading cause of death, after heart disease, by 2020 (Lopez, 1998), and it is the leading cause of disability for working age adults in America (Kessler, Chiu, Demler, Merikangas, & Walters, 2005) with an economic burden estimated at $83.1 billion (Greenberg et al., 2003). The most severe burden of depression is the high suicide rate. Deaths attributable to suicide among individuals diagnosed with MDD is as high as 15% (Guze & Robins, 1970).

Treatment response in depression

For individuals who do receive treatment, it is anything but a "quick fix", and partial response and treatment resistance is common among interventions for depression (Fava & Davidson, 1996). Response to treatment is slow and hard to predict, taking an average of 4-6 weeks until any changes are noticed (Nierenberg, 2000), and a significant proportion of people will develop treatment-resistant depression despite receiving adequate courses of therapy (Fava & Davidson, 1996). For individuals with depression, this can become an arduous process of trial and error, with each trial taking up to two months before determining whether it is effective or not.

Unfortunately, in addition to the barriers to seeking help and identifying the appropriate medication, the response and remission rates for first line antidepressants are quite low. Randomized control trials typically define MDD treatment response as a 50% or greater reduction in depression symptoms relative to baseline, while the remission of depression symptoms has typically been defined using the Hamilton Depression Rating Scale (Hamilton, 1960), with most studies using a cutoff of 7-10 or less (Nierenberg, 2001). As many as 45% of individuals with depression fail to respond to antidepressant treatment of adequate dose and duration (Fava & Davidson, 1996), and full remission of depressive symptoms is much lower. Some estimate that as few as 11 percent of individuals with depression reach remission, even after 8–12 months (Cipriani et al., 2009).

The age of personalized medicine: a brief history

Following the Decade of the Brain (Jones & Mendell, 1999), the National Institutes of Health increased funding for personalized medicine research that aims to match individuals with

interventions using a number of clinically relevant variables (Hamburg & Collins, 2010; Insel & Cuthbert, 2015).

One of the first major studies of treatment response in depression was the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Trivedi, 2006). STAR*D was able to provide data that dispelled prior clinical intuition including the belief that switching from one SSRI to another SSRI within the same class or switching from an SSRI to a dual-action agent (e.g. Venlafaxine) would be unlikely to be successful. Rather, when switching medications within the SSRI class or switching to a dual-action agent was demonstrated to be an effective treatment strategy (Fava, 2010). Further, it provided evidence that individuals with MDD and comorbid anxiety were more likely to suffer increased functional impairment and a longer duration of illness (Fava, 2000; Fava, 2004). While the STAR*D was undoubtedly useful for demonstrating the feasibility of conducting a large-scale investigation into antidepressant treatment response, it had several limitations. It did not include a placebo arm, which prohibited the analysis of relative effectiveness, only allowing for information on medication non-response and toxicity (Rush, 2007). Further, while it provided demographic information on who is likely to respond, remit, or derive no benefits from antidepressant treatment, it did not provide information that could allow a patient or a provider to predict what treatment option is likely to be most effective.

Further, while there were numerous scientific advancements resulting from the Decade of the brain, investigations in the field turned towards the search for "biomarkers" and less research was published on the contextual and psychological variables that are likely to be relevant to depression treatment. As argued by Miller (2010), the allure of identifying biological variables that are assumed to cause psychological processes, has led biological investigations to receive

preferential attention relative to psychological investigations. As a result, measures of psychological function that had previously demonstrated preliminary promise have received little attention recently including studies of personality (Joyce, Mulder, & Cloniger; 1994), cognitive (Reynaert et al., 1995), and social (Peslow et al., 1992) processes. Nonetheless, biomarkers *are* likely to demonstrate utility, in conjunction with other contextual and psychological units of analysis, for predicting antidepressant treatment response. More recent investigations have demonstrated the possible utility of biomarkers for determining antidepressant treatment response including electroencephalographic (EEG) rostral anterior cingulate (rACC) theta activity (Pizzagalli, 2011), the event related potential (ERP) P300 (Jaworska, 2013), and the loudness dependence of the auditory evoked potential (LDAEP; Hegerl, 1993).

Thus, out of an awareness of the limitations of the STAR*D study and the need to incorporate contextual and psychological units of analysis, the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study was born, and it is the source of data for two of the studies presented in this dissertation. The EMBARC study is a multisite study that recruited more than 300 outpatients with recurrent, nonpsychotic MDD from 4 sites: Columbia University, New York; Massachusetts General Hospital, Boston; University of Michigan, Ann Arbor; and the University of Texas Southwestern Medical Center, Dallas. It is an 8-week, placebo-controlled, randomized controlled trial, of sertraline, with a second randomization arm of either bupropion (for sertraline non-responders) or sertraline (for placebo non-responders) for individuals who do not respond during the first 8-weeks. An aim of EMBARC was to study “biosignatures” of treatment response rather than “biomarkers”. While “biomarkers” were typically biological variables from a single unit of analysis, it was hoped that the study of “biosignatures” would provide for a more personalized

approach to identifying appropriate treatment recommendations. “Biosignatures” were defined by EMBARC (Trivedi, 2016) to encompass a number of variables from several of units of analysis, including performance on behavioral tasks, clinical history, current clinical status, and personality pathology, in addition to more recent developments in the study of “biomarkers” including genetics, functional magnetic resonance imaging (fMRI), and electroencephalography (EEG).

Therefore, through three distinct investigations, this dissertation aims to utilize prior research to study “biosignatures", encompassing “biomarkers”, psychological, and contextual variables that may be relevant for predicting antidepressant treatment response.

Study 1

Study 1, included in Chapter 2, summarizes results from an ancillary study that recruited participants who had recently completed their participation in the EMBARC study. This study aimed to identify psychological variables that might moderate treatment response to either a selective serotonin reuptake inhibitor (SSRI) or a norepinephrine dopamine reuptake inhibitor (NDRI). Through the collection of data using self-report instruments, this study assessed measures of cognition (Reynaert et al., 1995), personality (Joyce, Mulder, & Cloniger; 1994), and social (Peslow et al., 1992) processes that were previously reported to be relevant to antidepressant treatment response. This study aimed to identify low cost instruments that have the possibility of easy and swift translation into routine care (Clarke & Kuhl, 2014) by reviewing prior evidence to identify self-report measures that may be useful for predicting antidepressant treatment response.

Study 2

Study 2 (Chapter 3) focuses on identifying variables associated with the placebo response, with a focus on the positive valence systems and arousal/regulation systems. Utilizing functional magnetic resonance imaging data, (Schweinhardt, Seminowicz, Jaeger, Duncan, & Bushnell, 2009) defined several neuroanatomical regions that are believed to be necessary for the placebo response, known as the mesolimbic reward system. The mesolimbic reward system is a sub-system of the positive valence systems that facilitates reward processing. As the expectation of reward is believed to be an essential ingredient in the placebo response (Murray & Stoessl, 2013), this dissertation discusses results the relevance of physiological, self-report, and behavioral data to the placebo response from a paradigm reported to index reward systems.

Study 3

Study 3 (chapter 4) assesses the effectiveness of an intervention that is believed to target the transdiagnostic phenotype of negative self-referential processing. Negative self-referential processing encompasses both rumination and worry (Mennin & Fresco, 2013). Negative self-referential processing has been described as dysfunctional in depression and, in part, responsible for maintaining negative moods (Beck, 1979). Study 3 aimed to target negative self-referential processes using the psychotherapy technique of cognitive defusion. Cognitive defusion is an empirically supported intervention (Mandavia et al., 2015; Masuda et al., 2010), adapted from Acceptance and Commitment Therapy (ACT), that trains participants to create psychological distance from their thoughts (Kross, 2001; Masuda, Hayes, Sackett, & Twohig, 2004) in order to facilitate adaptive self-reflection, interrupt negative self-referential cognitions, and reduce subjective distress associated with thoughts (Deacon, Fawzy, Lickel, & Wolitzky-Taylor, 2011; Mori & Tanno, 2015; Yovel, Mor, & Shakarov, 2014). In order to assess the effectiveness of this

cognitive intervention on its intended target, physiological and behavioral methods were utilized to index and assess for changes in the cognitive and socio-affective processes that have been reported to be dysfunctional in depression.

Taken together, results from this dissertation may inform future personalized approaches toward depression care that aims to identify relevant indices that may reduce the time to receiving adequate treatment in depression and, possibly, identify easily translatable assessment measures that can swiftly be implemented in routine clinical care.

Specific Aims

Study 1

To investigate the role of positive valence systems, corresponding to reward circuitry, for facilitating the placebo response in individuals with MDD.

Study 2

To assess whether non-biological measures from the self-report unit of analysis believed to assess RDoC systems relevant to psychopathology are useful for differentiating antidepressant treatment responders from non-responders who participated in a clinical trial of antidepressant medication.

Study 3

To investigate whether a single-session intervention believed to target the cognitive systems can reduce emotional distress associated with a difficult thought, and to explore whether this cognitive system intervention is associated with changes in psychophysiological responses that index the cognitive systems of attention and response inhibition.

References

Ahrnsbrak, R., Park-lee, E., & Tice, P. (2016). *Key Substance Use and Mental Health Indicators in the United States : Results from the 2016 National Survey on Drug Use and Health*. Rockville, MD.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. *Arlington*. https://doi.org/10.1176/appi.books.9780890425596.744053

Clarke, D. E., & Kuhl, E. A. (2014). DSM-5 cross-cutting symptom measures: a step towards the future of psychiatric care? *World Psychiatry: Official Journal of the World Psychiatric Association* (*WPA)*, *13*(3), 314–316. https://doi.org/10.1002/wps.20154

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine*, *11*(1). https://doi.org/10.1186/1741-7015-11-126

Deacon, B. J., Fawzy, T. I., Lickel, J. J., & Wolitzky-Taylor, K. B. (2011). Cognitive Defusion Versus Cognitive Restructuring in the Treatment of Negative Self-Referential Thoughts: An Investigation of Process and Outcome. *Journal of Cognitive Psychotherapy*, *25*(3), 218–232. https://doi.org/10.1891/0889-8391.25.3.218

Fava, M., & Davidson, K. G. (1996). Definition and epidemiology of treatment-resistant depression. *The Psychiatric Clinics of North America*, *19*(2), 179–200. https://doi.org/10.1016/S0193-953X(05)70283-5

Greenberg, P. E., Kessler, R. C., Birnbaum, H. G., Leong, S. A., Lowe, S. W., Berglund, P. A., & Corey-Lisle, P. K. (2003). The economic burden of depression in the United States: how did it change between 1990 and 2000? *The Journal of Clinical Psychiatry*, *64*(12), 1465–1475. https://doi.org/10.4088/JCP.v64n1211

Guze, S. B., & Robins, E. (1970). Suicide and primary affective disorders. *The British Journal of Psychiatry : The Journal of Mental Science*, *117*(539), 437–438. https://doi.org/10.1192/bjp.117.539.437

Insel, T. R. (2014). The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *The American Journal of Psychiatry*, *171*(4), 395–397. https://doi.org/10.1176/appi.ajp.2014.14020138

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617–627. https://doi.org/10.1001/archpsyc.62.6.617

Kross, E. (2001). Mindfulness Training & Cognitive Behavioral Therapy in the context of Anxiety Disorders. *Perspectives in Psychology*, *Spring*, 3–13. Retrieved from https://paloaltou.idm.oclc.org/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2012-14157-009

Luty, S. E., Carter, J. D., McKenzie, J. M., Rae, A. M., Frampton, C. M. A., Mulder, R. T., & Joyce, P. R. (2007). Randomised controlled trial of interpersonal psychotherapy and cognitive-behavioural therapy for depression. *The British Journal of Psychiatry : The Journal of Mental Science*, *190*, 496–502. https://doi.org/10.1192/bjp.bp.106.024729

Mandavia, A., Masuda, A., Moore, M., Mendoza, H., Donati, M. R., & Cohen, L. L. (2015). The application of a cognitive defusion technique to negative body image thoughts: A preliminary analogue investigation. *Journal of Contextual Behavioral Science*, *4*(2), 86–95. https://doi.org/10.1016/j.jcbs.2015.02.003

Masuda, A., Hayes, S. C., Sackett, C. F., & Twohig, M. P. (2004). Cognitive defusion and self-

relevant negative thoughts: examining the impact of a ninety year old technique. *Behaviour Research and Therapy*, *42*(4), 477–485. https://doi.org/10.1016/j.brat.2003.10.008

Masuda, A., Twohig, M. P., Stormo, A. R., Feinstein, A. B., Chou, Y.-Y., & Wendell, J. W. (2010). The effects of cognitive defusion and thought distraction on emotional discomfort and believability of negative self-referential thoughts. *Journal of Behavior Therapy and Experimental Psychiatry*, *41*(1), 11–17. https://doi.org/10.1016/j.jbtep.2009.08.006

Mennin, D. S., & Fresco, D. M. (2013). What, Me Worry and Ruminate About DSM-5 and RDoC? The Importance of Targeting Negative Self-Referential Processing. *Clinical Psychology : A Publication of the Division of Clinical Psychology of the American Psychological Association*, *20*(3), 258–267. https://doi.org/10.1111/cpsp.12038

Mori, M., & Tanno, Y. (2015). Mediating Role of Decentering in the Associations between Self-Reflection, Self-Rumination, and Depressive Symptoms. *Psychology*, *06*(05), 613–621. https://doi.org/10.4236/psych.2015.65059

Murray, D., & Stoessl, A. J. (2013). Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. *Pharmacology & Therapeutics*, *140*(3), 306–318. https://doi.org/10.1016/j.pharmthera.2013.07.009

Sanislow, C. A., Pine, D. S., Quinn, K. J., Kozak, M. J., Garvey, M. A., Heinssen, R. K., … Cuthbert, B. N. (2010). Developing constructs for psychopathology research: research domain criteria. *Journal of Abnormal Psychology*, *119*(4), 631–639. https://doi.org/10.1037/a0020909

Sanislow, C. A., Quinn, K. J., & Sypher, I. (2015). NIMH Research Domain Criteria (RDoC). In *The Encyclopedia of Clinical Psychology* (pp. 1–6). Hoboken, NJ, USA: John Wiley & Sons, Inc. https://doi.org/10.1002/9781118625392.wbecp541

Schweinhardt, P., Seminowicz, D. A., Jaeger, E., Duncan, G. H., & Bushnell, M. C. (2009). The anatomy of the mesolimbic reward system: a link between personality and the placebo analgesic response. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *29*(15), 4882–4887. https://doi.org/10.1523/JNEUROSCI.5634-08.2009

Thase, M. E., Entsuah, A. R., & Rudolph, R. L. (2001). Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *The British Journal of Psychiatry : The Journal of Mental Science*, *178*, 234–241. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11230034

Trivedi, M. H., McGrath, P. J., Fava, M., Parsey, R. V., Kurian, B. T., Phillips, M. L., … Weissman, M. M. (2016). Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design. *Journal of Psychiatric Research*, *78*(1), 11–23. https://doi.org/10.1016/j.jpsychires.2016.03.001

Yovel, I., Mor, N., & Shakarov, H. (2014). Examination of the core cognitive components of cognitive behavioral therapy and acceptance and commitment therapy: an analogue investigation. *Behavior Therapy*, *45*(4), 482–494. https://doi.org/10.1016/j.beth.2014.02.007

Chapter 2: Sociotropy and Autonomy - A cognitive-personality style predicative of antidepressant treatment outcomes

Introduction

The restoration of socioemotional functioning appears to be an important therapeutic mechanism of SSRI treatment (Challis, 2015; Levitan, Hasey and Sloman, 2000). Social rank theory has been used to describe the etiology of socioemotional dysfunction in depression (Santor, 2003) and the role of serotonergic interventions in socioemotional function restoration (Levitan, Hasey and Sloman, 2000).

Social Rank Theory

Social rank theory is an evolutionary model of typical sociobiological development of animals and humans that is used to understand the mechanisms by which dysfunctional processes contribute to the etiology of psychopathology (Price & Sloman, 1987). This theory states that animals living in a group have the advantage of gaining resources and increasing reproductive success in the evolutionary process. This theory assumes that humans and animals are motivated to achieve dominant status because it leads to more chances of gaining access to food and to potential mates. Living together exposes them to constant conflict in the competition for dominance, which is key to successful reproduction (Gilbert, 2006). Animals with dominant statuses are more successful in gaining access to food and mates, compared with those in subordinate positions. In this context, displays of submission signal to dominant individuals that

subordinate group members are not a threat to their rank within the social hierarchy. This helps to achieve social cohesion.

Social Rank Theory as a Model of Depression

According to the sociobiological perspective of social rank theory, anxiety and depression are natural experiences that are common to all mammalian species, and it is the pathological exaggeration of anxiety and depression that contributes to psychological disorders. The involuntary subordinate strategy is a model that was developed by Price (1972) who noted depressed-like states occur in animals and humans who have been defeated and lose rank, and in subordinates who are regularly harassed or threatened by more dominant animals and cannot escape. The function of these depressed states in a social rank context are two-fold: (1) to down-regulate an animal/ person's goal pursuits and behavior and avoid directly challenging dominants (or seeking resources, e.g. sexual contacts) that could stir their attack, and keep a low and vigilant profile; and (2) to impact on the mind of the dominant such that the dominant either accepts a submission and/or sees them as inhibited/timid/ compliant and 'out of action' and, therefore, as no threat to him/her (Price, 1972). According to social rank theory, the involuntary subordinate strategy is an evolutionarily adaptive strategy, and it is the pathological exaggeration of this strategy that is associated with psychopathology (Gilbert, 1992, 2000). This led to the theory by Price and Sloman (1987) that animals who experience involuntary submission after social defeat would show biochemical and behaviors resembling depressive symptoms in humans including lower serotonergic transmission, social motivation, and affiliative behavior and higher levels of stress and sleeping problems. A more specific theory of involuntary subordination called the Involuntary Defeat Strategy (IDS) was proposed by Sloman (2000) to be specifically relevant to depression. The Involuntary Defeat Strategy (IDS) is a genetically

preprogrammed strategy triggered by the individual's recognition that defeat in social competition is inevitable. In sum, social rank theory locates affiliative and ranking structures at the core of many psychological disorders (Price & Sloman, 1987).

The relationship of serotonin to social rank regulation

Social rank theory has been used to model the depression-like effects of social defeat in monkeys (Shively et al. 1997) and rodents (Rygula et al. 2005), and they have even been detected in "primitive" animals (Yeh, 1996). Consequently, the social defeat model is now regularly used to model depression in animals (Rygula et al. 2005). There is growing evidence that social defeats and social harassment set in motion a set of long-lasting physiological and behavioral responses that appear depression-like (Gilbert, 2000; Levitan et al. 2000) via a variety of neurotransmitters [e.g. serotonin (Raleigh, 1991) and dopamine (Morgan, 2002) and social neuroendocrines [e.g. testosterone (Terburg, 2013) and cortisol (Mehta & Josephs, 2010)]. Raleigh et al. (1984) were among the first to record elevated blood serotonin concentration in primates who occupied the dominant male social position. Further, they found that elevated blood serotonin concentration is a state-dependent consequence of active occupation of the dominant male social position, as spontaneous and induced gains or losses in social status were accompanied by corresponding increases or decreases in whole-blood serotonin concentrations. A follow up experimental study by Raleigh et al. (1991) replicated the prior findings identifying a dominant male with twice the blood serotonin levels of the other males, and demonstrated that enhancement or suppression of serotonin signaling can respectively induce dominance or subordination in treated velvet monkeys (Raleigh, 1991). The relation between social rank and serotonergic function appear to be bidirectional such that manipulations of social rank or serotonergic transmission will have a reciprocal reaction on the other. Pharmacological

interventions that increase brain serotonin can increase the frequency of positive socially affiliative behavior and improve social rank, and the opposite is true when serotonin is pharmacologically reduced (Raleigh, 1986; Raleigh, 1991). Conversely, changes in social rank may affect serotonin functioning: higher social ranking is associated with increased serotonergic transmission, and when social ranking is reduced, serotonergic transmission is correspondingly reduced (Raliegh, 1984). Yeh and colleagues (1996) reported that in subordinate crayfish, serotonin suppresses firing in the neurons controlling tail flick (a threat response) but it increases probability of firing in dominants. More recently, a trait aspect of the serotonin-dominance hypothesis was identified: higher-ranked monkeys have been shown to demonstrate more gray matter in the dorsal raphe nucleus, which contains serotoninergic neurons (Noonan, 2014). In sum, serotonin appears to exhibit both state (Raleigh, 1991; Raleigh, 1984) and trait (Noonan, 2014) relationships to social dominance.

Manipulation of serotonin levels in humans has provided evidence for the role of serotonin in human social behaviors such as social dominance and social affiliation. In line with the preclinical findings in animal models, Tse and Bond (2002a) found that two weeks of citalopram treatment enhanced expression of dominant social behaviors on a number of different measures (e.g. eye gaze behavior and communication) and were suggested to be important for promotion of social relationships. Further supporting the relationship between serotonin levels and socially dominant behaviors, Moskowitz et al. (2001) found that enhancing serotonin levels through a precursor of serotonin biosynthesis (1 g tryptophan) administered over 12 days enhanced dominance-related behaviors in friendship as reported by participants' friends. More recently, Tse and colleagues (2014) provided evidence to demonstrate that a single dose of an

SSRI (escitalopram) enhanced motivation for social dominance through the initiation of a combination of aggressive and affiliative behaviors

In addition to serotonin's role in facilitating socially dominant behavior, evidence suggests that serotonin is important for socially affiliative behavior as well (Insel, 1998). Socially dominant individuals acquire tactics (e.g. coercive or pro-social behavior) to exert control over resources in the belief that on one hand, these tactics promote their ability to acquire resources and on the other hand, they minimize the personal cost of conflict (Hawley, 1999). Therefore, an important developmental goal in humans is to learn how to read social signals and identify socially competent ways to achieve dominance flexibly, using prosocial strategies (Hawley, 2002). Serotonin plays a crucial role in social affiliation through the promotion of competent social behavior and through de-escalation by controlling impulses that regulate aggression (Higley, 1996; Soubrie, 1986). In support of the role of serotonin for facilitating socially affiliative behaviors, Knutson et al. 1998 reported that 1 week treatment with a selective serotonin reuptake inhibitor (paroxetine) relative to a placebo reduced focal indices of hostility through a more general decrease in negative affect, and increased a behavioral index of social affiliation, after both 1 week and 4 weeks of treatment in healthy volunteers. Data from Wood and colleagues (2006) provided additional evidence that serotonin is important for facilitating socially affiliative behaviors by experimentally attenuating serotonin levels in humans. In healthy volunteers, experimentally induced tryptophan depletion that reduced the availability of serotonin for biosynthesis produced significant reductions in the level of cooperation from behavior associated with more long-term gain toward in favor of short-term profit shown by participants when playing the game (Wood, Rilling, Sanfey, Bhagwagar, & Rogers, 2006). This suggested that serotonin may modulate reward information to facilitate socially cooperative

behavior. Several other studies have found that nonhuman primates with high CSF 5-HIAA concentrations are more likely to engage and spend time in positive social interactions (Higley, 1994; Mehlman, 1995; Raleigh, 1983; Raliegh 1994). Taken together, this evidence suggests that increased social competence could be a potential therapeutic mechanism for serotonergic antidepressants.

