MOVING PSYCHOPATHOLOGY FORWARD: COMBINING A TRANSDIAGNOSTIC AND DIMENSIONAL APPROACH TO CLINICAL ANXIETY, DEPRESSIVE, AND SUBSTANCE USE CONSTRUCTS

A thesis presented to the faculty of the Graduate School of Western Carolina University in partial fulfillment of the requirements for the degree of Master of Arts in Psychology.

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April 2017

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ABSTRACT

MOVING PSYCHOPATHOLOGY FORWARD: COMBINGING A TRANSDIAGNOSTIC AND DIMENSIONAL APPROACH TO CLINICAL ANXIETY, DEPRESSIVE, AND SUBSTANCE USE CONSTRUCTS

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The National Institute of Mental Health Research Domain Criteria (RDoC) initiative calls for systemic efforts to integrate neurobehavioral traits into dimensional models of psychopathology (Nelson et al., 2016). Examples are needed of how RDoC constructs can be linked to clinical symptoms. Thus, researchers evaluate two domains proposed by the RDoC model, Positive and Negative Valence System. Relevant MMPI-2-RF subscales, RC2 (Low Positive Emotion), RC7 (Negative Emotionality), and DISC-r (Disconstraint) are used to examined the extent to which depressive, anxiety, and substance use disorders share underlying neurobehavioral constructs in 2,873 inpatients and outpatients from the Minneapolis Veterans Affairs (VA) Medical Center and the Hennepin County Medical Center. Predictions were partially supported, clinical symptoms of depression and substance use overlap on neurobehavioral domains of positive valance, anxiety and substance use overlap on neurobehavioral domains of anxiety and substance use, however depression and anxiety did not overlap with cognitive systems. Results partially provide support for building a bridge between neurobehavioral constructs derived from neurophysiologic research (i.e., RDoC model) with core features of co-occurring psychopathology using a dimensional approach (MMPI-2-RF). With regards to inhibitory control (Cognitive Systems Domain), more research is needed to conceptualize INH as transdiagnostic.

CHATPER 1: INTRODUCTION

For several decades, little progress has been made to explain commonalities and distinctions in clinical psychopathology despite an established neurophysiological research literature which can move conceptualization of psychopathology forward. This is partly due to the outdated nosology, the Diagnostic and Statistical Manual (DSM; 2013), which defines psychopathology based on meeting symptom benchmarks that are defined by an appointed panel of professionals. The key problem with the DSM is that it separates disorders with the same underlying etiologies into different categories solely on the basis of differing self-reported clinical symptoms (Sharp, Miller, & Heller, 2015) rather than on the basis of their pathology and etiology (Lilienfeld, 2014). This antiquated, symptom-based model may explain both the extensive co-occurrence among disorders and the lack of reliability and validity of psychopathological measurement in the DSM's categorical approach.

Due to increasingly apparent limitations of the DSM as a diagnostic tool and the growing discrepancy between DSM diagnoses and neurophysiology research, the National Institute of Mental Health has developed a system, Research Domain Criteria (RDoC), to transform current views of psychopathology into a system that is grounded in biological and psychological research, with an emphasis on "transdiagnosic components of psychopathology" (Sharp et al., 2015, p. 365).Transdiagnostic components of psychopathology are conceptualized as "neurobehavioral traits" that reflect current biological and psychological findings (Sharp et al., 2015). Using the RDoC domains, various neurobehavioral constructs which manifest across several disorders can be measured behaviorally as well as neurobiologically, creating a more integrated conceptualization of psychopathology.

This study is one of the first that investigates neurobehavioral domains set forth in the RDoC based on neurophysiology of depressive, anxiety, and substance use, and then utilizes these evidence-based domains (i.e., positive valance system and negative valence system) as a bridge to view clinical psychopathological constructs inclusively. In doing so, this study provides an initial effort to integrate the neurophysiologic "map" set forth by the RDoC with self-reported psychopathological constructs.

The present goal of this project is to observe transdiagnostic components of psychopathology from the perspective of the RDoC model and translate these neurobehavioral findings into the clinical symptoms observed in co-occurring psychopathology, and evaluate these symptoms using the lens of a more valid, dimensional measure of clinical constructs associated with psychopathology.