Sociotropy-Autonomy & Social Rank

Given the role of serotonin in social dominance and social affiliation behaviors, and the changes that occur in social dominance and social affiliation behaviors in response to pharmacological manipulations of serotonin, the present study sought to examine the relationship of a measure of social dominance and social affiliation to the antidepressant treatment response. A number of diverse theories of psychopathology have converged to suggest that sociotropy (relatedness) and autonomy (self-definition) are two fundamental psychological dimensions that provide a theoretical understanding for variations in normal personality organization and the mechanisms by which dysfunction within these dimensions leads to the development of psychopathology (see Luyten & Blatt, 2011 for a comprehensive review). The cognitive-personality domains of sociotropy and autonomy introduced by Beck (1983) have been described as two domains of personality that are highly relevant for understanding vulnerability to depression in the context of social rank theory (Santor, 2003). Autonomy refers to an achievement-oriented personality style associated with attempts to maximize control over the environment. Sociotropy involves investment in and attachment to others. Beck (1983) proposed that a balance between autonomy and sociotropy characterizes adaptive personality development. Highly sociotropic individuals are prone to interpersonal dependency characterized by a high need for close relationships and tend to be very concerned with how they are viewed by others

whom they often work hard to please. Individuals high in autonomy are characterized by a heavy emphasis on personal achievements, independence, and control. It was hypothesized that highly sociotropic individuals are prone to depression as a result of interpersonal loss, and highly autotropic individuals are prone to depression as a result of perceived life failures (Joyce, 1994).

Sociotropic and autonomic individuals have different goal sets that can be understood in relationship to the social rank theory (Santor, 2003). Autonomic individuals are motivated to preserve and enhance a dominant status, whereas submissive and dependent sociotropic individuals are motivated to preserve and enhance interpersonal relations. Different behavioral tactics are used to pursue these goals; sociotropic individuals are more likely to be submissive, appease others, and downplay disagreements, whereas autonomic individuals are more likely to retaliate against threats to status and make frequent social comparisons. In a series of experiments, Santor and Zuroff (1997, 1998) found that autonomous and sociotropic women did indeed employ these behavioral tactics when outperforming, or being outperformed by, a friend on a task. Santor & Zuroaff (1997) suggested instead, that autonomous and sociotropic individuals are characterized by both insecure attachment and insecure social rank, but that they employ different strategies in response to their dual insecurities. Taken together, autonomous individuals tend to be motivated by goals to pursue social dominance, whereas sociotropic individuals tend to be motivated by goals to pursue social affiliation, which can manifest as submissiveness or dependency in response to insecure attachment.

Peselow and colleagues (1992) were among the first to assess the ability of the Sociotropy-Autonomy scale to predict antidepressant treatment response in individuals with depression. They found that the combination between high autonomy and low sociotropy scores predicted a positive response to antidepressant treatment. Moreover, individuals with high

autonomy and low sociotropy were more likely to respond to an antidepressant than a placebo, whereas no difference was found between active treatment and placebo among the high sociotropy and low autonomy group. Another study (Scott, 1996) upheld these findings and found that higher autonomy scores predicted lower symptom severity after 3 months of antidepressant treatment and recovery from depression at 6 months. They did not find an association between sociotropy treatment outcomes. Mazure and colleagues (2000) extended this work by examining the moderating effects of adverse life events and found that a congruency between the frequency of adverse life events (interpersonal vs. achievement) and cognitive-personality style (sociotropy vs. autonomy, respectively) predicted better treatment outcomes, accounting for 65% of the variance. Marhsall, Zuroff, McBride, & Bagby (2008) found differential patterns of treatment response depending on the individuals cognitive-personality style such that individuals high in self-criticism were more likely to benefit from pharmacotherapy, individuals high in dependency were less likely to benefit from CBT, individuals high in self-criticism were less likely to benefit from pharmacotherapy and IPT. Taken together, these studies suggest that the cognitive-personality styles of sociotropy and autonomy may be useful indicators of antidepressant treatment response. Taken together, evidence suggests that increased social dominance-submissiveness and socially affiliative behaviors could also be a potential therapeutic mechanism for serotonergic antidepressants.

Study Aims

Despite the compelling evidence provided by early studies, little research has been conducted in recent years to assess the utility of the cognitive-personality styles of sociotropy and autonomy in predicting antidepressant treatment response. This study aimed to extend prior work by examining the relationship of sociotropy and autonomy to antidepressant treatment

outcomes in people with major depression. Further, we aimed to assess the accuracy by which these cognitive-personality styles can distinguish between treatment responders and non-responders.

Hypotheses

It was hypothesized that 1) indices of sociotropy and autonomy would be useful for differentiating treatment responders from non-responders; 2) individuals with high autonomy and low sociotropy would be more likely to respond to treatment than individuals with low autonomy and high sociotropy; and, 3) higher levels of autonomy and lower levels of sociotropy would be linearly related to changes in depression scores from pre to post treatment.

Methods

Participants

Participants in this study were recruited from the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study. EMBARC was a multi-site collaboration among the University of Michigan, the University of Texas Southwestern, Columbia University, and Massachusetts General Hospital supported by the National Institute of Health to examine biomarkers of treatment response in depression. Participants in the EMBARC study were first randomized to receive either sertraline or a placebo during the first 8 weeks of the study. During the second 8 weeks, sertraline non-responders (as determined by a Hamilton Depression Rating Scale [HDRS] reduction of 50% or less) were then randomized to receive bupropion or a placebo, and placebo non-responders were then randomized to receive either sertraline or a second placebo.

This ancillary study was approved by the EMBARC team in order to collect and assess cognitive styles and personality traits that may differentiate treatment responders from non-responders. IRB approval was obtained from the boards at the University of Michigan, University of Texas - Southwestern, Columbia University, and Massachusetts General Hospital sites. Participants who completed the study within the past year and signed a consent to be contacted for future research studies were contacted by phone or in person at the end of their final (Week 16) follow up visit in the larger EMBARC project and asked about their interest in participating in this project. Participants who completed participation in the larger EMBARC study within the past six months and were in the sample of individuals with depression (healthy controls were excluded) were eligible to enroll in this study.

Thirty-seven individuals were contacted for participation in this follow-up study. Of the 37 participants contacted, 30 have completed this ancillary study, 2 declined to participate, and 5 were unreachable. Of the 30 who completed the ancillary study, 4 were excluded from these analyses as they were randomized to receive a placebo, and 2 were abnormal terminations that did not complete the antidepressant trial. Data collection was approved and began at the University of Michigan approximately one year prior to approval at the other sites. Seventeen of the participants originated from the University of Michigan site; 3 are from UT Southwestern; and 4 are from Massachusetts General Hospital.

Table 1: Descriptives for the Sociotropy-Autonomy Study

	Responder		Non-responder			
	M	SD	M	SD	*t*	*p*
Age (18-65)	41.56	16.11	36.27	14.12	0.84	.41
HDRS Reduction	72%	15%	4%	34%	5.61	<.01*
HDRS Baseline	17.67	5.57	16.73	5.19	0.42	.68
HDRS Change	12.78	5.37	1.40	4.56	5.54	<.01*
Sociotropy	77.00	7.94	89.47	15.36	-2.25	.04*
Autonomy	61.00	8.44	63.73	9.66	-0.70	.49
	N	%	N	%	χ^2	*p*
Sex						
Male	5	55.6	10	66.7	.30	.59
Female	4	44.4	5	33.3		
Race						
Caucasian	7	77.8	14	93.3	1.24	.26
Non-Caucasian	2	22.2	1	6.7		

Procedure

Participants who indicated they were willing to participate were given a questionnaire packet with mailing materials to take home. The following questionnaires were included in the questionnaire packet: Behavioral Activation System and Behavioral Inhibition System Scale; International Physical Activity Questionnaire; Mental Health Locus of Control Scale; Mood and Anxiety Symptom Questionnaire; Sociotropy-Autonomy Scale; Big Five Inventory; Edinburgh Handedness Inventory; Marlowe-Crowne Social Desirability Scale; Ruminative Responses Scale; and the Quick Inventory of Depressive Symptoms – Self-Report (QIDS-SR). This manuscript focuses on the results from the Sociotropy-Autonomy Scale. Compensation for participation was $10.

Data Analysis

Participants who received sertraline either during the first phase of the study or during the second phase of the study (after a placebo non-response) were included in the present analyses, and change scores were calculated relevant to the first and last week they received sertraline

treatment. No differences were detected between phase 1 and phase 2 participants among any of the variables (see Table 2).

Table 2: Comparison of Phase 1 and Phase 2 participants

	Phase 1 Pts. (n=17) Mean (standard dev.)	Phase 2 Pts. (n=7) Mean (standard dev.)	*t*	*p*-value
HDRS Percent Change	19% (4%)	54% (33%)	-1.884	.073
HDRS Baseline Score	17.35 (5.17)	16.33 (5.57)	.466	.645
HDRS Change Score	4.00 (6.87)	9.71 (7.46)	-1.810	.084
Sociotropy	86.29 (14.68)	83.78 (13.44)	.427	.673
Autonomy	63.76 (9.34)	61.89 (8.45)	.503	.620

Prior to conducting the classification analyses, we assessed for outliers and ensured the statistical assumption of normality was met. No data points were deemed outliers. Participants were deemed responders if they exhibited a 50% or greater reduction in depression scores, as measured by the Hamilton Depression Rating Scale over 2 months of antidepressant treatment.

The first analysis conducted aimed to replicate prior work by assessing the role of autonomy in distinguishing between treatment responders and non-responders utilizing discriminant function analysis (Peselow, 1992; Scott, 1996). Secondly, we assessed the discriminating ability of the sociotropy scale. Finally, we examined the accuracy of separating treatment responders from non-responders utilizing both the sociotropy and autonomy scales.

To examine whether a linear relationship exists between the sociotropy and autonomy scale and changes in depression scores on the Hamilton Depression Rating Scale, which was the scale used to determine whether participants are labeled treatment responders or non-responders, we conducted a follow-up multiple linear regression analysis to estimate the amount of variance in depression change scores were accounted for by sociotropy, autonomy, and their interaction. Baseline depression severity was controlled for in all three models.

Results

Discriminant Function Analysis – Autonomy

The statistical assumption of Homogeneity of Covariance Matrices was satisfied as indicated by a non-significant Box's *M* of 0.181 ($F(1,1185)=0.172$, $p=0.678$).

The overall estimated function was not significant (Wilk's Lambda=0.978, χ-square(1)=0.476, $p=0.490$). The estimated function was only able to explain 2.19% of the variance in treatment response, with a canonical correlation of 0.148.

Discriminant Function Analysis – Sociotropy

The statistical assumption of Homogeneity of Covariance Matrices was satisfied as indicated by a non-significant Box's *M* of 3.742 ($F(1,1185)=3.571$, $p=0.059$).

The overall estimated function was significant (Wilk's Lambda=0.813, χ-square(1)=4.446, $p=0.035$), with a canonical correlation of 0.432. The estimated function explained 18.66% of the variance in treatment response. Classification analyses utilizing the estimated function correctly classified 7/9 responders and 12/15 non-responders with 77.8% sensitivity and 80% specificity. Overall, Sociotropy correctly classified 79.2% of originally grouped cases.

Discriminant Function Analysis – Sociotropy & Autonomy

The statistical assumption of Homogeneity of Covariance Matrices was satisfied as indicated by a non-significant Box's *M* of 4.178 ($F(1,9605)=1.240$, $p=0.293$).

The overall estimated function was not significant (Wilk's Lambda=0.767, χ-square(2)=5.560, $p=0.062$). The estimated function explained 23.23% of the variance in

treatment response, with a canonical correlation of 0.482. Classification analyses utilizing the estimated function correctly classified 8/9 responders and 12/15 non-responders with 88.9% sensitivity and 80% specificity. Overall, the Sociotropy and Autonomy subscales together correctly classified 83.3% of originally grouped cases.

Multiple Linear Regression Analysis

Sociotropy was a significant predictor of changes in depression severity resulting from treatment (Table 3). Lower sociotropy scores were associated with an increased degree of treatment response. Consistent with the discriminant function analysis that used sociotropy as an independent variable and explained 18.6% of the variance in treatment response, sociotropy explained 17.3% of the variance in treatment response, and the overall model explained 30.9% of the variance in treatment response. Autonomy did not significantly predict changes in depression severity resulting from treatment (Table 4). When sociotropy and autonomy were entered into the model along with the interaction variable, none of the variables were significant (Table 5).

Table 3: Sociotropy - multiple linear regression analysis

Source	B	F	Sig.	R^2
Intercept	22.123	2.594	.122	.110
Sociotropy	-0.241	4.389	.048	.173
Baseline depression severity	0.233	.552	.466	.026

Table 4: Autonomy - multiple linear regression analysis

Source	B	F	Sig.	R^2
Intercept	6.633	.429	.520	.020
Autonomy	-0.200	1.710	.205	.075
Baseline depression severity	0.677	6.443	.019	.235

Table 5: Sociotropy & Autonomy - multiple linear regression analysis

Source	B	F	Sig.	R^2
Intercept	14.894	.069	.796	.004
Baseline depression severity	0.220	.452	.509	.023
Autonomy	0.166	.029	.866	.002
Sociotropy	-0.001	.000	.999	.000
Interaction	-0.004	.167	.688	.009

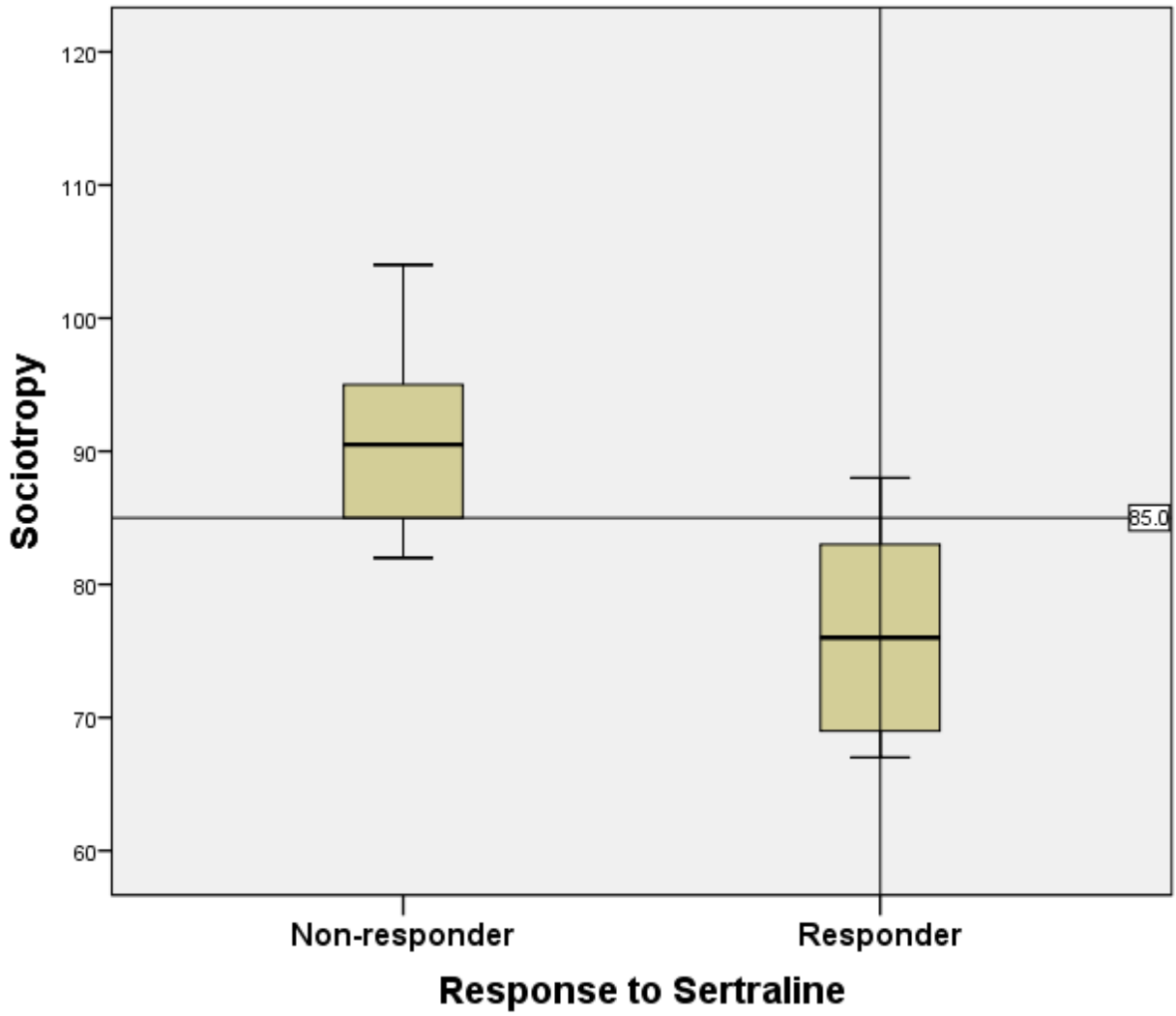

Figure 1: Sociotropy by Tx. Response

Discussion

Serotonin plays an important role in facilitating social dominance and social affiliation behaviors (Insel, 1998; Levitan, Hasey and Sloman, 2000), alongside dopamine (Morgan, 2002) and the social neuroendocrines [e.g. testosterone (Terburg, 2013) and cortisol (Mehta & Josephs, 2010)]. Deficits in serotenergic activity have been reported among individuals who occupy involuntarily subordinate social positions (Noonan, 2014; Levitan et al. 2000; Raleigh, 1984; Raleigh, 1991; Yeh, 1996), and may correspond to a reduction in socially affiliative behavior (Higley, 1994; Mehlman, 1995; Raleigh, 1983; Raliegh 1994; Insel, 1998; Woods et al., 2006). The restoration of socioemotional functioning appears to be an important antidepressant mechanism of SSRI treatment (Challis, 2015; Levitan, Hasey and Sloman, 2000). Successful serotonin treatment in depression may in part be facilitated via improvements in socially affiliative behavior (Knutson, 1998) and perceptions of increased social rank (Raleigh, 1986; Raleigh, 1991; Tse and Bond, 2002; Moscowitz, 2001; Tse and Bond, 2014).

Dysfunction within the systems responsible for socially dominant and affiliative behaviors is hypothesized to contribute to the depressed state (Raleigh, 1991). Sertotenergic enhancing interventions have been reported to produce increases in social rank and socially affiliative behaviors (Tse, 2002) that may correspond to improved social functioning. The present study sought to examine the relationship of a self-report measure of social dominance and social affiliation (Santor, 2003) is useful for distinguishing antidepressant treatment responsers from non-responders.

Sociotropy and autonomy, which were proposed by (Beck, 1983), are two fundamental psychological dimensions that provide a theoretical understanding for variations in normal personality organization (see Luyten & Blatt, 2011 for a comprehensive review). Dysfunction

within these dimensions is thought to be useful as a model for the development of psychopathology. Dysfunctionally high levels of sociotropy are associated with excessive submissiveness in a maladaptive attempt to increase affiliation, while dysfunctionally high levels of autonomy are associated with excessive dominance behaviors (Santor, 2003). It was hypothesized that highly sociotropic individuals are prone to depression as a result of interpersonal loss, and highly autotropic individuals are prone to depression as a result of perceived life failures (Joyce, 1994). Results from the current study add to a body of evidence suggesting that the Sociotropy-Autonomy Scale is useful for differentiating antidepressant treatment responders and non-responders (Mazure, 2000; Peselow, 1992; Scott, 1996; McBride, 2008). The current work extends prior investigations by utilizing discriminant function analysis to examine the ability of the sociotropy-autonomy scale to classify participants as treatment responders or non-responders. Notably, the sociotropy-autonomy scale was able to correctly classify 83.3% of participants into responder and non-responder categories. The sociotropy subscale alone was able to correctly classify 79.2% of the participants, with the autonomy scale only improving classification by 4.1%.

Social rank theory is useful for understanding the context in which sociotropy and autonomy convey vulnerability to depression (Santor, 2003). Social rank theory has been used to describe the etiology of socioemotional dysfunction in depression (Santor, 2003) and the role of serotonergic interventions in socioemotional function restoration (Levitan, Hasey and Sloman, 2000). Social rank theory is an evolutionary model of typical sociobiological development of animals and humans to respond appropriately to dominance hierarchies (Gilbert, 2006) that is used to understand the mechanisms by which dysfunctional processes contribute to the etiology of psychopathology via socially affiliative and social ranking structures (Price & Sloman, 1987).

Socially dominant individuals acquire tactics (e.g. coercive or pro-social behavior) to exert control over resources in the belief that on one hand, these tactics promote their ability to acquire resources and on the other hand, they minimize the personal cost of conflict (Hawley, 1999; Hawley, 2002; Higley, 1996; Soubrie, 1986). According to social rank theory, the involuntary subordinate strategy (Price, 1972; Price & Sloman, 1987; Gilbert, 1992, 2000) and, more recent, involuntary defeat strategy (Sloman, 2000) is an evolutionarily adaptive strategy (Shively et al. 1997; Rygula et al. 2005; Yeh, 1996) whereby depressed states in a social rank context function to (1) to down-regulate an animal/ person's goal pursuits and behaviour and avoid directly challenging dominants (or seeking resources, e.g. sexual contacts) that could stir their attack, and keep a low and vigilant profile; and (2) to impact on the mind of the dominant such that the dominant either accepts a submission and/or sees them as inhibited/timid/ compliant and 'out of action' and, therefore, as no threat to him/her (Price, 1972). It has been argued that it is the pathological exaggeration of this strategy that is associated with psychopathology.