The goal of this study is to provide critical evidence that depression, anxiety, and substance use disorders co-occur largely due to common underlying neurophysiologic pathways. We propose that these pathways involve neural circuitry that generates positive and negative affect in the limbic system, and that the manifestation of clinical symptoms is determined by location and degree of frontal lobe involvement. By observing this marked overlap both in neural circuitry and in self-reported clinical symptoms, we suggest a novel explanation for the striking co-occurrence of common forms of psychopathology and an improved, more comprehensive neurobehavioral model for conceptualizing psychopathologic syndromes.

CHAPTER 2: LITERATURE REVIEW

The following section reviews the relevant literature which forms the rationale for the proposed study. It will begin by describing the current debate over ways to define and diagnose psychopathology. In doing so, current categorical limitations of the DSM approach will be discussed, followed by an overview of how a dimensional approach to psychopathology yields more relevant data. For this reason, we will use a dimensional approach in this study. Since our theoretically-driven hypotheses also propose that unitary disorders, such as depression, anxiety, and substance use disorders share common underlying physiologic pathways, we will introduce the RDoC model and describe how using domains of this model relevant to the above-mentioned psychopathology provide the theoretical basis for understanding and translating neurobehavioral traits, focusing on positive valence and negative valence domains. Finally, we will provide the specific rationale and hypotheses for the current study, and the methods we propose to use.

Categorical versus Dimensional Conceptualization of Psychopathology

A current and critical issue in the field of clinical psychopathology is determining the most useful way to conceptualize psychopathology. The dilemma involves distinguishing between categorical and dimensional models of psychopathology (Haslam, Holland, & Kuppens, 2011). The categorical model of conceptualizing and diagnosing psychopathology has been under scrutiny for quite some time (Zachar, 2013), yet it remains as the prevailing standard in the assessment of clinical diagnoses. In support of a categorical, or dichotomous, approach to diagnosis, Berenbaum (2013) asserts that classification approaches describe "objects of study in science and to serve as a source of concepts to be used within a scientific theory" (p. 894).

For numerous decades, the categorical approach to psychopathology has been intricately connected with clinical psychology. For example, taxometric research methods have historically

played a major role in adoption of either a categorical approach to psychopathology or dimensional. Meehl and colleagues' methodological work promoted researchers to "determine whether observed variation is underpinned by non-arbitrary latent class, or 'taxon', such as a discrete psychopathology" (Haslam et al., 2012, p. 903). Specifically, Meehl (1977) identified taxa as specific etiologies, much like discrete entities, whereas nontaxonic variables result from various influences. Establishing if a variable is better described as taxonic is fundamentally important in moving research forward.

Research suggests that internalizing disorders, such as mood and anxiety disorders, as well as externalizing disorders are better described as nontaxonic variables that stem from several causal influences (Haslam et al., 2012). Researchers as well as clinicians acknowledge that categorical approaches to psychiatric disorders have been ineffective in moving science closer to understanding etiologies of mental disorders (Frances & Widiger, 2012). Dimensional models of psychopathology have the ability to shift current classifications into a more empirically based and etiologically based nosology.

In summary, much criticism has focused on its inability to defend apparently arbitrary distinctions between categories of psychopathology, and also that high frequencies of co-occurring symptoms exist among different forms of psychopathology (Goekopp & Goekoop, 2014). Recent research suggests no evidence for the continued use of the categorical approach to clinical diagnosis (Poland, 2015). Specifically, strict phenotypical separations that were presumed to occur between analogous categories have not been replicated in clinical reality (Goekopp & Goekoop, 2014). On the other hand, there is copious evidence suggesting pathways of psychopathology "involve causal processes that act both at micro levels and macro levels, that act within and outside of the individual, and that involve processes best understood from

biological, psychological, and sociocultural perspectives" (Kendler, 2008, p. 695). Thus, the preponderance of current research suggests that a dimensional approach to psychopathology may capture the underlying mechanisms and clinical symptoms of psychiatric disorders more effectively. Based on this evidence, the present study will measure psychopathological constructs using a continuous instrument (i.e, MMPI-2-RF) rather than the DSM-5 to capture the underlying common features of psychopathology.