In response to involuntary defeat, sociotropic and autonomic individuals may respond in different patterns depending on their cognitive-personality orientation. Autonomic individuals are motivated to preserve and enhance a dominant status, whereas submissive and dependent sociotropic individuals are motivated to preserve and enhance interpersonal relations. Santor & Zuroaff (1997) suggested instead, that autonomous and sociotropic individuals are characterized by both insecure attachment and insecure social rank, but that they employ different strategies in response to their dual insecurities. Sociotropic individuals are more likely to be submissive, appease others, and downplay disagreements, whereas autonomic individuals are more likely to retaliate against threats to status and make frequent social comparisons.

The results from the present study are consistent with the pattern of results demonstrated by Peselow (1992) who found that the group of high autonomy and low sociotropy experienced greater reductions in depression severity relative to the other combinations of autonomy and sociotropy. While another study (Scott, 1996) found that autonomy was a better predictor of treatment outcomes than sociotropy, this study is consistent with general pattern of lower sociotropy relative to autonomy being indicative of a positive treatment response. However, in contrast to Scott and colleagues (1996), data from this study suggest that the sociotropy subscale was more useful than the autonomy subscale at differentiating treatment responders from non-responders. Although they did not find direct associations of autonomy or sociotropy to treatment outcomes, the effect sizes found in this study are consistent with work by Mazure (2000) that found the frequency of adverse life experiences and sociotropy-autonomy scores were able to account for 65% of the variance in treatment outcomes.

It is possible that measures of the cognitive-personality styles of sociotropy-autonomy are useful indices of antidepressant treatment response due to their relationship to socially dominant and affiliative behaviors (Santor, 2003), which have been reported to be facilitated in part via the neurotransmitter serotonin (Tse, 2002). It is possible that for individuals high in autonomous traits, to whom social dominance is an important motivator, decreases in social ranking that have been reported to predict the onset of major depressive episodes (Joyce, 2004) may be reversed via pharmacotherapy that acts on the serotonin system. Whereas for individuals high in sociotropic traits, whose depressive episodes tend to correspond to interpersonal losses rather than losses in social rank (Joyce, 2004), may not necessarily benefit from the social rank boost that serotonin offers.

Limitations

Limitations to the current study that should be noted include the small sample size and the lack of assessment of the moderating effects of adverse life events reported in prior investigations. Further, this study assessed sociotropy and autonomy scores after treatment had concluded rather than prior to, which may have biased or findings as some personality trait assessment results can vary with degrees of depression (Hirschfeld et al., 1983),

However, this is unlikely as prior investigations have reported that sociotropy and autonomy subscales remain stable from before to after antidepressant treatment (Moore & Blackburn, 1996). Despite these limitations, this small sample demonstrated robust classification effects, with findings that were in a direction consistent with prior investigations.

Conclusions

In sum, this study adds to a prior body of evidence (Mazure, 2000; Peselow, 1992; Scott, 1996; McBride, 2008) that indicates the utility of the well-established cognitive-personality dimensions of sociotropy and autonomy (Luyten & Blatt, 2011) for differentiating antidepressant treatment responders and non—responders. Due to the relatively low amount of resources necessary for its inclusion, and the ease of translation into routine clinical care, these data suggest that the sociotropy-autonomy scale warrant further contemporary investigation. Future investigations may benefit from an exploration of the congruence of the precipitating stressors to cognitive-personality style of individuals undergoing antidepressant treatment. If the proposed relationship of sociotropy-autonomy to antidepressant treatment response in the context of social rank theory holds, it may provide useful directions for future investigations into interventions that specifically target the unique patterns of dysfunction that are present in highly sociotropic non-responders.

References

Bieling, P. J., & Alden, L. E. (2001). Sociotropy, autonomy, and the interpersonal model of depression: An integration. Cognitive Therapy and Research, 25(2), 167–184. https://doi.org/10.1023/A:1026491108540

Bieling, P. J., Beck, A. T., & Brown, G. K. (2000). The Sociotropy-Autonomy Scale: Structure and implications. Cognitive Therapy and Research, 24(6), 763–780. https://doi.org/10.1023/A:1005599714224

Dodd, S., & Berk, M. (2004). Predictors of antidepressant response: A selective review. International Journal of Psychiatry in Clinical Practice. https://doi.org/10.1080/13651500410005423

Fresco, D. M., Sampson, W. S., Craighead, L. W., & Koons, A. N. (2001). The relationship of sociotropy and autonomy to symptoms of depression and anxiety. Journal of Cognitive Psychotherapy: An International Quarterly.

Fresco, D. M. (2000). Cognitive styles as moderators of the relationship of life stress to depression and anxiety. Dissertation Abstracts International: Section B: The Sciences and Engineering.

Mazure, C. M., Bruce, M. L., Maciejewski, P. K., & Jacobs, S. C. (2000). Adverse life events and cognitive-personality characteristics in the prediction of major depression and antidepressant response. The American Journal of Psychiatry. https://doi.org/10.1176/appi.ajp.157.6.896

Moore, R. G., & Blackburn, I. M. (1996). The stability of sociotropy and autonomy in depressed patients undergoing treatment. Cognitive Therapy and Research. https://doi.org/10.1007/BF02229244

Moore, R. G., & Blackburn, I. M. (1994). The relationship of sociotropy and autonomy to symptoms, cognition and personality in depressed patients. Journal of Affective Disorders. https://doi.org/10.1016/0165-0327(94)90087-6

Peselow, E. D., Robins, C. J., Sanfilipo, M. P., Block, P., & Fieve, R. R. (1992). Sociotropy and Autonomy: Relationship to Antidepressant Drug Treatment Response and Endogenous-Nonendogenous Dichotomy. Journal of Abnormal Psychology. https://doi.org/10.1037/0021-843X.101.3.479

Robins, C. J., & Luten, a G. (1991). Sociotropy and autonomy: differential patterns of clinical presentation in unipolar depression. Journal of Abnormal Psychology. https://doi.org/10.1037/0021-843X.100.1.74

Robins, C. J. (1997). Sociotropy, autonomy, and patterns of symptoms in patients with major depression: A comparison of dimensional and categorical approaches. Cognitive Therapy and Research. https://doi.org/10.1023/A:1021874415967

Scott, J., Harrington, J., House, R., & Ferrier, I. N. (1996). A preliminary study of the relationship among personality, cognitive vulnerability, symptom profile, and outcome in major depressive disorder. Journal of Nervous and Mental Disease. https://doi.org/10.1097/00005053-199608000-00008

Chapter 3: Placebo response in major depression - the moderating effects of anhedonia

Introduction

Major Depression places a significant burden on both individuals and families and contributes to a worldwide disease burden of up to 11 percent (Greden, 2001). Despite substantial effort, a method for identifying the appropriate treatments for individuals suffering from depression has remained elusive. Less than 10 percent of individuals with depression receive adequate treatment (Hirschfeld et al., 1997). For individuals with depression who do receive treatment, as few as 11–30% reach remission, even after 8–12 months (Cipriani et al., 2009). Among those who are lucky enough to demonstrate benefits from treatment, medication side effects can be an obstacle to obtaining tolerable management of depression symptoms (Carvalho, Sharma, Brunoni, Vieta, & Fava, 2016).

One factor reducing effectiveness of treatment is the inability to personalize treatment (Insel & Cuthbert, 2015). Clinicians attempt to identify an appropriate treatment strategy via a prolonged period of trial and error, delaying clinical improvement and prolonging suffering. As such, studies that aim to reduce the time to receive adequate treatment are urgently needed. There is a substantial literature investigating possible predictors and moderators of "active" antidepressant (Simon & Perlis, 2010) and placebo (Walsh, Seidman, Sysko, & Gould, 2002) treatment response.

The placebo has been defined as an *inert* agent or procedures that soothe the patient (Price, Finniss, & Benedetti, 2008). However, recent research has called this into question as

placebo interventions have been reported to exhibit biological changes that mimic *active* interventions (Finniss, Kaptchuk, Miller, & Benedetti, 2010; Petrovic et al., 2005). Up to 30% of people who are given a placebo antidepressant will show a clinically significant treatment response, and such a response rate exceeds what would otherwise be expected over time without any intervention (Charlesworth et al., 2017; Walsh et al., 2002) indicating that the placebo is anything but "inert". Due to the lack of evidence suggesting substantially greater response rates among those receiving antidepressant treatment relative to those receiving a placebo, the efficacy of first-line antidepressants has been called into question (Kirsch, 2014). A controversial conclusion from a comprehensive meta-analysis suggested that up to 75% gains from antidepressants are actually driven by the placebo effect (Kirsch & Sapirstein, 1998). More recently, a meta-analysis (Rief et al., 2009) came to a similar conclusion, reporting that placebo-induced effects account for 68% of antidepressant efficacy. One study even went as far as to conclude that placebo treatment is more effective than antidepressant treatment (Howick et al., 2013). Taken together and exclaimed by Wampold, Minami, Tierney, Baskin, & Bhati (2005), "the placebo is powerful."

Investigations focused on identifying the processes associated with positive placebo responses have the potential to enhance pharmacological interventions, even if the effects of active therapy are predominantly mediated by a placebo response. Further, if researchers are able to identify who may benefit as much from a placebo as they might otherwise benefit from a first-line antidepressant intervention, placebos provide the potential for the avoidance of chemically-induced side-effects and possibly improved treatment tolerance. Recent data has suggested that placebo interventions without deception are possible (Petkovic et al., 2015), removing the ethical barrier of informed treatment consent.

An essential ingredient in the placebo response is the expectation of reward (Murray & Stoessl, 2013). Schweinhardt, Seminowicz, Jaeger, Duncan, & Bushnell (2009) proposed that the placebo response is facilitated via reward processing in a neural network defined as the mesolimbic reward system, which incorporates the ventral striatum, insula, and prefrontal cortex. Within the mesolimbic reward system, the nucleus accumbens (NAC) initiates the placebo response via "reward expectancy" (Scott et al., 2007), and frontal cortical regions help to modulate "reward responsiveness" (Faria, Fredrikson, & Furmark, 2008). Up to 43% of the variance in symptom improvement at the end of an antidepressant trial was attributable to placebo-induced endogenous opioid release in the nucleus accumbens, subgenual anterior cingulate cortex, midline thalamus, and amygdala (Peciña et al., 2015). Further emphasizing the role of expectation-reward circuitry in the placebo response, increased metabolic activity in the ventral striatum after one week of treatment (i.e. prior to symptomatic benefit) distinguished placebo responders from non-responders (Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005). Taken together, the expectation of reward in an essential component of the placebo response, which is facilitated by the mesolimbic reward system. As such, indices of mesolimbic reward system processing capacity may be useful for differentiating placebo responders from non-responders, with individuals who demonstrate an attenuated capacity for reward system processing being less likely to benefit from a placebo.

Behaviorally, the probabilistic reward task was developed and validated as a behavioral measure hedonic capacity (D. A. Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). In this task, participants must choose between two responses that are linked to different probabilities of reward. Due to this probabilistic nature, participants cannot infer which stimulus is more advantageous based on the outcome of a single trial, but, rather, need to integrate reinforcement

history over time in order to optimize their choice. Participants with reduced hedonic capacity take significantly more trials to correctly discriminate between the stimuli than participants without reduced hedonic capacity.

Psychophysiological methods and behavioral paradigms have been employed in an attempt to identify objective indices of reward system activity and the capacity to respond to rewarding stimuli (i.e. hedonic capacity). Psychophysiological investigations have identified resting frontal delta electroencephalography (EEG) activity a possible index of mesolimbic reward system activity and hedonic capacity (Knyazev, 2012). A follow-up study to Pizzagalli et al. (2008) found that greater reward learning on the probabilistic reward task was linearly related to increased resting rostral anterior cingulate cortex (rACC) delta activity (D. A. Pizzagalli et al., 2009).

Anhedonia is a common subjective experience among individuals with depression defined by attenuated hedonic capacity including: reduced motivation, reduced anticipatory pleasure (wanting), reduced consummatory pleasure (liking), and deficits in reinforcement learning (Shankman et al., 2014). Rizvi, Lambert, and Kennedy (2018) reviewed a wide body of literature that suggests that anhedonia is a reflection of deficits in the mesolimbic reward circuit. Further, volumetric MRI data from Harvey and colleagues (2007) indicated that self-reported trait anhedonia severity was negatively correlated with the volume of the anterior caudate, a key region in the mesolimbic reward system. Taken together, both state and trait anhedonia appear to result from deficits in mesolimbic reward system processing. Elevated self-reported anhedonia, potentially indirectly indicative of defective mesolimbic reward system processing, may thus be useful for identifying individuals who will not benefit from a placebo. The Mood and Anxiety Symptom Questionnaire is a self-report measure that has demonstrated reliability for

distinguishing comorbid anhedonic symptoms from general depression symptoms, general anxiety symptoms, and anxious arousal symptoms (Watson et al., 1995).

In sum, the MASQ-AD subscale, resting frontal delta EEG activity, and the probabilistic reward task have had demonstrated utility as subjective and objective indices of hedonic capacity. While resting frontal delta EEG activity is thought to more directly measure mesolimbic reward system activity, the probabilistic reward task and the MASQ-AD subscale may be indirect indicators of mesolimbic reward system dysfunction that could be useful for determining a placebo response likelihood.

Study Aims

As the expectation of reward is integral to the placebo response, this study sought to examine whether anhedonia, an indirect indicator of mesolimbic reward system dysfunction, may moderate the placebo response in individuals with depression. Our team is unaware of any studies that have investigated whether anhedonia, a state commonly experienced during episodes of depression, may moderate the placebo response. Reward system processing capacity was estimated via behavioral performance on a probabilistic reward task indexing reward learning, indexed via rACC Delta EEG activity, and indirectly assessed via self-reported scores on the MASQ Anhedonic Depression subscale to explore their possible role as moderators of placebo treatment response.

Hypotheses

We hypothesized that PRT, and rACC Delta would positively correlate among one another based on prior studies that suggest they each index the mesolimbic reward system from the separate units of analysis of behavioral (PRT) and physiological (rACC Delta). Further, we hypothesized that self-report eleveaded MASQ-AD scores would indicate mesolimbic reward

system dysfunction, and possibily correspond to attenuated reward learning on the PRT and reduced mesolimbic reward system activity indexed by rACC Delta. Further, we hypothesized that individuals randomized to receive a placebo who exhibit impaired mesolimibic reward system functioning will have the smallest reductions in HAM-D as indicated by: 1) greater self-reported anhedonic depression symptoms, 2) reduced rACC delta EEG, and 3) reduced reward learning on a probabilistic reward task, indicating reduced hedonic capacity.

Method

Participants

A multicenter randomized clinical trial screened (n=634) and enrolled (n=296) outpatients (age, 18-65 years) meeting criteria for MDD without psychotic features based on the Structured Clinical Interview for DSM-IV Axis I Disorders between July 29, 2011, and December 15, 2015 (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care [EMBARC]). Participants had a Quick Inventory of Depressive Symptomatology score of 14 or higher (Rush et al., 2003), indicating moderate depression at both the screening and randomization visits. To minimize clinical heterogeneity, only individuals reporting early-onset (before age 30 years) MDD that was chronic (episode duration >2 years) or recurrent (≥2 recurrences including the current episode) were enrolled. Additional exclusion criteria are published elsewhere (Pizzgalli et al., 2018) and are available in the supplemental materials. The study was approved by the institutional review board at all four sites (University of Michigan – Ann Arbor, Columbia University, University of Texas Southwest Medical Center – Dallas, and Massachusetts General Hospital). A detailed description of the study design, randomization

procedures, and power analyses has been published elsewhere (Trivedi et al., 2016) and is available in the supplemental materials.

Table 6: Descriptives for the Placebo Study

	Responder Mean (SD)	Non-Responder Mean (SD)	t	p
Baseline Depression	18.38 (4.11)	18.75 (4.44)	-.410	.682
PRT Change (B2-B1)	0.09 (0.19)	0.03 (0.18)	1.555	.123
MASQ Anhedonia (reverse coded)	1.93 (0.79)	1.59 (0.76)	2.150	.034
rACC Delta	-3.22 (0.17)	-3.29 (0.23)	1.945	.055
rACC Theta	-3.35 (0.17)	-3.44 (0.21)	2.243	.027
Age	34.54 (11.99)	39.38 (13.21)	-1.830	.070
Age Range	18-65	19-57		
Sex	M=14, F=23	M=27, F=36		

EEG Recordings and Preprocessing

Of the 296 who were randomized, 266 had electroencephalographic (EEG) recordings, 248 had usable EEG data. Data were collected until 100 participants were randomized to receive a placebo, completed the study, and had useable data. Resting EEG data were recorded at baseline and 1 week after trial onset, and rACC delta (1.5-6Hz), theta (6.5-8Hz), alpha (8.5-10Hz & 10.5-12Hz), beta (12.5-18Hz & 21.5-30Hz), and gamma (36.5-44Hz) EEG activity was extracted using source localization.

At all sites, resting EEG was recorded during four 2-minute periods, half with eyes closed and half with eyes open in a counterbalanced order (Pizzgalli et al., 2018). Because different EEG acquisition systems were used across sites, a manual was developed to standardize recordings and instructions provided to participants. To minimize cross-site differences, EEG data were interpolated to a common montage (72 channels) and sample rate (256 Hz), and a single, standardized analysis pipeline (Tenke et al., 2017) was implemented to extract

nonoverlapping, artifact- free, 2-second epochs for source localization analyses (Pizzgalli et al., 2018)

Source Localization Analyses

Source localization analyses were conducted using low- resolution electromagnetic tomography (Pascual-Marqui et al., 1999; D. Pizzagalli et al., 2001), which infers the intracranial generators of scalp-recorded EEG signals and followed identical procedures as in prior studies (Korb, Hunter, Cook, & Leuchter, 2009; D. Pizzagalli et al., 2001). A full description of the analytical strategies are available in the supplemental materials, which were adapted from the first EMBARC study to publish on these data (Pizzagalli et al.; 2018). Current density within the delta band (1.5-6Hz) was extracted from the rACC cluster (14 voxels) previously associated with better antidepressant outcome (D. Pizzagalli et al., 2001). This cluster has been previously used (Korb et al., 2009) and spatially overlapped with the cluster linked to treatment outcome in 2 additional EEG studies (Mulert et al., 2007; Rentzsch, Adli, Wiethoff, Gómez-Carrillo De Castro, & Gallinat, 2014).

Probabilistic Reward Task

The probabilistic reward task (D. A. Pizzagalli, Jahn, & O'Shea, 2005) utilizes signal-detection theory to assess a participant's propensity to modify their behavior based on prior reinforcements. Participants are asked to select whether stimulus A or B was presented by responding with either A or B. Performance on the task can be analyzed in terms of discriminability and response bias. Discriminability refers to the participants' ability to differentiate between the two stimuli. Response bias refers to the participants' propensity to select response A or B irrespective of the stimulus presented. Prior research has demonstrated that reinforcing one stimulus more frequently than the other following a correct response

produces a systematic preference for the response paired with a more frequent reward (McCarthy, 1991). The more frequently reward stimulus allocation and the key presses are counterbalanced across participants.

Hedonic capacity was behaviorally operationalized as reward learning during a probabilistic reward task. The primary variable of interest is change in response bias scores from the first to the second block, which is thought to index reward learning (D. A. Pizzagalli et al., 2005). Discriminability scores were included as a covariate within the reward learning analyses.

Statistical Analysis

To address hypothesis 1, we estimated the relationships among the behavioral (PRT reward learning), self-reported MASQ-AD, and psychophysiological (rACC delta EEG) indices of hedonic capacity using Pearson's *r.* Follow-up multiple linear regression analyses including age and sex as covariates were conducted to control for extraneous variance.

To address hypotheses 2-4, the psychophysiological (rACC delta EEG) and behavioral (PRT reward learning) indices of hedonic capacity, along with self-reported MASQ-AD (indirectly indicating impaired hedonic capacity), were entered into independent multiple linear regression analyses with initial severity, age, and sex as covariates in each model. A stepwise multiple linear regression model was utilized to explore the unique variance explained by the significant moderators of the placebo response from the analyses for hypotheses 2-4.

Results

Contrary to Hypothesis 1, we did not find significant relationships among the two hypothesized indices of mesolimbic reward system hedonic capacity: behavioral reward learning on the probabilistic reward task and psychophysiological rACC delta EEG, nor on the indirect

measure of hedonic capacity using the self-reported anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire (see Table 7: Correlations among study variables). Self-reported anhedonic depression symptoms were unrelated to rACC delta EEG activity, $r(98)=.01$. Controlling for age, sex, and task discriminability, did not alter this pattern of findings: reward learning on the probabilistic reward task was not associated with self-reported anhedonia scores (Table 8) or rACC delta EEG (Table 9).

Table 7: Correlations among study variables

	Baseline	HDRS Change	Stimuli Discriminability	Response Bias	MASQ AD	rACC Delta	rACC Theta
Baseline	1	.25*	-.10	-.08	-.09	.15	.18
HDRS Change	.25*	1	.11	.10	.22*	.32**	.30**
Discriminability	-.10	.11	1	-.08	-.14	.18	.09
Response Bias	-.08	.10	-.08	1	.1	.18	.15
MASQ AD	-.09	.22*	-.14	.1	1	.01	.09
rACC Delta	.15	.32**	.18	.18	.01	1	.83**
rACC Theta	.18	.30**	.09	.15	.09	.83**	1

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Table 8: Self-reported anhedonia & behavioral reward learning

Source	B	F	Sig.	R^2
Intercept	1.933	98.789	.000	.505
PRT Discriminability	-.408	1.830	.179	.019
PRT Response Bias Reward Learning	.376	.787	.377	.008

Table 9: rACC delta & behavioral reward learning

Source	B	F	Sig.	R^2
Intercept	-3.234	1415.866	.000	.937
PRT Discriminability	.142	3.111	.081	.032
PRT Response Bias Reward Learning	.185	2.613	.109	.027
Age	-.003	3.740	.056	.038
Sex	-.007	.478	.491	.005

In support of hypothesis 2, the anhedonia subscale of the MASQ was a significant moderator of the magnitude of changes in depression symptoms during the placebo trial, accounting for 6.0% of the variance (see Table 10). Higher baseline self-reported anhedonic depression symptoms were associated with attenuated reductions in depression symptoms over the course of the randomized control trial, when controlling for baseline depression symptoms, age, and sex. The baseline depression covariate accounted for a significant amount of variance within the model. Age and sex were non-significant covariates (age was marginal).