The DSM and its Limitations

The Diagnostic and Statistical Manual (DSM) of mental disorders is one of the most extensively used referenced texts in the mental health field (American Psychiatric Association [APA], 2013). The latest edition, DSM-5, has amassed significant attention among researchers and clinicians (First, 2014). Rejoinders to revisions of the DSM, put forth by the DSM task force, have varied from fervent support (McCarron, 2013) to apprehensiveness (Welch, Klassen, Borisova, & Clothier, 2013) and even appeals to disband the use of the manual in its entirety (Frances & Widiger, 2012). Advocates for the DSM argue that classification systems were designed primary for clinical purposes, particularly to provide a common language in the diagnosis and treatment of clients with mental health disorders, and developments in the treatment of mental health disorders have emerged from categorical classification systems (Casey et al., 2013).

The most recent edition of the DSM includes updated clinical research from the past 20 years in psychopathology, but it still fails to integrate highly informative and relevant advances in neuroscience and genetic research on the neurophysiological underpinnings of psychopathology that have emerged within the last several decades (Casey et al., 2013). Instead the DSM-5 continues to base diagnoses of psychopathology on self-reports of feelings and

experiences by clients, and on clinicians' subjective interpretation of observed psychiatric signs and symptoms (First, 2014). Yet, clinicians continue to use the DSM despite its subjective interpretations, lack of empirical evidence, and inadequate integration of neurophysiological research.

Emerging neurophysiologic and psychological literatures demonstrate that common neural pathology, etiology, and symptom clusters underlie traditionally distinct categories entities of psychiatric disorders (Cuthbert & Insel, 2010; Lilienfeld, 2014). Thus, many professionals were in hopes of a paradigm shift from categorical descriptive approaches to an approach that would be more dimensional focused that incorporated the advances in neuroscience (First, 2014). There is no denying that classification systems have produced significant advances in the past; however, current research suggests a paradigm shift is needed in order to continue the advances in research and treatment for psychopathology.

Comorbidity

Comorbidity of psychiatric disorders is a topic of major practical and theoretical significance and despite the vast amount of research conducted on co-occurring disorders, the reasons for high incidence of multiple diagnoses is largely unknown (Dell'Osso & Pini, 2012). Yet, with each successive revision of the DSM, an increase in the prevalence of psychiatric comorbidity occurs (Pincus, Tew, & First, 2004). Thus, the rarity of well described cases meeting criteria for only a single form of psychopathology indicates the need for fundamental changes in the way psychopathology is classified (Krueger & Markon, 2006).

Traditionally, psychopathology is a concept of descriptive and distinct categories, where categorical inclusion simply requires a sufficient number of presenting symptoms; countless combinations of symptoms are sufficient enough to receive diagnoses, as long as the presenting

number of symptoms is correct (Krueger & Markon, 2006). So, according to the categorical approach, psychopathology is simply an agreed upon number of signs and symptoms with a plethora of ways to meet diagnostic criteria.

Based on this notion, research suggests that a large proportion of patients will concurrently meet diagnostic criteria for more than one diagnosis (Dell'Osso & Pini, 2012). Additionally, constancy of a diagnosis within individuals is relatively minimum; across clinicians individuals may actually meet criteria for a wide range of different disorders throughout their lifespan (Nolen-Hoeksema & Watkins, 2011). Therefore, if the comorbidity is greater than that expected by chance, as research suggests, the disorders are likely to be interrelated and perhaps the manifestation of the same etiological mechanism or the result of a shared influence (Dimaggio & Norcross, 2008). For example, a client who misuses substances, has severe and recurrent depressive episodes, and has anxiety symptoms would receive three separate diagnoses as opposed to a single, all-inclusive diagnosis that might better capture the underlying common neural pathology, etiology, and symptoms (Pincus et al., 2004).

Frequently co-occurring psychiatric disorders provides evidence against the notion that disorders represent discrete categorical entities. Conversely, any individual who meets the full diagnostics criteria for only one disorder may still have an increased frequency of symptoms from other categories, but fails to be diagnosed, and thus treated, due to the rigid confines of a categorical diagnostic system. Transdiagnostic approaches may explain co-occurring disorders by focusing on processes that are common across disorders and that causally contribute to underlying symptomology (Nolen-Hoeksema & Watkins, 2011). Thus, much evidence suggests that high rates of co-occurring disorders stem from shared underlying transdiagnostic mechanisms.

Reliability and Validity. A critical issue for both clinical decision making and clinical research advancement is the reliability of diagnosis (Regier et al., 2013). One of the major goals of the DSM-5 field trials was to produce a higher degree of inter-rater reliability among clinicians; however several of the most common psychiatric diagnoses failed to meet adequate thresholds of inter-rater reliability [e.g., depressive disorders (kappa .25-.34) and generalized anxiety disorder (kappa .34)]. Thus, if the diagnostic criteria defining a disorder in a given population cannot be measured consistently by two diagnosticians, then clients with those particular diagnoses cannot be expected to have common treatment response, or even similar etiological findings (Reiger et al., 2013). Consequently, greater attempts to improve reliability are called for.

Disorders, such as autism spectrum, that were moved to a more dimensional approach in the DSM-5 demonstrated good to very good reliability (Reiger et al., 2013). Dimensional measures of psychopathology were 15% more reliable and 37% more valid than categorical measures across several constructs (Haslam et al., 2012); this provides strong support for a paradigm shift in the way professionals assess psychiatric symptoms. Proponents of the DSM-5 as well as DSM-5 leaders compare diagnostic kappa values across medical setting and claim that most medical diagnose have comparable values; yet mental health professionals have expressed concerns regarding kappa values considering measures of inter-rater agreement were higher in the DSM-III (Ghaemi, 2013).

The validity of current classifications of psychopathology has been questioned (Reiger, et al., 2013), since DSM categories do not map well onto emerging neuroscience and genetic research (Cuthbert & Insel, 2013). As a result, translating research into systematic ways of understanding psychopathology has become increasing difficult because it appears that

underlying symptom constellations cross current diagnostic boundaries, or are better conceptualized as "transdiagnostic" (Krueger & Eaton, 2015). As mentioned previously, in the absence of biomarkers, the majority of psychiatric disorders were based on clinical descriptions which resulted in official nosological groupings. However, research has indicated that the DSM-5 groupings lack the ability to statistically predict crucial external benchmarks (Lilienfeld, 2014). For example, statistical analyses in one study detected patterns of comorbidity that suggested poor discriminant validity such that generalized anxiety disorder aligns more closely with mood disorders than with other anxiety disorders (Brown & Barlow, 2005). In line with these developments, a growing consensus among mental health care experts agree that the DSM, as the primary approach to clinical diagnosis of psychopathology, is a fundamentally flawed diagnostic tool which needs to be replaced for a host of compelling reasons, including the need to accurately characterize transdiagnostic symptom constellations.

Moving Research Forwards: The RDoC Initiative

The National Institute of Mental Health Research Domain Criteria Initiative (RDoC) is developing a new way to study psychopathology based upon dimensions of neurobiology and observable behavior (Casey, Oliveri, & Insel, 2014). The RDoC approach to psychopathology represents a much needed paradigm shift that conceptualizes psychopathology as dimensional rather than categorical model. This dimensional approach to psychopathology is based on three core assumptions, which include: 1) psychiatric disorders are "disorders of brain circuits" (p.749), and 2) dysfunctions in neural circuitry can be detected by neuroscience devices, such as functional neuroimaging, and lastly that 3) information from genes will produce biomarkers that will improve clinical psychology (Insel & Cuthbert, 2010).

The RDoC matrix includes five general areas of function (e.g., negative valence, positive valence) and different levels of analysis including genetic, neural circuits, and self-report measures; all of these levels affect both the biology and psychology of psychiatric disorders (Cuthbert & Insel, 2013). The RDoC initiative is ultimately designed to provide a basis for integrating empirical data from various sources of neuroscience as a way to better understand underlying transdiagnostic mechanisms of psychopathology (Lilienfeld, 2014; National Insititue of Mental Health [NIMH], 2009). The current study proposes to do just this by examining how the positive and negative valance, and cognitive systems, three systems arguably most relevant in the RDoC model to psychopathology examined in this study, helps characterize the transdiagnostic symptoms of depression, anxiety, and substance use disorders.

Negative Valence System

As defined by the RDoC approach, the Negative Valance System domain is predominantly associated with responses to aversive conditions. There are five constructs within this domain, which include; 1) responses to acute threat (fear); "the brain's defensive motivational system to promote behaviors that protect the organism from perceived danger", 2) potential harm (anxiety); activation of a specific brain area as a result of low probability threat behaviors, 3) sustained threat; aversive emotional conditions produced by sustained exposure to various internal and external circumstances that alter affect, cognition, physiology, and behavior even after the threat has subsided, 4) frustrative non-reward; consequences produced in response to the removal of reward, and 5) loss; "a state of deprivation of a motivationally significant con-specific, object, or situation" and the reaction to loss may be episodic or chronic (NIMH, 2009). Based on this neurobehavioral description of the Negative Valence System, clinical symptoms associated with both anxiety and depression are readily apparent. Furthermore, the common

neural circuitry underlying the negative valence system is based on a strong foundation of translational research, and clearly requires a dimensional and transdiagnostic approach to understanding and characterizing psychopathological syndromes.