Table 10: Moderating effects of anhedonia on treatment response

Source	B	F	Sig.	R^2
Intercept	-2.029	.221	.640	.002
Baseline Depression	.466	8.192	.005**	.079
Age	-.100	3.370	.070	.034
Sex	.190	.276	.600	.003
MASQ-AD	2.206	6.091	.015*	.060

In partial support of hypothesis 3, the hypothesized psychophysiological index of hedonic capacity (rACC delta) was significantly associated with the magnitude of change in Depression scores from before to after the placebo intervention (see

Table 11). However, the relationship was in the opposite of what was expected. We hypothesized that *increased* rACC delta EEG activity, potentially indicating reduced hedonic capacity, would predict an attenuated placebo response. However, we found that *decreased* rACC delta EEG was associated with an attenuated placebo response. To further explore the relationship of our psychophysiological measures to the placebo response, we conducted a post-hoc correlation analyses among the other rACC EEG bands (theta, alpha, beta, and gamma). We found that rACC theta EEG accounted for a greater proportion of the variance in the placebo response than rACC delta EEG (see Table 12).

Table 11: Moderating effects of rACC delta EEG on treatment response

Source	B	F	Sig.	R^2
Intercept	31.370	7.511	.007**	.073
Baseline Depression	.364	4.988	.028*	.050
Age	-.079	2.063	.154	.021
Sex	.134	.141	.708	.001
rACC delta	8.715	6.867	.010**	.067

Table 12: Moderating effects of rACC theta EEG on treatment response

Source	B	F	Sig.	R^2
Intercept	34.350	7.232	.008	.071
Baseline Depression	.355	4.688	.033	.047
Age	-.097	3.176	.078	.032
Sex	.126	.125	.725	.001
rACC theta	8.976	6.579	.012	.065

Inconsistent with hypothesis 4, the behavioral index of hedonic capacity (PRT reward learning), did not moderate the degree to which participants experienced benefits from the placebo (Table 13), when controlling for baseline depression symptoms, age, and sex.

Table 13: Relationship of rACC theta to behavioral reward learning

Source	B	F	Sig.	R^2
Intercept	-.572	.016	.900	.000
Baseline Depression	.464	7.675	.007	.075
Age	-.096	2.930	.090	.030
Sex	.138	.140	.710	.001
PRT Response Bias Reward Learning	4.459	1.309	.256	.014
PRT Discriminability	3.497	1.623	.206	.017

When self-reported index of anhedonic depression symptoms (MASQ AD), rACC theta EEG, and their interaction were entered into a stepwise multiple linear regression analysis

predicting changes in depression symptoms, they were able to estimate 20.6% of the variance (see Table 14 for a breakdown of each step; see Table 15 for the estimated model). Each variable contributed a significant amount of unique variance and the independent variables did not interact with each other.

Table 14: Stepwise Multiple Linear Regression

	R^2	R Square Change	F Change	Sig. F Change
1 – Baseline, Age, and Sex	.103	.103	3.671	.015
2 – Model 1 + MASQ Anhedonia	.157	.054	6.091	.015
3 – Model 2 + rACC Theta	.206	.049	5.807	.018
4 – Model 3 + interaction of Theta and MASQ AD	.211	.005	0.565	.454

Table 15: Anhedonia, rACC theta, and antidepressant treatment response

Source	B	F	Sig.	Partial Eta Squared
Intercept	27.259	4.490	.037*	.046
Baseline depression	.399	6.130	.015*	.061
Age	-.087	2.649	.107	.027
Sex	.231	.431	.513	.005
MASQ-AD	2.020	5.326	.023*	.054
rACC theta	8.279	5.807	.018*	.058

Discussion

Data from the present study provide further insight into the variables that may moderate placebo treatment response. We found that reduced self-reported anhedonic depression symptoms and higher pre-treatment resting rostral anterior cingulate cortex (rACC) electroencephalography (EEG) theta activity accounted for more than 20 percent of the variance in placebo treatment response.

In contrast to our initial hypothesis, we did not find evidence of convergent validity among the behavioral (reward learning on the probabilistic reward task [PRT]) and physiological (rACC delta activity) indices of hedonic capacity measured in this study. Further, we did not find a relationship of anhedonia (MASQ-AD) to either of the hypothesized indices of hedonic capacity. Consistent with Wacker, Dillon, & Pizzagalli (2009), change in response bias scores were not associated with the MASQ-AD subscale; however, in contrast to that study, this study did not find a significant link between PRT reward learning and rACC delta EEG activity. As described by Knyazev (2012), resting delta EEG oscillations may be influenced by appetitive and homeostatic processes such as hunger, cravings for substances of abuse, and sexual arousal. It is possible that extraneous appetitive or homeostatic variables that we did not measure, such as hunger, may have influenced our pattern of findings. Taken together, this study was unable to link the two suggested behavioral and psychophysiological indices of reward system activity, and neither demonstrated a relationship to self-reported anhedonic depression scores.

This study provides new insights into the role of self-reported anhedonic depression symptoms in moderating the placebo response. This study found that participants with impaired reward processing, indicated by self-reported anhedonia symptoms, were significantly less likely to benefit from a placebo. The moderating effect of self-reported anhedonia this study detected is consistent with prior literature linking reward processing with the placebo effect, albeit indirectly (Benedetti et al., 2005; Faria et al., 2008; Murray & Stoessl, 2013; Peciña et al., 2015; Schweinhardt et al., 2009; Scott et al., 2007). Anhedonia is an indicator of attenuated reward processing (Gong et al., 2018), and a large body of literature has identified the expectation of reward as an essential ingredient in the placebo response (Murray & Stoessl, 2013), which may indicate that anhedonia should be associated with a reduced likelihood of a placebo response. In

this sample, placebo non-responders self-reported significantly higher anhedonia scores relative to placebo responders. Taken together, these results, along with the prior literature, suggest that without in-tact reward system processing, the possibility of a placebo response is reduced.

The hypothesis that EEG activity in the rostral anterior cingulate cortex (rACC) would modulate placebo treatment response was partially supported. Based on prior literature suggesting that resting delta EEG activity is a useful index of mesolimbic reward system activity (Wacker et al., 2009), this study hypothesized that *increased* rACC delta EEG activity would attenuate the degree of placebo response. The data from this study did find that rACC delta activity moderated the degree of placebo response; however, this relationship was opposite of the direction hypothesized: *decreased* rACC delta EEG activity, not *increased*, was associated with an attenuated placebo response. Further, upon post-hoc analysis we found that rACC theta EEG activity accounted for a greater proportion of the variance in placebo response than rACC delta EEG activity. Given the high degree of intercorrelation among EEG frequency bands (Lazarev, 1998), it is likely that the moderating relationship of rACC theta EEG influenced the relationship of rACC delta to placebo treatment response. The moderating effect of pre-treatment rACC theta EEG activity is consistent with prior studies identifying rACC theta as a robust predictor of active antidepressant treatment response (D. A. Pizzagalli, 2011). This study extends these prior studies providing evidence of rACC theta EEG activity's potential utility as a moderator of both "active" antidepressant and placebo treatment response (Arns et al., 2015).

Although the link between higher baseline rACC theta activity and antidepressant non-response has been well-established in meta-analytical studies (Pizagalli, 2011), previous investigations have been unable to explain why (e.g. Arns, 2015; Pizzagalli, 2018). It is possible that elevated rACC theta activity is characteristic of a subtype of depression that is particularly

amenable to pharmacotherapy and the placebo effect. Marchetti (2012) reviewed a body of literature exploring the relationship of default mode network dysfunction to a potential type of recurrent depression. Given the central role of the rACC in the default mode network, it is possible that rACC theta activity is associated with a type of recurrent depression that exhibits dysfunction within this region.

Conclusions

Together, rACC theta activity and self-reported anhedonia scores were able to account for 20.6% of the variance in placebo treatment response. More specifically, higher pre-treatment theta activity and lower pre-treatment self-reported anhedonia scores were associated with a greater decrease in depression symptoms from before to after the intervention. If replicated, these findings may allow for identification of individuals who may benefit from a placebo and allow them to forego intolerable side effects that may present as a barrier to depression symptom reduction.

References

Arns, M., Etkin, A., Hegerl, U., Williams, L. M., DeBattista, C., Palmer, D. M., … Gordon, E. (2015). Frontal and rostral anterior cingulate (rACC) theta EEG in depression: implications for treatment outcome? *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*, *25*(8), 1190–1200. https://doi.org/10.1016/j.euroneuro.2015.03.007

Benedetti, F., Mayberg, H. S., Wager, T. D., Stohler, C. S., & Zubieta, J.-K. (2005). Neurobiological mechanisms of the placebo effect. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*. https://doi.org/10.1523/JNEUROSCI.3458-05.2005

Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. *Psychotherapy and Psychosomatics*, *85*(5), 270–288. https://doi.org/10.1159/000447034

Charlesworth, J. E. G., Petkovic, G., Kelley, J. M., Hunter, M., Onakpoya, I., Roberts, N., … Howick, J. (2017). Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *Journal of Evidence-Based Medicine*, *10*(2), 97–107. https://doi.org/10.1111/jebm.12251

Cipriani, A., Furukawa, T. A., Salanti, G., Geddes, J. R., Higgins, J. P., Churchill, R., … Barbui, C. (2009). Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* (*London, England)*, *373*(9665), 746–758. https://doi.org/10.1016/S0140-6736(09)60046-5

Faria, V., Fredrikson, M., & Furmark, T. (2008). Imaging the placebo response: a neurofunctional review. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*, *18*(7), 473–485. https://doi.org/10.1016/j.euroneuro.2008.03.002

Finniss, D. G., Kaptchuk, T. J., Miller, F., & Benedetti, F. (2010). Biological, clinical, and ethical advances of placebo effects. *Lancet* (*London, England)*, *375*(9715), 686–695. https://doi.org/10.1016/S0140-6736(09)61706-2

Gong, L., He, C., Zhang, H., Zhang, H., Zhang, Z., & Xie, C. (2018). Disrupted reward and cognitive control networks contribute to anhedonia in depression. *Journal of Psychiatric Research*, *103*, 61–68. https://doi.org/10.1016/j.jpsychires.2018.05.010

Greden, J. F. (2001). The burden of recurrent depression: causes, consequences, and future prospects. *The Journal of Clinical Psychiatry*, *62 Suppl 2*, 5–9. https://doi.org/0160-6689

Hirschfeld, R. M., Keller, M. B., Panico, S., Arons, B. S., Barlow, D., Davidoff, F., … Wyatt, R. J. (1997). The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. *JAMA*, *277*(4), 333–340. https://doi.org/10.1017/S1092852900001826

Howick, J., Friedemann, C., Tsakok, M., Watson, R., Tsakok, T., Thomas, J., … Heneghan, C. (2013). Are treatments more effective than placebos? A systematic review and meta-analysis. *PloS One*, *8*(5), e62599. https://doi.org/10.1371/journal.pone.0062599

Insel, T. R., & Cuthbert, B. N. (2015). Medicine. Brain disorders? Precisely. *Science* (*New York, N.Y.)*, *348*(6234), 499–500. https://doi.org/10.1126/science.aab2358

Kirsch, I. (2014). Antidepressants and the Placebo Effect. *Zeitschrift Für Psychologie*, *222*(3), 128–134. https://doi.org/10.1027/2151-2604/a000176

Kirsch, I., & Sapirstein, G. (1998). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prevention & Treatment*, *1*(2). https://doi.org/10.1037/1522-3736.1.1.12a

Knyazev, G. G. (2012). EEG delta oscillations as a correlate of basic homeostatic and motivational processes. *Neuroscience and Biobehavioral Reviews*, *36*(1), 677–695. https://doi.org/10.1016/j.neubiorev.2011.10.002

Korb, A. S., Hunter, A. M., Cook, I. A., & Leuchter, A. F. (2009). Rostral anterior cingulate cortex theta current density and response to antidepressants and placebo in major depression. *Clinical Neurophysiology*.

Lazarev, V. V. (1998). On the intercorrelation of some frequency and amplitude parameters of the human EEG and its functional significance. Communication II: Neurodynamic imbalance in endogenous asthenic-like disorders. *International Journal of Psychophysiology*, *29*(3), 277–289. https://doi.org/10.1016/S0167-8760(98)00008-7

McCarthy, D. (1991). Behavioral detection theory: Some implications for applied human research. In J. Nevin, M. Davison, & M. Commons (Eds.), *Signal Detection: Mechanisms, Models, and Applications* (pp. 239–255). Hillsdale, New Jersey: Erlbaum.

Mulert, C., Juckel, G., Brunnmeier, M., Karch, S., Leicht, G., Mergl, R., … Pogarell, O. (2007). Prediction of treatment response in major depression: Integration of concepts. *Journal of Affective Disorders*. https://doi.org/10.1016/j.jad.2006.07.021

Murray, D., & Stoessl, A. J. (2013). Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. *Pharmacology & Therapeutics*. https://doi.org/10.1016/j.pharmthera.2013.07.009

Pascual-Marqui, R. D., Lehmann, D., Koenig, T., Kochi, K., Merlo, M. C. G., Hell, D., &

Koukkou, M. (1999). Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. *Psychiatry Research*, *90*(3), 169–179. https://doi.org/10.1016/S0925-4927(99)00013-X

Peciña, M., Bohnert, A. S. B., Sikora, M., Avery, E. T., Langenecker, S. A., Mickey, B. J., & Zubieta, J.-K. (2015). Association Between Placebo-Activated Neural Systems and Antidepressant Responses: Neurochemistry of Placebo Effects in Major Depression. *JAMA Psychiatry*, *72*(11), 1087–1094. https://doi.org/10.1001/jamapsychiatry.2015.1335

Petkovic, G., Charlesworth, J. E. G., Kelley, J., Miller, F., Roberts, N., & Howick, J. (2015). Effects of placebos without deception compared with no treatment: protocol for a systematic review and meta-analysis. *BMJ Open*, *5*(11), e009428. https://doi.org/10.1136/bmjopen-2015-009428

Petrovic, P., Dietrich, T., Fransson, P., Andersson, J., Carlsson, K., & Ingvar, M. (2005). Placebo in Emotional Processing— Induced Expectations of Anxiety Relief Activate a Generalized Modulatory Network. *Neuron*, *46*(6), 957–969. https://doi.org/10.1016/j.neuron.2005.05.023

Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *36*(1), 183–206. https://doi.org/10.1038/npp.2010.166

Pizzagalli, D. A., Holmes, A. J., Dillon, D. G., Goetz, E. L., Birk, J. L., Bogdan, R., … Fava, M. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated subjects with major depressive disorder. *American Journal of Psychiatry*, *166*(June), 702–710. https://doi.org/10.1176/appi.ajp.2008.08081201.Reduced

Pizzagalli, D. A., Iosifescu, D., Hallett, L. A., Ratner, K. G., & Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *Journal of Psychiatric Research*, *43*(1), 76–87. https://doi.org/10.1016/j.jpsychires.2008.03.001

Pizzagalli, D. A., Jahn, A. L., & O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biological Psychiatry*, *57*(4), 319–327. https://doi.org/10.1016/j.biopsych.2004.11.026

Pizzagalli, D., Pascual-Marqui, R. D., Nitschke, J. B., Oakes, T. R., Larson, C. L., Abercrombie, H. C., … Davidson, R. J. (2001). Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *The American Journal of Psychiatry*, *158*(3), 405–415. https://doi.org/10.1176/appi.ajp.158.3.405

Price, D. D., Finniss, D. G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: recent advances and current thought. *Annual Review of Psychology*, *59*(1), 565–590. https://doi.org/10.1146/annurev.psych.59.113006.095941

Rentzsch, J., Adli, M., Wiethoff, K., Gómez-Carrillo De Castro, A., & Gallinat, J. (2014). Pretreatment anterior cingulate activity predicts antidepressant treatment response in major depressive episodes. *European Archives of Psychiatry and Clinical Neuroscience*. https://doi.org/10.1007/s00406-013-0424-1

Rief, W., Nestoriuc, Y., Weiss, S., Welzel, E., Barsky, A. J., & Hofmann, S. G. (2009). Meta-analysis of the placebo response in antidepressant trials. *Journal of Affective Disorders*, *118*(1–3), 1–8. https://doi.org/10.1016/j.jad.2009.01.029

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., … Keller,

M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*, *54*(5), 573–583. https://doi.org/10.1016/S0006-3223(02)01866-8

Schweinhardt, P., Seminowicz, D. A., Jaeger, E., Duncan, G. H., & Bushnell, M. C. (2009). The Anatomy of the Mesolimbic Reward System: A Link between Personality and the Placebo Analgesic Response. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.5634-08.2009

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., & Zubieta, J.-K. (2007). Individual differences in reward responding explain placebo-induced expectations and effects. *Neuron*, *55*(2), 325–336. https://doi.org/10.1016/j.neuron.2007.06.028

Shankman, S. A., Katz, A. C., DeLizza, A. A., Sarapas, C., Gorka, S. M., & Campbell, M. L. (2014). The different facets of anhedonia and their associations with different psychopathologies. In *Anhedonia: A Comprehensive Handbook Volume I: Conceptual Issues and Neurobiological Advances*. https://doi.org/10.1007/978-94-017-8591-4_1

Simon, G. E., & Perlis, R. H. (2010). Personalized medicine for depression: can we match patients with treatments? *The American Journal of Psychiatry*, *167*(12), 1445–1455. https://doi.org/10.1176/appi.ajp.2010.09111680

Tenke, C. E., Kayser, J., Pechtel, P., Webb, C. A., Dillon, D. G., Goer, F., … Bruder, G. E. (2017). Demonstrating test-retest reliability of electrophysiological measures for healthy adults in a multisite study of biomarkers of antidepressant treatment response. In *Psychophysiology*. https://doi.org/10.1111/psyp.12758

Trivedi, M. H., McGrath, P. J., Fava, M., Parsey, R. V, Kurian, B. T., Phillips, M. L., …

Weissman, M. M. (2016). Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design. *Journal of Psychiatric Research*, *78*(1), 11–23. https://doi.org/10.1016/j.jpsychires.2016.03.001

Wacker, J., Dillon, D. G., & Pizzagalli, D. A. (2009). The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. *NeuroImage*, *46*(1), 327–337. https://doi.org/10.1016/j.neuroimage.2009.01.058

Walsh, B. T., Seidman, S. N., Sysko, R., & Gould, M. (2002). Placebo Response in Studies of Major Depression. *JAMA*, *287*(14), 1840. https://doi.org/10.1001/jama.287.14.1840

Wampold, B. E., Minami, T., Tierney, S. C., Baskin, T. W., & Bhati, K. S. (2005). The placebo is powerful: Estimating placebo effects in medicine and psychotherapy from randomized clinical trials. *Journal of Clinical Psychology*. https://doi.org/10.1002/jclp.20129

Watson, D., Clark, L. A., Weber, K., Assenheimer, J. S., Strauss, M. E., & McCormick, R. A. (1995). Testing a Tripartite Model: II. Exploring the Symptom Structure of Anxiety and Depression in Student, Adult, and Patient Samples. *Journal of Abnormal Psychology*, *104*(1), 15–25. https://doi.org/10.1037/0021-843X.104.1.15

Chapter 4: Cognitive Defusion

Introduction

Cognitive theories of major depression (Haaga, Dyck, & Ernst, 1991; Williams, Watts, MacLeod, & Mathews, 1988) propose that repetitive, negative automatic thoughts about the self, the world, and the future characterize depressive cognition. Cognitive therapy, a component of cognitive behavioral therapy, was developed to challenge and change negative automatic thoughts associated with depression toward less emotionally salient and more helpful thoughts (Beck, Rush, Shaw, & Emery, 1979). Cognitive behavioral therapy is widely considered to be the gold standard treatment for depression (Butler, Chapman, Forman, & Beck, 2006).

A study by Deldin and colleagues (2001) provided support for the cognitive theory of depression using neurophysiological methods. Deldin et al. reported that healthy controls demonstrated preferential processing of positively valenced stimuli relative to negatively valenced stimuli, whereas individuals with depression did not demonstrate such an affective bias. More specifically, they found that healthy controls, but not individuals with depression, demonstrated an enhanced P300 event-related potential during encoding of positively valenced stimuli, relative to negatively valenced stimuli, and P300 was attenuated during recognition of positively valenced stimuli, relative to negatively valenced stimuli. Follow-up studies examining the slow-wave ERP component provided further evidence for a lack of a positivity bias in depression (Deveney & Deldin, 2004; Shestyuk, Deldin, Brand, & Deveney, 2005). Taken

together, these studies suggest that individuals with depression do not demonstrate the bias towards positively valenced stimuli that is detected in healthy control samples. Further, through the recording of event related potentials (ERPs), these studies were able to overcome self-report biases in order to examine cognition in depression to provide insight into the black box of the mind (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Garcia-Toro & Aguirre, 2007; Trivedi & Greer, 2014).

Two frequently studied ERPs are P300, an event-related potential with a peak positive polarity approximately 300ms post-stimulus onset, and No-Go N200, an ERP component with a peak negative polarity approximately 250-400 milliseconds post-stimulus (Patel & Azzam, 2005). P300 is an event-related potential with a peak positive polarity approximately 300ms post-stimulus onset (Duncan et al., 2009) and robustly elicited during oddball tasks, such as the Go/NoGo task, in which a subject responds to an infrequent target stimulus in a series of frequent nontarget stimuli (Duncan et al., 2009). Common analytical strategies for quantifying P300 and N200 are to measure a) latency from stimulus presentation to peak positive amplitude and b) peak amplitude (Duncan et al., 2009). P300 amplitude is thought to index resource allocation for higher-order cognitive operations involved in stimulus evaluation and categorization (Donchin & Coles, 1988; McCarthy & Donchin, 1981). P300 latency is thought to index classification speed, or the time required to detect and evaluate the target stimulus (Kutas, Mccarthy, & Donchin, 1977; Magliero, Bashore, Coles, & Donchin, 1984). No-go N200 amplitude has been argued by some to index response inhibition (Eimer, 1993; Van Boxtel, 2001), while others have argued for the conflict monitoring hypothesis of N200 stating that N200 is not only associated with response inhibition, but also response execution (Donkers & Van

Boxtel, 2004; Folstein & Van Petten, 2008; Nieuwenhuis, Yeung, Van Den Wildenberg, & Ridderinkhof, 2003).

P300 event related brain potential has received substantial attention in cognitive and affective neuroscience investigations due to its association with depression symptomology (Davidson et al., 2002; Garcia-Toro & Aguirre, 2007; Trivedi & Greer, 2014). Prolonged P300 latency has been associated with affective symptoms of depression, whereas reduced P300 amplitude has been associated with psychotic symptoms co-occuring with depression (Karaaslan, Gonul, Oguz, Erdinc, & Esel, 2003). More recently, Tripathi and colleagues (2015) found a linear relationship between P300 latency and depression severity whereby longer P300 latencies were associated with higher depression severity. In addition to the early evidence by Deldin and colleagues (2001) described above, evidence for biases during the processing of emotional stimuli in individuals with depression was also obtained by Cavanagh and Geisler (2006) for midline electrode sites. They recorded ERPs during a visual oddball task in which neutral faces served as standards and happy or fearful faces were targets, and they found that participants with depression had reduced P300 amplitude to happy faces when compared to individuals without depression. Providing further evidence of altered processing of facial stimuli in depression several studies have reported reduced right posterior No-Go N200 amplitude in response to facial stimuli among individuals with depression (Keller, Gergen, Miller, & Deldin, 2000; Sumich, Kumari, Heasman, Gordon, & Brammer, 2006). During an investigation of emotional biases in depression, Sass et al. (2014) reported that individuals with depression lacked the attentional bias towards positively valenced stimuli that is present in healthy controls, as indexed by N200

during an emotional stroop task. Taken together, No-Go N200 and P300 may be useful indices for studying the cognitive and affective processes that are disrupted in depression

More recent studies have shifted focus to identifying how these neurophysiological indices of cognitive and affective dysfunction may relate to depression treatment. Karaaslan et al., (2003) found that auditory P300 latency in depression decreased from pre to post medication treatment to a comparable latency with the healthy control sample, and no significant differences in P300 latency change were detected by medication type. More recently, Işintaş, Ak, Erdem, Öz, & Özgen (2012) reported that prolonged pre-treatment P300 latency in depression was associated with positive pharmacotherapy treatment response, and treatment responders demonstrated a "normalized" P300 latency. Published studies investigating the relationship of N200 to depression treatment have mostly been negative (e.g. Liogier D'Ardhuy et al., 1999). In sum, during treatment, deficits in cognitive and affective processing, as indexed by P300 latency, may improve during treatment for depression.

Although many studies have investigated the relationship of cortical physiology to pharmacological interventions for depression (see Kemp, Gordon, Rush, & Williams [2008] for a review), there have been few published repeated-measures investigations of cortical physiology patterns over the course of psychotherapy interventions. Ge et al. (2011) reported prolonged P300 latency at baseline in participants with internet addiction disorder, and they found that positive response to CBT was associated with significant decreases in P300 latency. Moscovitch (2011) found that increased right relative to left to increased left relative to right changes in resting EEG alpha power in the frontal regions was associated with cognitive behavioral therapy (CBT) treatment gains in individuals with social anxiety disorder. The present study recruited a sample of college students scoring highly on a depression inventory to explore whether a brief

skill building session, focused on identifying ways to reduce cognitive and emotional biases, might be associated with changes in neurophysiological indices of cognitive and affective processing.

Cognitive Defusion

Cognitive defusion is a mindfulness-based technique that aims to reduce distress associated with negative automatic thoughts by "de-fusing" or creating psychological distance from thoughts (Masuda, Hayes, Sackett, & Twohig, 2004). In contrast to traditional cognitive behavior therapy, mindfulness-based interventions do not aim to change the content or the frequency of thoughts, but, rather, individuals' relationship with their thoughts (see Kross, 2001 for a comparison). The core aspect of mindfulness-based therapies is to shift from a self-immersed perspective where thoughts are viewed as reality to a self-distanced perspective where thoughts are treated as "just thoughts", which may or may not have grounding in reality. During defusion exercises, individuals practice describing their thoughts in the third person (e.g. "I notice I am having the thought that …") or they practice exercises such as repeating a thought over and over again or singing out thoughts in order to reduce the thought's believability. The degree to which individuals are able to defuse or create psychological distance from their thoughts has been reported to mediate the relationship between rumination and depression symptomology and may facilitate adaptive self-reflection (Mori & Tanno, 2015). Cognitive defusion has demonstrated efficacy comparable to the cognitive therapy technique of cognitive restructuring for reducing distress associated with disturbing thoughts (B. J. Deacon, Fawzy, Lickel, & Wolitzky-Taylor, 2011; Yovel, Mor, & Shakarov, 2014) and has received empirical support as a standalone intervention for the treatment of depression (Masuda et al., 2010) and eating and body image concerns (Mandavia et al., 2015).

Study aims

This study sought to examine whether taking a step back from self-immersed ruminative thinking via a cognitive defusion technique might be associated with an improvement in cognitive and affective processing, as indexed by P300 and No-Go N200.

Hypotheses

This study hypothesized that 1) a brief cognitive defusion intervention will be associated with a decrease self-reported negative emotion associated with a difficult situation, while a control condition that provided psychoeducation on sleep hygiene will not be associated with significant reductions in negative emotions. 2) P300 latency will decrease from before to after the intervention in the cognitive defusion condition, but not the control condition, and may demonstrate a relative bias towards positive stimuli relative to negative stimuli. 3) No-Go N200 amplitude, indexing attentional processes recruited for response inhibition, will increase in right posterior regions and demonstrate an enhancement towards positively valenced facial stimuli from before to after the intervention.

Methods

Participants

Participants were recruited through the University of Michigan undergraduate psychology subject pool and the University of Michigan Health Research, an online portal where people interested in participating in research can create a profile indicating that they would like to be contacted (IRB number: HUM00004760). Inclusion criteria were: (1) vision equal to or better than 20/30 on a Snelling chart, with correction if necessary; (2) no chronic medical condition (such as seizure disorders), developmental disability or organic brain syndrome such as

mood disorders secondary to head injuries that could affect the ERP results; (3) Patient Health Questionnaire-9 depression score greater than 10; and (4) right handed (to control for brain hemispheric lateralization that affects the ERP; confirmed by the Edinburgh Handedness Inventory). This study was approved by the University of Michigan Institutional Review Board (IRB number: HUM00105105).

A total of 51 participants were consented, 46 completed the study, and 44 were included in the final analyses (see Table 16: Descriptives for the Defusion Study). Four participants ended their study participation early due to other commitments, and one participant was ineligible due to a Patient Health Questionnaire score less than 10 upon study arrival. Two study completers were not included in final analyses due to self-reported bipolar disorder and self-reported history of stroke.

Table 16: Descriptives for the Defusion Study

	Defusion	Sleep Hygiene	p-value
Age	20.6±2.7	20.2±1.6	ns
Sex (F/M)	14/7	17/6	ns
BDI	25.5±7.5	26.7±6.4	ns
RRS	61.0±8.3	61.8±6.4	ns
CFQ	35.6±7.6	37.0±4.4	ns
DAS	160.7±24.8	155.7±10.5	ns
MASQ-GD	118.6±17.4	120.8±21.4	ns
MASQ-AD	103.2±6.3	104.0±5.6	ns
MASQ-AA	37.8±11.0	40.6±8.7	ns

Procedure

This cross-sectional study involved a baseline battery of computerized questionnaires assessing various facets of mental health, which were completed during the ERP hookup, followed by a mood induction, an emotional go no-go task, either an active or control intervention, a second mood induction, and a post-intervention emotional go no-go task.

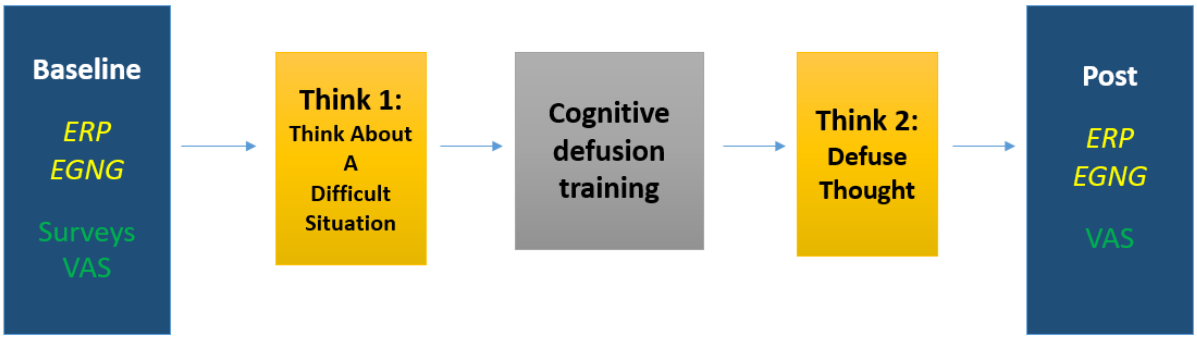

Figure 2: Defusion study flowchart

For the mood induction, participants were asked to think about a difficult life situation that has been bothering them the most recently. After the mood induction, participants completed a visual analog scale rating the intensity of positive (i.e. good, happy, calm, peaceful, excited) and negative emotions experienced (i.e. bad, guilt, fear, nervousness, sadness, anger, disgust). Next, participants completed an emotional go no-go task where they were asked to respond to certain valenced facial stimuli and ignore distractor neutrally valenced stimuli (e.g. press the space bar for happy faces, but not neutral faces) or, during other blocks, respond to neutrally valenced stimuli and ignore the distractor valanced (angry, happy, sad) stimuli. Participants were then randomized to receive either a cognitive defusion training session (see Appendix 3 for the cognitive defusion script) or a control condition (sleep hygiene; see Appendix 4 for the sleep hygiene script). After the intervention, participants in the control condition were asked to think about the same life difficulty again, while participants in the cognitive defusion group were asked to think about the same life difficulty, this time using the skills learned during the training session. Participants then completed a second visual analog assessment. Participants were then asked to complete the ERP tasks and for a second time.

Cognitive Defusion

Each participant engaged in a two-part introduction to cognitive defusion. The information provided is based upon the relational frame theory and acceptance and commitment therapy for depression (Hayes, Strosahl, & Wilson, 1999). The first 10-15 minutes of the session involved introducing individuals to the core concepts of ACT. Specifically, participants were introduced to the idea that attempting to "control" the mind can contribute to negative moods, and that willingness to experience unpleasant emotions can actually reduce them. The latter half of the session included a description of several methods for defusing negative automatic thoughts. Participants were given strategies to create psychological distance from their thoughts, and were informed that three ways to distance themselves from such thoughts include (a) repeat the difficult thought until you can notice the acoustic dimensions of the thought (b) treat the difficult thought as a monster on a bus you are driving (c) treat "the mind" as an external event; almost a separate person and thank your mind for that thought. The entire session lasted approximately 30 min, during which the experimenter was seated next to the participant with a small table between. To ensure full understanding of the information, several reality-based examples were provided with each concept, participants were given a review sheet, and prior to the next EEG recording session, participants were asked to review the material verbally with the experimenter. If necessary, additional examples were provided, and, if they chose, participants were given the opportunity to practice distancing themselves from their thoughts.

Emotional Go/NoGo

For the ERP recording, participants were seated in a darkened room 120 cm from the LCD monitor (60 Hz refresh rate). Participants completed twelve blocks of an emotional Go/NoGo task using facial stimuli of differing valences (happy, sad, angry, neutral) using the

keyboard while having their EEG recorded. All face stimuli consisted of grey-scaled faces with happy, sad, angry, and neutral expression from 32 individuals (9 female) taken from the NimStim set (Tottenham et al., 2009; http:// www.macbrain.org). In order to control race/ethnicity effect on amplitudes or latencies of ERP components, only Caucasian faces were used. All visual stimuli were created and presented via E-Prime software (Psychology Software Tools, Pittsburgh).

Each block contained two emotional valences, one as the target (Go) and one as the non-target (No-Go) stimuli, which were pseudorandomized across the blocks to control for presentation order effects. Three combinations of emotions (Happy-Neutral, Sad-Neutral, Angry-Neutral) were used as both the Go and NoGo stimuli. In order to obtain enough trails to complete the ERP analysis, these sets were repeated with a reversed order of stimulus presentation. Prior to each block, participants were instructed to respond to a particular emotion by pressing the spacebar, but not to respond to any other emotions as quickly as possible without making mistakes. In each trial, a fixation cross was presented for 500 ms followed by a facial image, which was presented for 150 ms on the center of the screen. The maximum amount of time to respond was1500ms. After completing a block, participants were shown the instructions for the next block followed by a 2000 ms fixation cross. Overall, they completed 50 trials per block (35 Go [70%] and 15 NoGo [30%]) in each of twelve blocks of the experiment, with a total of 600 trials.

Physiological preprocessing

The electroencephalogram (EEG) was recorded from 32 electrodes using an ActiCAP 32 (Brain Products GmbH, Germany) EEG cap. The electrode positions include all standard positions of the International 10/20 system. Common recording reference was set at FCz and

impedance was kept below 5 k Ω during the course of the study. Signals were digitally sampled at a sampling interval of 200 μS and a sampling rate of 5000 Hz. An electro-oculogram (EOG) electrode was placed beneath the left eye and at F7 to monitor eye blinks.

Vision Analyzer 2.0 (Brain Products GmbH, Germany) was used to preprocess and analyze the EEG data. P300 and No-Go N200 were analyzed including 9 caudal and lateral sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) consistent with scalp distribution analyses (D. Deacon, Breton, Ritter, & Vaughan, 1991). EEG data were re-referenced to Cz. A band-pass filter was set for 0.01 to 30 Hz, and data were down-sampled to 250Hz. The EOG artifact was corrected via the ocular correction independent components analysis (ICA) algorithm included within Vision Analyzer. The data were divided into 1150ms segments for each trial, beginning 150 ms prior to stimulus onset. Trials were baseline corrected and any trials containing any artifacts or were over 80μV in amplitude were eliminated before averaging. There were no significant between-group differences in NoGo response accuracy for any valence manipulation; therefore, to maximize statistical power, both correct and incorrect NoGo trials were included in the NoGo average. Further, NoGo waveforms with and without incorrect trials were visually inspected and did not exhibit any differences. To examine the relationship of the extracted ERP waveforms to prior literature, temporal principal components analysis (PCA) with varimax rotation was used. For the pre-intervention no-go trials, six temporal components were extracted corresponding to positive and negative fluctuations. The estimated P300 and No-Go N200 component windows were used to extract average amplitude for both go and no-go trials before and after the intervention.

Statistical Analysis

All statistical analyses were performed using the SPSS software package (Version 24.0, SPSS Inc, Chicago, USA). Outliers, defined as data points that fall beyond two standard deviations, were removed prior to statistical analyses. Significance values were calculated using the Wilks' lambda for the multivariate tests and the Greenhouse-Geisser correction for the tests of within-participant effects. Higher-order interactions for the ANOVA analyses were required to be significant for a lower-order interaction to be examined and for pair-wise comparisons to be conducted. Recruitment source was dropped from analyses that demonstrated no significant baseline differences.

Visual Analog Scale (VAS) data analysis

Baseline VAS responses for positively valenced and negatively valenced VAS scores were analyzed separately using a 2 x 2 x 2 x 5 mixed-effects ANOVA with time point (pre and post mood induction), Intervention (Defusion, control), Recruitment Source (UM subject pool, community), and emotion (happy, calm, excited, proud, good) for positively valenced emotions and a 2 x 2 x 2 x 7 mixed-effects ANOVA for negatively valenced emotions (sad, angry, scared, nervous, disgusted, bad, guilty). To examine for intervention effects, the time point effect was adjusted to add the additional level of VAS data collected after the post intervention mood induction. To test for post mood induction pre-post intervention effects among conditions, separate 2 x 5 and 2 x 7 ANOVAs were conducted to compare positively and negatively valenced emotions, respectively, from after the first mood induction to after the second mood induction.

Behavioral Data Analysis

Baseline reaction times (RT) to go stimuli on the emotional Go/NoGo task were examined using 2 x 2 x 3 repeated measures ANOVA with intervention (cognitive defusion or control) and recruitment source as between-groups factors, and valence (angry, sad, happy) as the within-groups factor. Baseline accuracy in responding to stimuli was examined using a 2 x 2 x 3 x 2 repeated measures ANOVA with intervention (cognitive defusion or control) and recruitment source as between-groups factors, and valence (angry, sad, happy) and trial type (go, no-go) as the within-groups factors. To examine for changes from before to after the intervention, an additional variable of time point (post mood induction 1, post mood induction 2) was added as a within-group factor to these models.

Physiological data analysis

Baseline No-Go N200 and P300 latencies to no-go stimuli were subjected to a 3 x 2 x 2 mixed-effects ANOVA with valence (happy, sad, angry) as the within-group factors and recruitment source (UM subject pool, community) and intervention (cognitive defusion or control) as the between-group factors, controlling for baseline emotional state. Baseline P300 amplitudes were also subjected to a mixed-effects ANOVA with the additional variable of stimuli (Go/NoGo). To examine for changes from before to after the intervention, an additional variable of time point (post mood induction 1, post mood induction 2) was added to these models. The clinical data obtained (i.e. Beck Depression Inventory II, Mood and Anxiety Symptom Questionnaire, Ruminative Responses Scale, Cognitive Defusion Questionnaire, Dysfunctional Attitudes Scale) were correlated with the electrophysiological findings.

Results

Negative emotions: changes detected

Between-subjects main effects for Negative emotion VAS data before and after the first think condition and prior to the intervention indicated no baseline differences by recruitment source ($F(1,40)=.917$, $P=.344$) or intervention condition ($F(1,40)=3.272$, $P=.078$), and no recruitment source by intervention interaction was detected ($F(1,40)=.302$, $p=.586$). For negative emotions, the mood induction prior to the intervention was effective, as demonstrated by a significant Main effect of timepoint (before & after) relative to the pre-intervention mood induction indicating that participants had more negative emotions after the Pre-intervention mood induction condition than before. ($F(1,40)=9.782$, $p<.01$). Changes in negative emotions from before to after the Pre-intervention mood induction condition were different by intervention group, as indicated by a significant Pre-Post by Intervention interaction ($F(1,40)=5.189$, $p=.028$); the defusion group had a greater increase in negative emotions from before to after the pre-intervention mood induction than SH did. Changes in negative emotions were not different by recruitment source as indicated by a non-significant Pre-Post by Group interaction ($F(1,40)=0.018$, $p=0.893$).

Significant differences by intervention condition were detected when examining changes in negative emotions across the research study as indicated by a Timepoint * Intervention interaction ($F(2,41)=12.704$, $p<.01$). Individuals in the defusion condition reported experiencing significantly less negative emotions after thinking about a difficult life situation using defusion than after thinking about the situation prior to learning defusion skills ($F(1,20)=42.109$, $p<.01$). Individuals in the control condition reported no changes in negative emotions after thinking

about a difficult life situation when compared to thinking about the difficult life situation after receiving psychoeducation on sleep hygiene ($F(1,22)=.165$, $p=.688$).

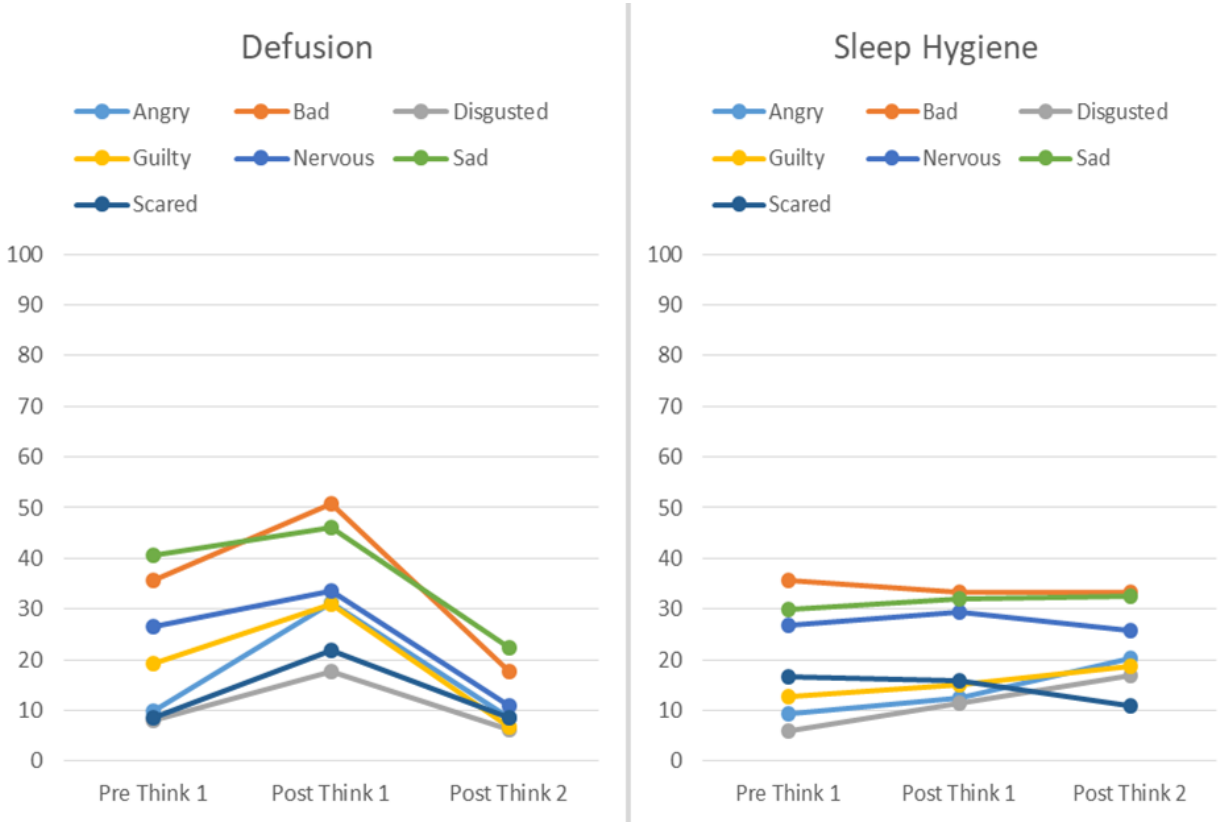

Figure 3: Negative Emotions by Timepoint

Positive emotions: changes detected

Between-subjects main effects for Positive emotion VAS data before and after the first think condition and prior to the intervention indicated no baseline differences by recruitment source ($F(1,40)=1.152$, $P=.289$) or intervention condition ($F(1,40)=3.155$, $P=.083$), and no recruitment source by intervention interaction was detected ($F(1,40)=.032$, $p=.858$). For positive emotions, the mood induction prior to the intervention was effective, as demonstrated by a significant Main effect of timepoint (before & after) relative to the pre-intervention mood induction indicating that participants had less positive emotions after the Pre-intervention mood

induction condition than before ($F(1,40)=4.914$, $p=.032$). Changes in positive emotions from before to after the Pre-intervention mood induction condition were not different by intervention group or recruitment source, as indicated by a non-significant PrePost by Intervention interaction ($F(1,40)=.549$, $p=.463$) and a non-significant PrePost by Group interaction ($F(1,40)=0.154$, $p=0.697$)

Significant differences by intervention condition were detected when examining changes in positive emotions across the research study as indicated by a Timepoint * Intervention interaction ($F(2,41)=17.284$, $p<.01$). Individuals in the defusion condition reported experiencing significantly more positive emotions after thinking about a difficult life situation using defusion than after thinking about the situation prior to learning defusion skills ($F(1,20)=10.381$, $p<.01$). Individuals in the control condition reported no changes in positive emotions after thinking about a difficult life situation when compared to thinking about the difficult life situation after receiving psychoeducation on sleep hygiene ($F(1,22)=3.852$, $p=.062$).