Positive Valence System. The Positive Valance System, as defined by the RDoC approach, relates to positive motivational situations, such as reward seeking, and behavioral patterns that occur in response to a stimulus that elicits pleasurable reinforcement and learned behaviors. This domain includes five constructs; 1) approach motivation; "a multi-faceted construct involving mechanisms/processes that regulate the direction and maintenance of approach behavior influenced by pre-existing tendencies, learning, memory, stimulus characteristics, and deprivation states", 2) initial responsiveness to reward; mechanisms related to pleasurable reactions, 3) sustained responsiveness to reward; "processes associated with the termination of reward seeking", 4) reward learning; a process of obtaining information about stimuli, actions, and contexts that are predictive of positive consequences, and how behavior is altered when novel rewards are presented (i.e., reinforced learning), and 5) habit; "sequential, repetitive, motor, or cognitive behaviors elicited by external or internal triggers that, once initiated, can go to completion without constant conscious oversight" (NIMH, 2009). The common neural circuitry underlying the Positive Valence Domain clearly reflects the clinical symptoms associated with both substance use and depression, and is also based on a strong foundation of transdiagnostic research that requires a dimensional approach to psychopathology.

Cognitive Systems. The Cognitive Systems, as defined by the RDoC approach, relates to various cognitive processes. This domain includes five constructs; 1) Attention; "a range of processes that regulate access to capacity-limited systems", 2) Perception; "process(es) that perform computations on sensory data to construct and transform representations of the external

environment, acquire information from, and make predictions about, the external world, and guide action", 3) Declarative memory; which is responsible for encoding, storing, and retrieving information, 4) Language; a system of shared symbolic representations of the world, one's self, and abstract thoughts that support communication, 5) Cognitive Control; a system that controls the operation of other cognitive and emotional systems in light of goal-directed behavior and when appropriate responses are needed to select from competing alternatives (NIMH, 2009). Based on RDoc descriptives and neuropsychological research, substance use also reflects this domain, particularly with the subconstruct of Response Selection; Inhibition/Suppression under the Cognitive Control construct. Inhibition/Suppression is focused on impulsive behaviors, such as substance use.

MMPI-2-RF Clinical Scales: A Dimensional Measure of Psychopathology

Rather than using a categorical approach to measuring neurobehavioral constructs set forth by the RDoC, the current study will use a more reliable and valid dimensional measure of psychopathological constructs. The most recent version of the MMPI, the MMPI-2-RF, includes restructured clinical (RC) scales to capture a dimensional approach to psychopathology.

The devolvement of the nine RC Scales used adequate samples sizes of male and female psychiatric inpatients and patients in substance use treatment (Tarescavage & Ben-Porath, 2014). Four strategic stages were used to develop the restructured scales; 1) isolate and measure the shared demoralization factor, 2) explore two to four factor solutions to identify at least one additional Core Clinical Scale besides the distinct demoralization factor, 3) to improve internal consistency and distinctiveness, core clinical scales were kept that resulted in both strong correlations with their core factors as well as weak correlation with the other previously identified core components (i.e., seed scales), and lastly, 4) by identifying the seed scales and

including items to the seed scales that demonstrated sound, distinctive, and sufficient associations with the particular scales, nine RC scales were developed resulting in 192 non-overlapping items (Tarescavage & Ben-Porath, 2014). The current study will focus on RC2-Low Positive Emotions, for measuring positive affect (PA), and RC7-Dysfunctional Negative Emotions, for negative affect (NA).

Also in the revision of the MMPI-2, Harkness and McNulty revised their Personality Psychopathology-5 (PSY-5) Scale by undergoing a series of internal and external analyses (Tarescavage & Ben-Porath, 2014). The five broad personality traits, as measured by the PSY-5, are applicable to normal and abnormal functioning, and have been subjected to extensive examination by researchers in order to systematically move psychopathology toward dimensional models that clinicians and self-reports could understand (Harkness, Finn, McNulty, & Shields, 2012). The MMPI-2-RF PSY-5 Scale includes a measure of inhibitory control (INH), Disconstraint-Revised (DISC-r), which is a focus of the current study.