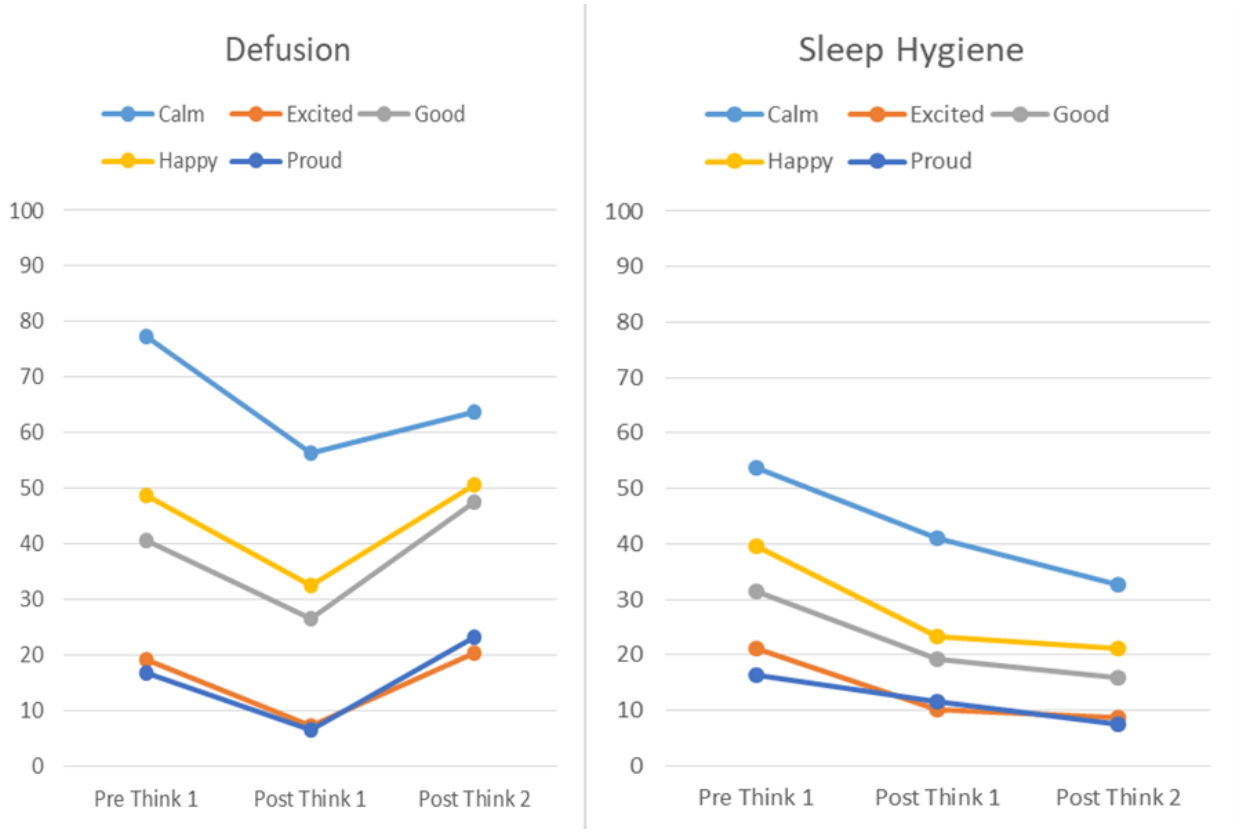

Figure 4: Positive emotions by timepoint

N200 Amplitude

A 234-182ms window was estimated from the temporal principal components analysis corresponding to N200 and was used to extract average N200 amplitudes across sites. After Think 1, Average N200 amplitude across caudal and lateral sites was equivalent across recruitment sources ($F(1,40)=.369$, $p=.547$) and intervention groups ($F(1,40)=1.702$, $p=.199$). Significant main effects of caudality ($F(2,80)=5.183$, $p=.026$) and laterality ($F(2,80)=4.944$, $p=.002$) were detected. N200 was larger over anterior sites relative to posterior sites. Consistent with the analysis of baseline data, main effects of caudality ($F(1,41)=13.491$, $p<.001$) and laterality ($F(1,41)=12.732$, $p=0.001$) were detected.

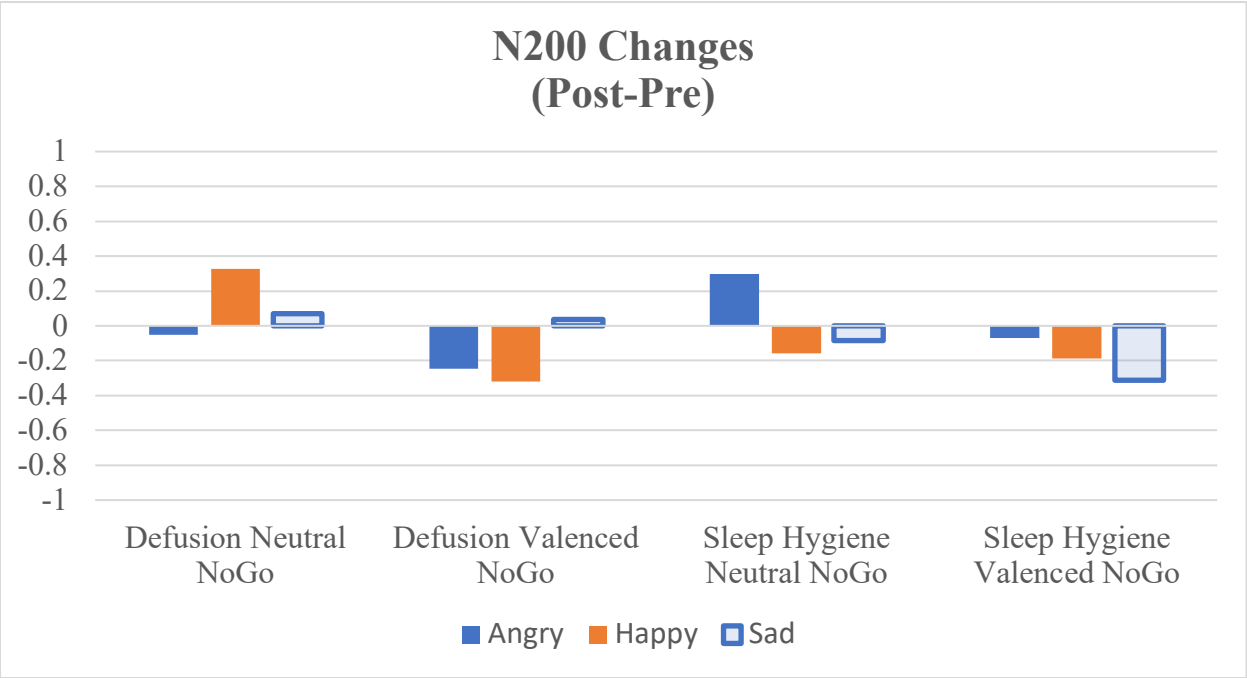

Figure 5: Changes in N200 Amplitude

A significant Pre-Post*Valence*Intervention interaction was detected ($F(2,40)=3.153$, $p=.048$). Analysis of the contrasts did not reveal any significant lower order effects. As shown in Figure 1, across valences, intervention groups, and timepoint, N200 amplitude varied. For the defusion group and on no-go trials with neutral stimuli contrasted by happy go stimuli, the N200 amplitude exhibited some attenuation, albeit not significantly, indicating that there was a trend towards less response inhibition being necessary to inhibit the neutral stimuli. For the sleep hygiene group on no-go trials with neutral stimuli contrasted by angry stimuli, the N200 also exhibited a non-significant trend toward reduced N200 amplitude for neutral no-go stimuli.

Figure 6: Changes in the ERP waveform

P300 Amplitude

P300 was initially analyzed including 9 caudal and lateral sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4); however, due to null results, the central-parietal site (Pz), where P300 is maximal (Polich, 2009), was selected to present P300 latency and amplitude findings here. A 290-475ms window was estimated from the temporal principal components analysis corresponding to P300 and was used to extract average P300 amplitudes at Pz. After Think 1, Average P300 amplitude at Pz was equivalent across intervention groups ($F(1,40)=.577$, $P=.452$). P300 amplitude was significantly greater among the UM psychology subject pool sample when compared to the community sample ($F(1,40)=4.166$, $p=0.048$); however, no recruitment source by intervention group interaction was detected ($F(1,40)=.297$, $p=.589$). A significant main effect of stimuli valence indicated differences across participants and Go-NoGo trials ($F(2,80)=3.940$, $p=.025$). P300 amplitude was greatest in response to Angry stimuli (4.51) when compared to Happy (4.09) and Sad (4.09) stimuli, which were similar in amplitude. A significant main effect of trial type indicated differences between go and no-go trials across participants and valences ($F(1,80)=10.824$, $p<.01$). P300 amplitude was higher on go trials (4.70) relative to no-go trials

(4.06). Pearson's correlational analyses found significant associations of baseline P300 amplitude to the anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire for happy-go ($r(44)=.276$, $p=.04$), sad-go ($r(44)=.254$, $p=.048$), and sad-no-go trials ($r(44)=.295$, $p=.026$); however, when entered together into a multivariate analysis, no significant main effects or interactions were present.

Consistent with the analysis of baseline data, main effects of valence ($F(2,83)=5.878$, $p<.01$) and trial type (go, no-go; $F(1,42)=4.976$, $p=0.031$) were detected. No significant differences in P300 amplitude were present from the first to second time point ($F(1,42)=0.127$, $p=0.723$), and no differences were detected between intervention groups.($F(1,42)=1.229$, $p=0.274$). A non-significant time point by intervention interaction indicated that P300 amplitude did not significantly change from before to after the intervention by intervention condition ($F(1,42)=0.619$, $p=.436$). Consistent with these lower-order findings, a lack of significant higher order interactions in the model indicated that, overall, no changes in P300 amplitude were detected from before to after the intervention for either intervention group.

P300 Latency

P300 elicited from no-go responses at baseline and Pz showed an average latency of 364ms for angry stimuli, 362 for sad, and 360 for happy. No main effect of valence was detected at baseline ($F(2,78)=0.838$, $p=.433$). After Think 1, Average P300 latency at Pz was equivalent across intervention groups ($F(1,40)=.093$, $P=.761$) and recruitment sources ($F(1,40)=1.99$, $p=.166$), and a recruitment source by intervention interaction was not present at baseline ($F(1,1.408$, $p=.242$). Baseline P300 latency in this study was unrelated to measures of depression or anxiety severity.

No significant differences in P300 latency were detected from the first to second time point ($F(1,42)=1.083$, $p=0.304$), and a PrePost*Intervention interaction found no significant differences P300 latency changes between intervention groups ($F(1,42)=0.075$, $p=0.785$). Consistent with these lower-order findings, a lack of significant higher order interactions in the model indicated that, overall, no changes in P300 latency were detected from before to after the intervention for either intervention group.

Behavioral Accuracy

For emotion go-no go data, accuracy in appropriately responding to go but not no-go stimuli was equivalent at baseline across both recruitment sources ($F(1,40)=.129$, $P=.721$) and intervention conditions ($F(1,40)=3.755$, $P=.060$), and no recruitment source by intervention interaction was detected ($F(1,40)=.746$, $p=.705$). A significant main effect of valence was detected, with accuracy being greatest for happy stimuli and lowest for sad stimuli ($F(2,39)=22.040$, $p<.01$). A significant main effect of Go-NoGo was detected, with accuracy being greater on go trials than no-go trials ($F(1,40)=9.057$, $p<.01$).

An analysis of differences from before to after the intervention revealed a significant 3-way interaction among time point, trial type (go, no-go), and intervention condition ($F(1,40)=42.00$, $p=0.045$). Separate analyses by intervention group revealed no differences from before to after the intervention in accuracy for the defusion group ($F(1,20)=3.488$, $p=0.077$). For the sleep hygiene group, accuracy increased on no-go trials and decreased on go trials ($F(1,22)=34.715$, $p<.01$).

Behavioral Reaction Time

For emotion go-no go data, reaction time in responding to go stimuli was equivalent at baseline across both recruitment sources ($F(1,40)=.258$, $P=.614$) and intervention

($F(1,40)=1.037$, $P=.315$) at baseline, and no recruitment source by intervention interaction was detected ($F(1,40)=1.171$, $p=.286$). A significant main effect of valence was detected, with reaction time being quickest for happy stimuli and slowest for sad stimuli ($F(2,80)=33.664$, $p<.01$).

An analysis of differences from before to after the intervention revealed significant main effects of time point and valence. Average reaction time from before to after the intervention decreased by 19 ms across participants in both intervention conditions ($F(1,42)=9.418$, $p=.004$). This study found a non-significant main effect of intervention ($F(0.658$, $p=0.422$), non-significant time point by intervention interaction ($F(1,42)=1.869$, $p=0.179$), and non-significant higher-order interactions among time point and intervention variables. Together, these results indicated no differences in reaction time by intervention group from before to after the intervention.

Discussion

Cognitive theories of major depression (Haaga et al., 1991; Williams et al., 1988) have described repetitive negative automatic thinking patterns and perseverative cognition as contributing factors to depression symptomology. Cognitive defusion is an empirically supported intervention (Mandavia et al., 2015; Masuda et al., 2010) that is used to train participants to create psychological distance from their thoughts (Kross, 2001; Masuda et al., 2004) in order to facilitate adaptive self-reflection (Mori & Tanno, 2015), interrupt perseverative cognitions and reduce distress associated with thoughts (B. J. Deacon et al., 2011; Yovel et al., 2014). The present study examined whether a cognitive defusion intervention is able to produce changes cognitive and affective processing and emotional experience immediately after thinking about a

distressing experience. This study provided preliminary evidence that a brief one session cognitive defusion intervention may reduce the experience of negative emotion when thinking about difficult situations, may increase the experience of positive emotion, and may alter cognitive affective processing.

Two ERPs thought to index cognitive affective processing were investigated in relationship to the course of treatment: P300 and N200. P300 is an event related potential thought to index resource allocation for higher-order cognitive operations involved in stimulus evaluation and categorization (Donchin & Coles, 1988; McCarthy & Donchin, 1981), and NoGo N200 has been reported to be associated with response inhibition, frequently detected during Go/NoGo paradigm (Eimer, 1993; Van Boxtel, 2001). Results from a principal components analysis indicated that the findings from this study were consistent with prior studies of response inhibition using the Go/NoGo task that reported the presence of the N200 ERP component in a time window of 250-400 milliseconds post-stimulus and the P300 component in a time window between 300 and 600 milliseconds after stimulus onset. In this study, the N200 and P300 occurred 235-285 milliseconds and 290-475 milliseconds post stimulus, respectively. In this study, both N200 and P300 were larger on NoGo trials than Go trials, which suggests that inhibiting responses to less frequent NoGo trials requires more attentional resources than executing responses for Go stimuli (for a review see Folstein & Van Petten, 2008; Polich, 2009).

Prior studies have reported a reduction of P300 latency from before to after antidepressant pharmacotherapy for depression (Işintaş et al., 2012; Karaaslan et al., 2003; Kemp et al., 2008). Further, Ogura and colleagues (1993) reported reduced N200 amplitude in 36 individuals with depression relative to healthy controls that normalized after a course pharmacotherapy. EEG changes have also been detected during psychotherapy (Moscovitch et

al., 2011). A reduction in P300 latency was detected after cognitive behavioral therapy for internet addiction (Ge et al., 2011). The present study used an emotional go-no oddball task (Duncan et al., 2009) to elicit an N200 and a P300 response in individuals with dysphoria.

This study found significant changes in attentional resources allocated to response inhibition on no-go trials, as indexed by the N200 ERP, were detected. Due to insignificant lower-order contrasts, this finding cannot be significantly parsed apart more separately; however, individuals in the defusion condition trended towards requiring less attentional resources to inhibit responses (smaller N200) to neutral stimuli during blocks with happy go trials, whereas individuals in the sleep hygiene control condition trended towards requiring less attentional resources to inhibit responses to neutral stimuli during blocks with angry go trials. This study expands on results from Ogura et al. (1993) by indicating the moderating role of stimulus valence in measuring N200 in individuals with dysphoria.

Contrary to the study hypothesis, this exploratory study found no significant changes in Emotional Go No Go task performance or P300 characteristics from before to after a brief one session cognitive defusion intervention. A significant relationship between baseline P300 amplitude and the anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire was detected; however, it was in the opposite direction than was expected. While prior studies have reported attenuated P300 amplitudes in depression (Cavanagh & Geisler, 2006; Patricia J. Deldin, Deveney, Kim, Casas, & Best, 2001; Deveney & Deldin, 2004; Shestyuk et al., 2005), data from this study indicated that higher scores on the anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire was associated with increased P300 amplitude to positively valanced stimuli. Further, in contrast to prior studies that reported a positive relationship between prolonged P300 latency and depression severity (Işintaş

et al., 2012; Karaaslan et al., 2003; Tripathi et al., 2015), baseline P300 latency was unrelated to measures of depression or anxiety symptom severity.

Limitations

Several limitations of the present study should be noted. First, the present study recruited individuals who scored highly on a measure of depression symptomology (Patient Health Questionnaire, score > 10), but did not formally diagnose study participants. Second, half of the study participants came from the University of Michigan psychology subject pool and were currently enrolled students, which limited the range of depression severity and cognitive dysfunction in that sample due to high cognitive demands associated with active enrollment in a university setting. Another limitation is the short temporal duration that was provided to participants to acquire and practice implementing the cognitive defusion techniques ~(45 min) may not have been sufficient to produce meaningful improvements in cognitive affective processing, and it is possible that the effect size that cognitive defusion might have on cognitive processing, if one exists, may be too small to detect with a participant sample of this size. Further, we chose to maximize statistical power by including incorrect NoGo trials within our analyses, and although there were no significant differences in NoGo accuracy among any of the comparisons we made, it is possible that error related neural responses (Gehring, Goss, Coles, Meyer, & Donchin, 1993) on incorrect NoGo trials may have biased our N200 amplitude findings. Lastly, the lack of a control sample and baseline equivalence between treatment conditions limit these findings; however, by utilizing a mixed-effects design and accounting for baseline differences within the model, this study attempted to minimize the effect of baseline differences on outcome results.

Conclusions

In sum, the present study demonstrated that a brief cognitive defusion training session may reduce emotional discomfort associated with distressing thoughts, may alter socio-emotional responses to affective stimuli, and may possibly increase positive emotions, perhaps related to feelings of agency over distressing thoughts. Further, the present study demonstrated the feasibility and positive participant response to a brief psychotherapy intervention in the context of an undergraduate psychology subject pool. Future studies may benefit from examining the individual components of psychotherapy interventions, such as cognitive defusion, to identify tools and techniques for aiding individuals in emotion regulation.

References

Beck, A. T., Rush, A., Shaw, B., & Emery, G. (1979). *Cognitive therapy of depression*. *Cognitive Therapy of Depression*.

Butler, A. C., Chapman, J. E., Forman, E. M., & Beck, A. T. (2006). The empirical status of cognitive-behavioral therapy: A review of meta-analyses. *Clinical Psychology Review*, *26*(1), 17–31. https://doi.org/10.1016/j.cpr.2005.07.003

Cavanagh, J., & Geisler, M. W. (2006). Mood effects on the ERP processing of emotional intensity in faces: A P3 investigation with depressed students. *International Journal of Psychophysiology*, *60*(1), 27–33. https://doi.org/10.1016/j.ijpsycho.2005.04.005

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002). Depression: Perspectives from Affective Neuroscience. *Annual Review of Psychology*, *53*(1), 545–574. https://doi.org/10.1146/annurev.psych.53.100901.135148

Deacon, B. J., Fawzy, T. I., Lickel, J. J., & Wolitzky-Taylor, K. B. (2011). Cognitive Defusion Versus Cognitive Restructuring in the Treatment of Negative Self-Referential Thoughts: An Investigation of Process and Outcome. *Journal of Cognitive Psychotherapy*, *25*(3), 218–232. https://doi.org/10.1891/0889-8391.25.3.218

Deacon, D., Breton, F., Ritter, W., & Vaughan, H. G. (1991). The Relationship Between N2 and N400: Scalp Distribution, Stimulus Probability, and Task Relevance. *Psychophysiology*. https://doi.org/10.1111/j.1469-8986.1991.tb00411.x

Deldin, P. J., Deveney, C. M., Kim, A. S., Casas, B. R., & Best, J. L. (2001). A slow wave investigation of working memory biases in mood disorders. *Journal of Abnormal Psychology*, *110*(2), 267–281. https://doi.org/10.1037/0021-843X.110.2.267

Deldin, P. J., Keller, J., Gergen, J. A., & Miller, G. A. (2001). Cognitive bias and emotion in neuropsychological models of depression. *Cognition and Emotion*, *15*(6), 787–802. https://doi.org/10.1080/02699930143000248

Deveney, C. M., & Deldin, P. J. (2004). Memory of faces: A slow wave ERP study of major depression. *Emotion*, *4*(3), 295–304. https://doi.org/10.1037/1528-3542.4.3.295

Donchin, E., & Coles, M. G. H. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences*. https://doi.org/10.1017/S0140525X00058027

Donkers, F. C. L., & Van Boxtel, G. J. M. (2004). The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. *Brain and Cognition*. https://doi.org/10.1016/j.bandc.2004.04.005

Duncan, C. C., Barry, R. J., Connolly, J. F., Fischer, C., Michie, P. T., Näätänen, R., … Van Petten, C. (2009). Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology*, *120*(11), 1883–1908. https://doi.org/10.1016/j.clinph.2009.07.045

Eimer, M. (1993). Effects of attention and stimulus probability on ERPs in a Go/Nogo task. *Biological Psychology*, *35*(2), 123–138. https://doi.org/10.1016/0301-0511(93)90009-W

Folstein, J. R., & Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: A review. *Psychophysiology*, *45*(1), 152–170. https://doi.org/10.1111/j.1469-8986.2007.00602.x

Garcia-Toro, M., & Aguirre, I. (2007). Biopsychosocial model in Depression revisited. *Medical Hypotheses*, *68*(3), 683–691. https://doi.org/10.1016/j.mehy.2006.02.049

Ge, L., Ge, X., Xu, Y., Zhang, K., Zhao, J., & Kong, X. (2011). P300 change and cognitive behavioral therapy in subjects with Internet addiction disorder: A 3-month follow-up study .

Neural Regeneration Research . https://doi.org/http://dx.doi.org/10.3969/j.issn.1673-5374.2011.26.007

Gehring, Goss, Coles, Meyer, & Donchin. (1993). A neural system for error detection and conpensation. *Psychological Science*, *4*(6), 385–390.

Haaga, D. A., Dyck, M. J., & Ernst, D. (1991). Empirical status of cognitive theory of depression. *Psychological Bulletin*, *110*(2), 215–236. https://doi.org/10.1037/0033-2909.110.2.215

Hayes, S. C., Strosahl, K. D., & Wilson, K. G. (1999). *Acceptance and commitment therapy: An experiential approach to behavior change*. *New York*. http://dx.doi.org/10.1016/S1077-7229(02)80009-8

Işintaş, M., Ak, M., Erdem, M., Öz, O., & Özgen, F. (2012). Event-related potentials in major depressive disorder: The relationship between P300 and treatment response. *Turk Psikiyatri Dergisi*. https://doi.org/10.5080/u6650

Karaaslan, F., Gonul, A. S., Oguz, A., Erdinc, E., & Esel, E. (2003). P300 changes in major depressive disorders with and without psychotic features. *Journal of Affective Disorders*, *73*(3), 283–287. https://doi.org/10.1016/S0165-0327(01)00477-3

Keller, J., Gergen, J. A., Miller, G. A., & Deldin, P. J. (2000). Right-posterior face processing anomaly in depression. *Journal of Abnormal Psychology*. https://doi.org/10.1037//0021-843X.109.1.116

Kemp, B. A. H., Gordon, E., Rush, A. J., & Williams, L. M. (2008). Improving the Prediction of Treatment Response in Depression : Integration of, (December), 1066–1086.

Kross, E. (2001). Mindfulness Training & Cognitive Behavioral Therapy in the context of Anxiety Disorders. *Perspectives in Psychology*, *Spring*, 3–13. Retrieved from

https://paloaltou.idm.oclc.org/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2012-14157-009

Kutas, M., Mccarthy, G., & Donchin, E. (1977). Augmenting Mental Chronometry: The P300 as a Measure of Stimulus Evaluation Time. *Source: Science, New Series*, *197*(4305), 792–795. Retrieved from http://www.jstor.org/stable/1744874

Liogier D'Ardhuy, X., Boeijinga, P. H., Renault, B., Luthringer, R., Rinaudo, G., Soufflet, L., … Macher, J. P. (1999). Effects of serotonin-selective and classical antidepressants on the auditory P300 cognitive potential. *Neuropsychobiology*, *40*(4), 207–213. https://doi.org/10.1159/000026621

Magliero, A., Bashore, T. R., Coles, M. G. H., & Donchin, E. (1984). On the Dependence of P300 Latency on Stimulus Evaluation Processes. *Psychophysiology*. https://doi.org/10.1111/j.1469-8986.1984.tb00201.x

Mandavia, A., Masuda, A., Moore, M., Mendoza, H., Donati, M. R., & Cohen, L. L. (2015). The application of a cognitive defusion technique to negative body image thoughts: A preliminary analogue investigation. *Journal of Contextual Behavioral Science*, *4*(2), 86–95. https://doi.org/10.1016/j.jcbs.2015.02.003

Masuda, A., Hayes, S. C., Sackett, C. F., & Twohig, M. P. (2004). Cognitive defusion and self-relevant negative thoughts: Examining the impact of a ninety year old technique. *Behaviour Research and Therapy*, *42*(4), 477–485. https://doi.org/10.1016/j.brat.2003.10.008

Masuda, A., Twohig, M. P., Stormo, A. R., Feinstein, A. B., Chou, Y.-Y., & Wendell, J. W. (2010). The effects of cognitive defusion and thought distraction on emotional discomfort and believability of negative self-referential thoughts. *Journal of Behavior Therapy and Experimental Psychiatry*, *41*(1), 11–17. https://doi.org/10.1016/j.jbtep.2009.08.006

McCarthy, G., & Donchin, E. (1981). A metric for thought: A comparison of P300 latency and reaction time. *Science*, *211*(4477), 77–80. https://doi.org/10.1126/science.7444452

Mori, M., & Tanno, Y. (2015). Mediating Role of Decentering in the Associations between Self-Reflection, Self-Rumination, and Depressive Symptoms. *Psychology*, *06*(05), 613–621. https://doi.org/10.4236/psych.2015.65059

Moscovitch, D. A., Santesso, D. L., Miskovic, V., McCabe, R. E., Antony, M. M., & Schmidt, L. A. (2011). Frontal EEG asymmetry and symptom response to cognitive behavioral therapy in patients with social anxiety disorder. *Biological Psychology*, *87*(3), 379–385. https://doi.org/10.1016/j.biopsycho.2011.04.009

Nieuwenhuis, S., Yeung, N., Van Den Wildenberg, W., & Ridderinkhof, K. R. (2003). Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial type frequency. *Cognitive, Affective and Behavioral Neuroscience*, *3*(1), 17–26. https://doi.org/10.3758/CABN.3.1.17

Ogura, C., Nageishi, Y., Omura, F., Fukao, K., Ohta, H., Kishimoto, A., & Matsubayashi, M. (1993). N200 component of event-related potentials in depression. *Biological Psychiatry*, *33*(10), 720–726. https://doi.org/10.1016/0006-3223(93)90122-T

Patel, S. H., & Azzam, P. N. (2005). Characterization of N200 and P300: Selected studies of the Event-Related Potential. *International Journal of Medical Sciences*, *2*(4), 147–154. https://doi.org/10.7150/ijms.2.147

Polich, J. (2009). Updating P300:An Integrative Theory of P3a and P3b. *Clin Neurophysiol*, *118*(10), 2128–2148. https://doi.org/10.1016/j.clinph.2007.04.019.Updating

Sass, S. M., Heller, W., Fisher, J. E., Silton, R. L., Stewart, J. L., Crocker, L. D., … Miller, G. A. (2014). Electrophysiological evidence of the time course of attentional bias in non-patients

reporting symptoms of depression with and without co-occurring anxiety. *Frontiers in Psychology*, *5*(APR), 1–11. https://doi.org/10.3389/fpsyg.2014.00301

Shestyuk, A. Y., Deldin, P. J., Brand, J. E., & Deveney, C. M. (2005). Reduced sustained brain activity during processing of positive emotional stimuli in major depression. *Biological Psychiatry*, *57*(10), 1089–1096. https://doi.org/10.1016/j.biopsych.2005.02.013

Sumich, A. L., Kumari, V., Heasman, B. C., Gordon, E., & Brammer, M. (2006). Abnormal asymmetry of N200 and P300 event-related potentials in subclinical depression. *Journal of Affective Disorders*, *92*(2–3), 171–183. https://doi.org/10.1016/j.jad.2006.01.006

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., … Nelson, C. (2009). The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Research*, *168*(3), 242–249. https://doi.org/10.1016/j.psychres.2008.05.006

Tripathi, S. M., Mishra, N., Tripathi, R. K., & Gurnani, K. C. (2015). P300 latency as an indicator of severity in major depressive disorder. *Industrial Psychiatry Journal*, *24*(2), 163–167. https://doi.org/10.4103/0972-6748.181726

Trivedi, M. H., & Greer, T. L. (2014). Cognitive dysfunction in unipolar depression: Implications for treatment. *Journal of Affective Disorders*, *152–154*(1), 19–27. https://doi.org/10.1016/j.jad.2013.09.012

Van Boxtel, A. (2001). Optimal signal bandwidth for the recording of surface EMG activity of facial, jaw, oral, and neck muscles. *Psychophysiology*, *38*(1), 22–34. https://doi.org/10.1017/S004857720199016X

Williams, J. M. G., Watts, F. N., MacLeod, C., & Mathews, A. (1988). *Cognitive psychology and emotional disorders*. *The Wiley series in clinical psychology*.

Yovel, I., Mor, N., & Shakarov, H. (2014). Examination of the core cognitive components of cognitive behavioral therapy and acceptance and commitment therapy: an analogue investigation. *Behavior Therapy*, *45*(4), 482–494. https://doi.org/10.1016/j.beth.2014.02.007

Appendix 1: Cognitive Defusion Script

Now I will tell you of a theory of how our mind can influence our feelings and moods. I will show you some ways that you can identify thoughts that your mind may be caught up in, and I will also show you some ways that you can get your mind off of the thoughts.

INTRODUCTION TO RELATIONAL FRAME THEORY

I will now tell you why research suggests that most of human suffering is due to human language. As humans, we are great problem solvers. For example, if you get a terrible haircut, you can choose to go back to your stylist or you may choose to see a new stylist and get a different haircut. Another example is if you don't like the color you just painted your walls, you can choose a new color and repaint them. However, we often wrongfully try to fix bad thoughts or feelings by trying to get rid of them in the same way you might fix your wall's paint color or change your haircut. We believe we should be able to control the way we think and feel in the same way we can control our hair and wall paint. When we experience thoughts that we don't want to have, we may try to fix or control our thoughts by telling our mind to be quiet or we may try to get rid of the thought by thinking about other things. However, this rarely works. Often the more we try to control our thoughts, the louder they become. If it is OK with you, I would like to do a quick experiment with you.

> *Please take a second and think of a pink elephant. Try to imagine what the pink elephant looks like and what it may be doing. (PAUSE) Now, for the next 20 seconds, I would like you to not think about pink elephants. You can think of anything else you'd like, but whatever you think about, don't think about pink elephants (Pause for ten seconds). What was that like? (PAUSE) Notice that when you try to not think of something such as pink elephants, that thought often becomes the thought that is at the forefront of your mind. The more you try to control the thought, the harder it becomes to ignore.*

When we become absorbed or stuck in our mind's cycle of thoughts, it can contribute to depressed mood. In this theory, becoming absorbed by our thoughts is called "thought fusion". In a state of thought fusion, we're completely focused on the thought: we're absorbed, fixated on, consumed by, or so caught up by the thought that we may not even be aware of the thought. We treat thoughts as though they are the literal or absolute truth, a command you have to obey, a description that is completely accurate, or a rule you have to follow. We may act as though the thought is a threat that you must get rid of as soon as possible, or something that is very important and requires all of your attention.

Thought fusion in and of itself is not bad-our mind naturally becomes absorbed by thoughts and naturally treats thoughts as reality. There are times when we may want to be fused with our thoughts. For example, when reading a novel, I want to be completely engaged and absorbed by the story so that I may enjoy reading the novel.

Is what I am saying clear?

In the next part, I will describe several types of thought fusion that can contribute to negative mood: “thoughts about the past”, “thoughts about the future”, “rules that our mind creates”, and “thoughts about the self”. [Hand the overview sheet to participants]

Thoughts about the past or future

The first type of thought fusion is “thoughts about the past or future”. “Thoughts about the past or future” can involve both unpleasant and pleasant thoughts such as fusion with bad memories, wishing to recapture positive experiences from the past, getting hooked by fears about the future, or wishing for brighter days ahead. These forms of thought fusion pull you out of the present moment.

Here is an example of fusion with “thoughts about the past”. Joe was trying to quit smoking, and he had not smoked any cigarettes for two months. One day at the supermarket, he bought a pack of Marlboros. As he left the market, Joe’s mind had the thought: “The last time I tried to quit smoking, I was not able to do it.” His mind also told him “The fact that I bought these cigarettes today is proof that *I have not been able to quit smoking*, and the next time is bound to be the same”. In this case, Joe’s mind is fused with the thought “I have not been able to quit smoking”. Fusion with the thought “I have not been able to quit smoking” made Joe feel guilty, disappointed, worthless, and hopeless about his ability to change. His mind is so stuck on his past failings that he does not realize he now has the ability to choose whether to use the cigarettes he has just purchased. When your mind is fused with thoughts of the past, it can keep you from recognizing the possibilities of the present.

Do you understand what I mean about “thoughts of the past” and how they can influence how you feel?

Thoughts about the past or future

“Thoughts about the future” are similar to “thoughts about the past”. They occur when you strongly desire the future to happen in a certain way. For example, Molly has an upcoming job interview. Her mind had the thought that it would be “terrible” if something were to go wrong and she loses control. She began to think about all the things that could go wrong, which made her even more nervous about the interview. In this case, Molly’s mind is fused with the thought “this interview will not go well”. Molly’s mind is so absorbed by thoughts about how the future *could* go that her thoughts are making her even more nervous about the upcoming interview. When your mind is fused with thoughts about the future, it can increase negative feelings such as anxiety, insecurity, and fear in the present, and it can keep you from feeling calm, cool, and confident. Fusion with thought about the future may also distract you from the present and keep you from thinking clearly.

Do you understand what I mean about “thoughts of the future” and how they can influence how you feel?

Mental Rules

Our mind can also become fused with “mental rules”. These rules are used to describe what our mind believes is right or wrong or what is good or bad. Rules created by our mind can often be identified by the words “should”, “must”, “ought”, “have to”, or “if-then”. For example, while Amy was on a diet, she ate two donuts, and afterwards her mind had the thought “I shouldn’t have eaten that donut. I should have resisted.” In this case, the rule Amy’s mind is fused with is “I must not eat any unhealthy foods”. When Amy broke her mind’s “mental rule”, it made her feel disappointed, ashamed, and inadequate.

Fused “Mental rules” may also be applied to others. For example, Fred was waiting for his wife to return from work so they could be on time for their dinner reservations. His mind was fused with the rule “We cannot be late”. Fred’s wife was late getting home, and his mind had the thought “She should be home now. She shouldn’t be late on a day we have plans!” Fred did not know why his wife was late from work, and an attitude of blame guaranteed a fight. In this case, Fred’s mind was fused with the rule “We cannot be late”, and Fred became frustrated and angry when his wife broke his mind’s mental rule even though he did not know her reasons for being late.

Fused “mental rules" may increase negative feelings if you feel that you or the other person have to follow the rule perfectly. When your mind becomes fused with “rules”, you will tend to make yourself feel disappointed if you do not follow your mind’s “rule”, and you may end up feeling guilty or frustrated with yourself. When you apply fused “rules” to others, you might feel anger or frustration toward the other person if they do not live up to the “rule” and it may make the situation worse. Another problem with fused “rules” is that they give certain situations much more emotional intensity than they really need.

Do you understand what I mean by fusion with “rules” and how they can influence your feelings and moods?

Thoughts about the self

“Thoughts about the self” occur when you use “I am” statements to describe yourself. These may be negative self-descriptions such as “I am stupid”, “I am ugly”, “I am unlovable”, “I am a loser”, or “I am a failure”. For example, Curtis was at home alone on a Friday night and his mind became absorbed by the thought “I am lonely”. This thought kept playing over and over in his mind, and it made him feel sad, isolated, and inferior. Fusion with the thought “I am lonely” prevented Curtis from thinking of things he could do to enjoy the evening such as calling a friend, watching a show, or going for a walk. In this case, fusion with a “thought about the self” fueled his negative mood and prevented Curtis from realizing the possibilities of the present such as doing an enjoyable activity.

Summary

Okay, now I have told you of three kinds of fused thoughts – thoughts about the past or future, mental rules, and thoughts about the self – and how they can cause negative feelings. In the

examples we discussed, the thoughts themselves are not the problem – these types of thoughts are not good or bad. The problem occurs when we become fused, absorbed, focused on, or stuck in these thoughts. When you are fused with your thoughts, you may be missing out on what is around you because you are not able to engage effectively. I'll now show you some ways to de-fuse or un-stick yourself from these thoughts.

INTRODUCTION TO COGNITIVE DEFUSION TECHNIQUES

One way you can reduce thought fusion is by using thought de-fusion exercises. Defusion means separating, detaching, untangling, or distancing ourselves from the thoughts that our mind has. In a state of defusion, you can see a thought for what it is: *just a* thought. In a state of defusion, you recognize that a thought may or may not be true; it is definitely not a command you have to obey or a rule you have to follow; it is definitely not a threat to you; it is not something happening in the real world – it is merely words or pictures inside your head; it may or may not be important. You have the choice to pay attention to the thought or not. When we use de-fusion exercises, we do not try to control the thoughts just like we could not control the thought of a pink elephant earlier. In a state of defusion, your thoughts may pass through your mind without any need for you to focus on the thought or to try to push the thought away.

Now we will discuss three ways that you can de-fuse yourself from fused thoughts. The first is called "observing the mind".

Observing the mind

Thought defusion works by noticing, naming, and neutralizing the fused thought. We want to be open and curious about the thoughts that our mind creates. The first way that you can begin to practice thought defusion is by observing the mind. Think of your mind as a separate event; almost as another person. In this example, there are four people in this room: you, me, your mind, and my mind. Can you notice what your mind is thinking right now? What is your mind telling you right now? (pause). Now, I would like you to name the thought by saying to yourself "I am having the thought that …" or "I notice that I am having the thought that" Congratulations! You have just taken the first steps of thought defusion by observing your mind and naming your thoughts!

Is what I am saying clear? Please let me know if you have any questions because you'll be applying these techniques to your own thoughts in the next part.

Titchner's Repetition

Another way you can create distance from your thoughts and reduce their believability is through repetition. Is it ok if I try another exercise with you? This may seem like a funny exercise to be doing, but it has helped many people to defuse themselves from stuck thoughts. I would like you to think about the word "orange". What comes to mind? The word "orange" can bring up all sorts of associations such as the color orange, the sweet taste, the round shape, the tart smell, or the rubbery feel. Notice that the sensations that the word orange brings up makes it seem almost as if there is an orange in this room right now. As far as I know, there isn't an orange in the

room. In a few seconds, I would like you to repeat the word orange over and over with me. Are you ready? "orange, orange, orange…" What did you notice as we did this exercise? Notice, as you repeat the word over and over again, the word begins to lose its original meaning and you begin to notice other things like its sound characteristics. Your mind may have the thought that "orange" is a funny sounding word.

In practice, the first step of using this thought defusion technique is to identify the thought that is particularly disturbing. For example, the thought may be "I am stupid". After identifying the thought, restate the thought into a single meaningful word such as "stupid". Then repeat that word over and over again until it begins to lose its meaning. This often takes around 45 seconds of repeating.

Does this strategy make sense? Any questions?

Altering the context of thoughts

A third way you can create distance from your thoughts is to "sing out your thoughts" or to think of your thoughts in silly voices. You might sing your thoughts to the tune of a song such as "happy birthday to you" or "Mary had a little lamb". Or, you might say your thoughts in a silly voice such as the voice of Donald Duck. For example, if your mind was fused to the thought "I am so stupid", you might sing that the thought to the tune of "happy birthday to you." (Experimenter provides a demonstration). I know these exercises may seem unusual, but research has shown that changing the voice or tune of the fused thought allows your mind to become disentangled from the literal, verbal meaning of the thoughts.

Do you have any questions about this or any of the other two thought defusion exercises?

Summary

Okay, we've seen that negative moods can be created from thought fusion.
I've shown you three common types of fused thoughts and three thought de-fusion exercises that can be used to create distance between you and your thoughts.
Would you review them with me? (provide participants with review sheet)

1. How would you explain each of these?

Identifying and De-fusing Fused Thoughts

Thought fusion: becoming fixated on or absorbed by a thought; treating thoughts as the literal or absolute truth
De-fusion: seeing a thought for what it is: nothing more or less than a bunch of words or pictures in your head

---

3 types of fused thoughts:

Thoughts about the future or the past
How to identify: Fusion with the past or future can involve both unpleasant and pleasant thoughts: fusion with bad memories, wishing to recapture positive experiences from the past, getting hooked by fears about the future, or wishing for brighter days ahead. These forms of thought fusion pull you out of the present moment.

Rules
How to identify: Fusion with rules occurs when your mind creates rules that describe things as right or wrong or good or bad. Rule-governed thinking often consists of the words "should", "must", "ought", "have to", or "if-then".

Thoughts about the self
How to identify: Thoughts about the self are the stories we tell or labels we use that make up our sense of identity. They typically begin with "I am".

3 ways to de-fuse fused thoughts:

Observing the mind
Treat "the mind" as an external event; almost as a separate person. Describe your thoughts using the following: "I am having the thought that …" or "I notice that I am having the thought that …"

Repetition
Identify the fused thought (e.g. "I am stupid"). Restate the thought into a single meaningful word (e.g. "stupid"). Then repeat the word for approximately 45 seconds until it begins to loose its meaning.

Altering the voice
Sing your thoughts using tunes such as "happy birthday to you" or "Mary had a little lamb".
Say your thoughts in a silly voice – a Donald Duck voice for example.

Appendix 2: Sleep Hygiene Script

INTRODUCTION TO SLEEP HYGEINE

Now I will tell you a theory of how the amount and quality of our sleep can influence our feelings and moods. I will show you some ways that you can improve your sleep.

You are probably aware that sleep can affect your mood. After a sleepless night, you may feel grumpy, irritable, or stressed. Once you are able to get a good night's sleep, your mood often improves. Studies have shown that even partial sleep deprivation has a large effect on our mood. Lack of sleep increases anxiety, stress, and agitation. Stress affects sleep by making the body aroused and alert, which makes it difficult to fall asleep.

Many people struggle with not getting enough sleep. While many people believe they can function well on less than seven hours of sleep, this is usually not the case. Remember that these recommendations are based on averages - so you personally may need more or less sleep than average.

Sleep problems can lead to more significant psychological problems, such as depression. In one study, people with insomnia were 5 times more likely to develop depression and 20 times more likely to develop an anxiety disorder. For some people, sleep difficulties are a result of mental health concerns such as depression, anxiety, or sleep disorders. For others, sleep difficulties develop from poor sleep behaviors (i.e., sleep hygiene). Others have lifestyles that interfere with their ability to get an adequate amount of sleep. In both of these cases, poor sleep can contribute to mental health concerns such as depression or anxiety.