Low Positive Emotions (RC2)

As described by Ben-Porath (2012), Low Positive Emotions (RC2), a lack of, or inability to experience positive emotions (anhedonia), has been associated as a core risk factor for depression across a wide range of settings and populations (i.e., inpatient and outpatient faculties, substance abuse treatment). An elevated score on RC2 is associated with an increased probability that the individual suffers from depressive symptoms (Ben-Porath, 2012). Specifically, researchers found depressive symptoms, such as anhedonia, loss of interest, decreased appetite and sleep, weakened concentration, depleted energy, suicide, and feelings of worthlessness or hopelessness to be correlated with RC2 in psychiatric inpatients (Arbisi, Sellbom, & Ben-Porath, 2008). In sum, an elevated score on RC2 (T score $\geq$ 65) has clinical

importance across a wide range of populations, settings, and psychiatric disorders when considering the core symptom, anhedonia.

Dysfunctional Negative Emotions (RC7). According to Ben-Porath (2012), Tellegen hypothesized that positive affect and negative affect are "trait counterparts" (p.79), thus suggesting that high negative emotionality is correlated with anxiety-related psychopathology, while low positive emotionality is associated with depressive-related psychopathology. Negative Emotionality (RC7) is described as a "tendency to worry, be anxious, feel victimized and resentful, and appraise situations generally in ways that foster negative emotions" (Ben-Porath, 2012, p. 79). Watson (2005) postulated that NA may account for the variance and comorbidity among distress and fear psychopathology. Elevated RC7 scores have been associated with various anxiety related disorders in psychiatric inpatients, veterans, as well as patients receiving treatment for substance use problems (Ben-Porath, 2012). Generally, negative emotionality is a core indicator of developing an anxiety related disorder.

PSY-5 Disconstraint (DISC-r). Disconstraint (DISC-r), or inhibited self-control, tends to be associated with more risk-taking, impulsiveness, and excitement seeking behaviors, whereas low scores on DISC-r are associated with individuals who tend to follow the rules and are in general more inhibited people (Harkness, 2009). Elevated DISC-r scores have been associated with a wide array of externalizing problems, such as being diagnosed with a substance use disorder or having a history of substance misuse, juvenile delinquency, engaging in antisocial behaviors, domestic difficulties, problems with authority figures, and most notably, poor impulse control (Ben-Porath, 2015). These problems have been replicated in numerous settings such as, VA mental health and medical inpatient and outpatient facilities (Ben-Porath, 2012; Harkness et al., 2012). In addition, in a sample of National Guard soldiers, disconstraint scores were

associated with drinking and binge drinking frequency, quantity consumed in one sitting, and total yearly drinking (Harkness et al., 2012). DISC-r scores tend to been negatively correlated with an individual's ability to sustain controlled behaviors.

Mapping Clinical Constructs onto the RDoC Matrix: Neurophysiological Pathways

Anxiety Constructs

Anxiety disorders are characterized by the clinical symptoms of excessive fear and avoidance, which are often a response to certain objects or situations even when true danger is absent, and collectively are among the most common disorders in the general population (Shin & Liberzon, 2010). Recent neuroimaging research has attempted to understand underlying brain circuits that may be related to the onset and maintenance of clinical anxiety symptoms. The accumulating evidence of common neural circuitry which underlie behavioral manifestations of anxiety led to its inclusion in the RDoC model. Specifically, given the nature of anxiety symptoms in conjunction with its purported underlying neural pathways, the RDoC matrix has conceptualized anxiety as a component of its Negative Valence Domain. The RDoC based its conclusion primarily on neuroimaging studies which examine anxiety at the level of neural circuitry, and concludes that excessive anxiety is produced by the inability to regulate negative emotional input within the overall cortical-limbic pathway (Martin, Ressler, Binder, & Nemeroff, 2009).

Although it is been well-established that the amygdala and its connections to the medial prefrontal cortex regulate the normal expression of both positive and negative emotions in many organisms (Kim et al., 2011), an excessive level of activity in parts of this circuitry in humans may relate to the manifestation of anxiety, which focuses specifically on the production of negative emotion and a simultaneous relative decrease in levels of activity in the mPFC, which

tend to regulate, or dampen down, negative emotion (Liotti et al., 2000). In general, this research has concluded the abnormality in this functional circuitry lies in the inability to successfully regulate negative emotional input from the amygdala by the mPFC, resulting in the expression of anxiety symptoms.