The first step towards improving your sleep is assessing your sleep habits to see if there are steps you can take to improve your sleep quality. Today, I will give you some general tips and techniques to improve your sleep quality. Even if you do not have sleep problems, taking steps to ensure you are getting adequate sleep will lead to improved mood and well-being.
Do you have any questions?

Our brain has an internal clock that determines what time of day it is and what should be happening. This 24-hour process is known as our circadian rhythm. This "clock" is a very smart clock. It's aware of changes in our environment such as traveling across the country or differences in the amount of daylight between summer and winter days. However, the same things that help the brain's clock adapt to new situations can also lead it to become out of sync.

We can learn a lot about how to regulate our sleep and activity from cavemen. Think back to their time - before the Internet, the telephone and light bulbs. Cavemen used the rise and fall of the sun and moon to determine what time of day it was and what they should be doing. Nowadays, we're able to turn on and off our version of the sun whenever we'd like by using light bulbs. The light from light-bulbs influences our circadian rhythm in the same way the sun does. In the morning, the rise of the sun was the caveman's signal that the day was beginning. Like the cavemen, in your mornings, strive for bright light (sunlight if possible) upon awakening. **The most important thing you can do to set your circadian rhythm and improve sleep is to wake up at the same time each day--even on the weekends.**

For the cavemen, during the day, an abundance of sunlight was a sign that it was time to explore and adventure out to collect food. **During your daytime, eat at about the same times every day and engage in activities that get the body moving to simulate exploration and physical activity.**

In the evening, the sunset was a sign that it is time to return home and relax before bed.

In your evenings, make the last hour before bed a wind-down period. Engage in relaxing activities and dim the lights to signal bedtime (no brighter than a campfire). Avoid using computers, cellphones, or large televisions prior to bed - the brain confuses this light with sunlight. Make sure your bedroom is dark, quiet, and cool (around 65 degrees).

Research suggests that the deep sleep stage is the most important for refreshing our body and mind. It's critical for reducing fatigue and improving our mood. However, just because we're asleep during the night, doesn't mean we're getting enough deep sleep. In fact, it's possible to sleep all night and not get deep sleep. Common barriers to deep sleep include substance use, sounds in our environment, and difficulties breathing. The following tips may help you get more deep sleep:

Research shows that keeping a consistent wake time (along with morning bright light exposure) is the most important cue for setting your circadian rhythm.

SLEEP HYGEINE

Now I would like to turn towards an overview of what we call sleep hygiene. Sleep hygiene are habits that lead towards improved sleep quality and possibly improved mood.

1) **Don't consume caffeinated products (e.g., coffee, tea, many sodas, chocolate) in the evening.** Caffeine makes it difficult to fall asleep and disrupts your sleep during the night. Try to eliminate caffeine within eight hours of bedtime.
2) **Don't use alcohol to help you sleep or consume alcohol too close to bedtime.** Although alcohol may help you to fall asleep more easily, it disrupts your sleep during the night by causing frequent awakenings. Try to eliminate alcohol within three hours of bedtime. **Smoking and other drugs also disrupt your sleep.** If you smoke, don't smoke too close to bedtime and don't smoke if you awaken.
3) **Allow your body to process food and drinks before bed.** Try not to eat a big meal within three hours of bedtime. Restrict liquids in the evening (less than 8-10 oz) and use the toilet right before bed. If necessary, have a light carbohydrate snack (e.g., crackers, bread, cereal) during the last hour before bed to prevent nighttime hunger.

Do these tips make sense? Any questions?

1) **Create a calm, quiet and comfortable sleeping environment.** If you live in a noisy area, creating a constant background noise in the sleep environment using a white-noise machine, fan, or humidifier will eliminate unexpected sounds that would otherwise wake you up. Other tips: use a dark room/eye mask, don't use a TV/electronics, remove your clock, sleep at a cool temperature (i.e., 60-65 degrees), use earplugs, and use comfortable bedding and pajamas.
2) **Exercise regularly, but do not engage in activities that raise body temperature (e.g., warm bath) too close to bedtime.** Regular exercise can improve sleep quality, but exercising or having a warm bath too close to bedtime can disrupt sleep onset. Warm baths can be taken in the evening, but not within 1.5 hours of going to bed.

3) **Keep regular daily activity and sleep schedule.** Wake and sleep around the same time each day (plus or minus a half hour--even on weekends).

Do these tips make sense? Any questions?

1) **Make the last hour before bed a "wind-down" time.** Engage in relaxing and pleasant activities, dim the lights, and/or have a light snack.
2) **Strive for bright light in the morning on awakening but limit exposure to bright light in the evening.**
3) **Snoring can be a sign of sleep apnea.** If you regularly snore, there is a good chance you have sleep apnea. Sleep apnea is a common sleep disorder that occurs when you have difficulty breathing while sleeping. Difficulties breathing can prevent your brain from going into deeper stages of sleep to protect you from suffocating.

Do you have any questions about these or any of the other sleep hygiene tips?

SUMMARY

Okay, now I have discussed how our sleep is related to our mood. I've shown you some ways to improve your sleep hygiene. Let's briefly review them.

1. Keep a regular daily activity and sleep schedule.
2. Eat regular meals every day.
3. Make the last hour before bed a "wind-down" time.
4. Do not consume more than 8-10 oz of liquids in the evening.
5. Do not consume caffeinated products in the evening.
6. Do not use alcohol to help you sleep or too close to bedtime.
7. Smoking and other drugs will disrupt your sleep.
8. Do not nap during the day.
9. Exercise regularly, but do not engage in activities that raise body temperature (e.g. warm bath) too close to bedtime.
10. Create a sleep-friendly bedroom environment.

11. Strive for bright light in the morning on awakening, but limit exposure to bright light in the evening

Sleep Hygiene Recommendations

1. Keep a regular daily activity and sleep schedule. Keeping a regular bedtime and rise time every night, including weekends, stabilizes the biological clock. Regular daily activity keeps the biological clock timed to daylight hours.
2. Eat regular meals every day. Regular meals are signals to the biological clock about time of day. Do not eat a big meal within about three hours of bedtime. Have a light carbohydrate snack (e.g., crackers, bread, cereal) during the last hour before bed to signal bedtime and prevent nighttime hunger.
3. Make the last hour before bed a "wind-down" time. Engage in relaxing and pleasant activities, dim the lights, and have a light snack.
4. Do not consume more than 8-10 oz of liquids in the evening. A or semi-full bladder can contribute to awakenings. Restrict liquids in the evening after dinner and void right before bed.
5. Do not consume caffeinated products (e.g., coffee, tea, many sodas, chocolate) in the evening. Caffeine makes it difficult to fall asleep and disrupts your sleep during the night. Eliminate caffeine within 8 hours of bedtime.
6. Do not use alcohol to help you sleep or consume alcohol too close to bedtime. Although alcohol may help you to fall asleep more easily, it disrupts your sleep during the night by causing frequent awakenings. One drink of alcohol should not be consumed within 3 hours of bedtime.
7. Smoking and other drugs will disrupt your sleep. If you smoke, do not smoke too close to bedtime and do not smoke during the night if you are awake. All drugs of abuse worsen your sleep.
8. Do not nap during the day. Napping makes it harder to fall asleep and stay asleep at night.
9. Exercise regularly, but do not engage in activities that raise body temperature (e.g., warm bath) too close to bedtime. Regular exercise can improve sleep quality, but exercising or having a warm bath too close to bedtime can disrupt sleep onset. The best time to exercise to help sleep is in the late afternoon or early evening. Warm baths can be taken in the evening, but not within 1.5 hours of going to bed.
10. Create a sleep-friendly bedroom environment. Make sure that your bed is comfortable and that your bedroom is dark, quiet, and cool (around 65 ^{0} F). Darkness signals to the biological clock that it is night time. Creating constant background noise in the sleep environment (e.g., a fan, humidifier) will eliminate unexpected sounds that would otherwise wake you up.
11. Strive for bright light in the morning on awakening but limit exposure to bright light in the evening.

Chapter 5: General Discussion

Dissertation Aim

Current antidepressant response rates are unacceptably low, hovering around 50-70% (Fava & Davidson, 1996). Worse, full remission rates are estimated at only 35-45% (Thase, Entsuah, & Rudolph, 2001), with some estimates as low as 11 percent - even after 8–12 months of treatment (Cipriani et al., 2009). This dissertation aimed to produce research that may inform personalized approaches toward depression care in order to improve response rates.

Study 1

The first study collected data from the National Institutes of Mental Health Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) and provided evidence to suggest that the Sociotropy-Autonomy scale is a robust moderator of antidepressant treatment response. In fact, this scale was able to accurately classify nearly 80% of participants into categories of antidepressant treatment responders and non-responders. Seventy-five percent of socio responders had a score below 85, while 75% of socio non-responders had a score above 85. Based on this criterion, out of 24 participants, only 3 non-responders were incorrectly categorized and 2 responders were incorrectly categorized. The classification strength of the sociotropy subscale of this measure by itself was unexpected, and given the limited research examining sociotropy in relationship to treatment outcomes, the

interpretations here are speculative. Individuals high in sociotropy tend to be more dependent on others and are more likely to experience significant interpersonal events that are theorized to trigger a depressive episode (Connor-Smith, 2002; Hammen, 1989; Hammen, 1992). It is possible that if interpersonal stress is the proximal cause of a depressive episode, medication may be unable to address the interpersonal stress, but, rather, a reduction in interpersonal stress may require a shift in interpersonal relationships that the individual with high sociotropy has to those around them. Accordingly, a recent study demonstrated that among a sample of 380 high school freshman, students high in sociotropy are more likely to experience reductions in depressive symptoms during interpersonally focused group psychotherapy than those who received group cognitive behavioral therapy (Horowitz, 2007). A future study could test this theory by randomizing individuals with depression to either receive medication or receive interpersonal therapy (IPT) and examine the relationship of baseline sociotropy to outcomes. Taken together, if data from this study are replicated, the Sociotropy-Autonomy scale provides a reliable, cheap and simple way to predict whether medication is a good treatment strategy for an individual who is experiencing major depression.

Study 2

Study 2, which focused on the relationship of reward processing to the placebo response, provides novel data linking anhedonia to placebo non-response. Based on prior literature, it was hypothesized that individuals with attenuated mesolimbic reward system activity would be less likely to respond to a placebo. This study's theory was based on prior research that proposed the placebo response is facilitated via reward processing in the mesolimbic reward system (Schweinhardt, Seminowicz, Jaeger, Duncan, & Bushnell 2009; Tracey, 2010). In order to test

this theory, we used two measures that are thought to index mesolimbic reward system activation from various units of analysis including a behavioral paradigm (Pizzagalli, 2008) and physiological data (Wacker, 2009), along with an indirect self-report measure of anhedonia that may indicate dysfunctional mesolimbic reward system processing (MASQ-AD; Keller, 2013),

Prior to investigating the relationship of mesolimbic reward system activity to the placebo response, it was important to determine the convergent validity of the various hypothesized indices of mesolimbic reward system activity. However, contrary to our hypothesis, the indices of mesolimbic reward system activation proposed by prior research did not demonstrate significant relationships among each other. The tested behavioral index (reward learning on a probabilistic reward task) was unrelated to the tested physiological index (rACC delta EEG). Further, the indirect self-report index of mesolimbic reward system dysfunction (MASQ-AD) was unrelated to the tested physiological index (rACC delta EEG) or behavioral index (reward learning on a probabilistic reward task). The lack of convergent validity among these measures signals the need for further investigation into the independent relationships of each of these measures to reward system activity.

Based on results from Wacker, Dillon, and Pizzagalli (2009), who reported a strong association between rACC delta EEG activity and the MASQ-AD (r=.54), we expected a similar strength of relationship; however, the strength of association between rACC delta EEG and MASQ-AD in this dataset was r=.01. It is possible that the prior pattern of results depends on the population they were acquired form. While the data from the present study was acquired from a sample of individuals diagnosed with MDD, the data from Wacker (2009) came from a sample of healthy controls. It is also possible that extraneous noise may have been introduced based on

differences in preprocessing steps used when analyzing the EEG data; however, it is unlikely as the EEG data from this study was preprocessed by the same research team that preprocessed the EEG data from the prior publication. Nonetheless, differences in noise introduced during the recording of the EEG data (e.g. EMG artifacts, environmental noise) may also account for some of the differences in findings.

The lack of an association between the self-report measure of anhedonia (MASQ-AD) and the behavioral index of mesolimbic reward system processing (reward learning on the probabilistic reward task) is not necessarily a new finding. Data from Pizzagalli et al. (2008) was unable to detect a relationship between reward learning on the probabilistic reward task and the MASQ-AD. However, Pizzagalli (2008) did report a significant relationship between the MASQ-AD and "rich misses" on the probabilistic reward task. Unfortunately, that subset of the data was unavailable for further analysis, and, through personal communication with Dr. Pizzagalli, it was suggested that the lack of an effect from the more general reward learning index indicates to him that it may not be useful to analyze lower level effects. Taken together, it is unclear whether reward learning on the probabilistic reward task and the MASQ Anhedonic Depression subscale are measuring the same construct.

In sum, the two hypothesized indices of reward learning included in this study do not appear to be measuring the same construct, and they were unrelated to anhedonia. More broadly, it is possible that these measures index distinct non-overlapping facets of the reward system. Future research may benefit from a better understanding of the how these measures are each independently related to the mesolimbic reward system. For example, it may be that neural activation in the hypothesized reward regions (e.g. rostral anterior cingulate cortex) of the brain

may be confounded by non-reward neural activation such as self-referential processing (Wagner, 2012). Further, a limitation of EEG data is that it is unable to provide completely accurate source localization of the signals even with advanced source localization techniques, such as those employed in the present study; therefore, it possible that neural activation from non-reward regions of the brain may be confounding these findings. Or, it may be that while the construct of anhedonia is believed to indicate attenuated reward system processing, in samples of individuals with depression the MASQ-AD may also be capturing depression symptomology unrelated to reward system processing. Lastly, it may be useful to study how the associations among these various measures strengthen or weaken depending on the population they are tested in. With stronger theory and the ability to isolate extraneous sources of noise that may be influencing the present findings, it is possible that the relationship of reward system activity to the placebo response may become clearer.

As mentioned above, the lack of intercorrelation among the hypothesized indices of reward system processing is contrary to the theory that led to this study's hypotheses. Nonetheless, rostral anterior cingulate cortex (rACC) EEG activity was significantly related to the placebo response - just in the opposite direction than was hypothesized. Post-hoc analyses were conducted aimed at better understanding the reasons why the data might exhibit this pattern, and were initiated based on theories from the antidepressant treatment response literature (e.g. Arns, 2015). It was revealed that rACC theta EEG provided superior predictive ability relative to rACC delta. Although the link between higher baseline rACC theta activity and antidepressant non-response has been well-established in meta-analytical studies (Pizagalli, 2011), previous investigations have been unable to explain why (e.g. Arns, 2015; Pizzagalli,

2018). It is possible that elevated rACC theta activity is characteristic of a subtype of depression that is particularly amenable to pharmacotherapy and the placebo effect. Marchetti (2012) reviewed a body of literature exploring the relationship of default mode network dysfunction to a potential type of recurrent depression. Given the central role of the rACC in the default mode network, it is possible that rACC theta activity is associated with a type of recurrent depression that exhibits dysfunction within this region.

Taken together, this study adds to prior reports linking rACC theta EEG to the depression treatment response (Arns et al., 2015), and, consistent with prior theories (e.g. Schweinhardt, Seminowicz, Jaeger, Duncan, & Bushnell, 2009; Wacker, Dillon, & Pizzagalli, 2009), this study provides novel data linking anhedonia to placebo non-response in individuals with depression.

Study 3

The third study targeted negative self-referential processing (Mennin & Fresco, 2013) in individuals with dysphoria using a cognitive defusion intervention (Mandavia et al., 2015; Masuda et al., 2010) and results indicated that a brief single-session cognitive defusion intervention, which was well-received by students, produced significant decreases in negative emotions and significant increases in positive emotions associated with a difficult life situation. The data from this study was unable to provide evidence to suggest that cognitive defusion techniques could alter the cognitive processes indexed by the P300 event related potential (ERP). While this study did provide evidence of changes in cognitive processes indexed by NoGo N200 amplitude, these results were not interpretable using the current body of literature on N200 or cognitive and affective processes in depression. In short, these data suggest that a brief one-session cognitive defusion intervention may reduce negative emotions, increase positive

emotions, and may lead to unspecified shifts in cognitive and affective processing indexed by NoGo-N200 ERP amplitude.

Conclusion

In sum, the studies included in this dissertation provide new directions for research that aims to improve treatment outcomes. If replicated, studies 1 and 2 provide the possibility for swift translation into routine clinical care through the identification of the Sociotropy-Autonomy Scale and the MASQ Anhedonic Depression subscale as possible predictors of treatment outcomes. Studies that examine the relationship of the Sociotropy-Autonomy scale to various forms of treatment, such comparing Interpersonal Psychotherapy (IPT) to antidepressant pharmacotherapy, may provide insight into not only who doesn't respond to antidepressants, but also whom will benefit from psychotherapy instead. Further, studies that examine the relationship of higher pre-treatment MASQ anhedonic depression symptoms to different forms of treatment may also show benefit. As Behavioral Activation psychotherapy is designed to reduce symptoms of anhedonia by increasing contact with pleasurable stimuli (Dimidjian, 2011), Behavioral Activation may be a useful alternative for individuals higher baseline MASQ anhedonic depression symptoms.

While study 2 also provided further evidence of the utility of pre-treatment rACC theta for predicting treatment outcomes, the utility of EEG in routine clinical care is still a distant possibility as EEG methodologies involve substantial financial, personnel, and time requirements for adequate implementation. However, computing costs are decreasing, and biofeedback devices that measure EEG activity outside of the laboratory environment are becoming more readily available (see this report on wearable EEG devices: Casson, Yates, Smith, Duncan, &

Rodriguez-Villegas, 2010). This raises the possibility for EEG findings such as these to be more feasibly translated into routine clinical care. On the other side of the coin, for individuals who do have higher pre-treatment rACC theta activity, it is possible that referral to a sleep clinic for an assessment for possible sleep disorders such as obstructive sleep apnea or insomnia may lead to positive outcomes as well, as treatment for obstructive sleep apnea (Schroder & O'Hara, 2005; Manber, 2014) and insomnia have been shown to reduce depression symptoms independently of depression focused treatment.

References

Aragona, M. (2014). Epistemological reflections about the crisis of the DSM-5 and the revolutionary potential of the RDoC project. *Dialogues in Philosophy, Mental and NeuroSciences*, *7*(1), 11–20.

Arns, M., Etkin, A., Hegerl, U., Williams, L. M., DeBattista, C., Palmer, D. M., … Gordon, E. (2015). Frontal and rostral anterior cingulate (rACC) theta EEG in depression: implications for treatment outcome? *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*, *25*(8), 1190–1200. https://doi.org/10.1016/j.euroneuro.2015.03.007

Casson, A. J., Yates, D. C., Smith, S. J. M., Duncan, J. S., & Rodriguez-Villegas, E. (2010). Wearable electroencephalography. *IEEE Engineering in Medicine and Biology Magazine*. https://doi.org/10.1109/MEMB.2010.936545

Curci, A., Lanciano, T., Soleti, E., & Rimé, B. (2013). Negative emotional experiences arouse

rumination and affect working memory capacity. *Emotion*. https://doi.org/10.1037/a0032492

Fava, M., & Davidson, K. G. (1996). Definition and epidemiology of treatment-resistant depression. *The Psychiatric Clinics of North America*, *19*(2), 179–200. https://doi.org/10.1016/S0193-953X(05)70283-5

Joormann, J., Levens, S. M., & Gotlib, I. H. (2011). Sticky thoughts: Depression and rumination are associated with difficulties manipulating emotional material in working memory. *Psychological Science*. https://doi.org/10.1177/0956797611415539

Keller, J., Young, C. B., Kelley, E., Prater, K., Levitin, D. J., & Menon, V. (2013). Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. *Journal of Psychiatric Research*. https://doi.org/10.1016/j.jpsychires.2013.05.015

Kupferberg, A., Bicks, L., & Hasler, G. (2016). Social functioning in major depressive disorder. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2016.07.002

Mandavia, A., Masuda, A., Moore, M., Mendoza, H., Donati, M. R., & Cohen, L. L. (2015). The application of a cognitive defusion technique to negative body image thoughts: A preliminary analogue investigation. *Journal of Contextual Behavioral Science*, *4*(2), 86–95. https://doi.org/10.1016/j.jcbs.2015.02.003

Masuda, A., Twohig, M. P., Stormo, A. R., Feinstein, A. B., Chou, Y.-Y., & Wendell, J. W. (2010). The effects of cognitive defusion and thought distraction on emotional discomfort and believability of negative self-referential thoughts. *Journal of Behavior Therapy and Experimental Psychiatry*, *41*(1), 11–17. https://doi.org/10.1016/j.jbtep.2009.08.006

Mennin, D. S., & Fresco, D. M. (2013). What, Me Worry and Ruminate About DSM-5 and RDoC? The Importance of Targeting Negative Self-Referential Processing. *Clinical Psychology : A Publication of the Division of Clinical Psychology of the American Psychological Association*, *20*(3), 258–267. https://doi.org/10.1111/cpsp.12038

Miller, G. A. (2010). Mistreating psychology in the decades of the brain. *Perspectives on Psychological Science*. https://doi.org/10.1177/1745691610388774

Pizzagalli, D. A., Webb, C. A., Dillon, D. G., Tenke, C. E., Kayser, J., Goer, F., … Trivedi, M. H. (2018). Pretreatment Rostral Anterior Cingulate Cortex Theta Activity in Relation to Symptom Improvement in Depression: A Randomized Clinical Trial. *JAMA Psychiatry*, *75*(6), 547–554. https://doi.org/10.1001/jamapsychiatry.2018.0252

Thase, M. E., Entsuah, A. R., & Rudolph, R. L. (2001). Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *The British Journal of Psychiatry : The Journal of Mental Science*, *178*, 234–241. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11230034

Wacker, J., Dillon, D. G., & Pizzagalli, D. A. (2009). The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. *NeuroImage*, *46*(1), 327–337. https://doi.org/10.1016/j.neuroimage.2009.01.058