Emerging neuroimaging literature also shows that altered mPFC activity is associated with anxiety as well. Exact regions of the circuitry implicated between the amygdala and mPFC activity differ across studies. For instance, some studies have revealed that higher levels of anxiety are correlated with both decreased ventromedial prefrontal cortex (vmPFC) and increased dorsomedial prefrontal cortex (dmPFC), suggesting different functions for regions of the mPFC (Bishop, Duncan, Brett, & Lawrence, 2004). Recent research suggests that the interplay between the amygdala and mPFC that allows individuals to react to cues that predict threat as well as regulate the reactions when the environment is in need (Kim et al., 2011). For example, diffusion tensor imaging suggested that the strength of the shared connections in the amygdala and the mPFC is correlated with levels of anxiety; meaning the weaker the pathway, the higher the probability of anxiety (Graham & Milad, 2011). Collectively, evidence suggests dysfunctions in the mPFC, as well as the shared pathway of the amygdala and the mPFC, may account for the predisposition of anxiety disorders.

The bed nucleus of the stria terminalis (BNST) has also been associated with increased anxiety; more precisely it plays a central role in sustained threat monitoring (Avery, Clauss, & Blackford, 2015). For instance, when compared to the control group, patients with anxiety disorders displayed hyperactivation of the BNST during an ambiguity gambling task, and the BNST is activated during hypervigilance in people higher trait anxiety (Adhikari, 2012). During fMRI scanning, activity in the BNST "continuously monitored changes in environmental threat

level and also subserved hypervigilant threat-monitoring processes in more highly trait anxious individuals" (Somerville, Whalen, & Kelley, 2010, p. 416). In sum, neuroimaging paradigms offer promising evidence for transdiagnostic mechanisms that underlie anxiety disorders.

Depressive Constructs. The DSM-5 (2013) defines depressive disorders as the presence of sadness, emptiness, or irritable mood that are often accompanied by somatic and cognitive changes that result in significant impairment in one's daily functioning. Depressive disorders are debilitating negative emotional states that may be related to dysfunctions in brain regions associated with emotional regulation (Seager, Rowley, & Ehrenreich-May, 2014) and abnormalities in neural reward circuity (Kujawa, Proudfit, & Klein, 2014). Given the clinical traits of depressive symptoms in conjunction with purported underlying neural pathways, we seek to integrate the literature on neural circuitry in depression with specific reference to the RDoC's Positive Valence Domain.

Depression should be conceptualized as a "multidimensional, systems-level disorder affecting discrete, but functionally integrated, pathways" (Mayberg, 2003, p. 194); which may affect the brain's capacity to sustain homeostatic emotional regulation during times of intensified cognitive and somatic stress (Zeng et al., 2012). Specifically, neuroimaging studies purport that limbic pathways are dysregulated in depression as well as altered activity in the prefrontal cortical regions and amygdala (Sliz & Hayley, 2012), which, as mentioned above, are the same neural circuitry that tends to be involved in anxiety.

Heightened negative affect describes anxiety and depression; however, anhedonia is central to depression, and anxiety is highly correlated with an increased concern over uncertain situations (Dillion et al., 2014). Anhedonia and reward processing is associated with dysfunctions in the medial orbitofrontal cortex (mOFC), vmPFC, and the amygdala;

abnormalities in these neural reward circuits may also be a crucial feature underlying depressive disorders (Dillion et al., 2014). Functional MRI studies have revealed that depressed individuals display decreased activation in reward circuits of the brain (i.e., mOFC, vmPFC, amygdala) and are less apt to regulate their behavior in response to rewards; left frontal asymmetry was also found in depressed individuals' EEGs, reflecting low approach-related motivation to rewards (Kujawa et al., 2014). Therefore, suggesting that abnormalities in response to reward may be a vulnerability marker of depression.

Functional imaging studies implicate the ventromedial (vmPFC) and dorsolateral (dlPFC) areas of the prefrontal cortex as key neural substrates underlying depression; specifically, hyperactive vmPFC plays a role in the generation of negative affect, and dlPFC hypoactivity is associated with cognitive control functions that may also pertain to emotions (Koenigs & Grafman, 2009). Depression has also been associated with abnormalities in the amygdala, particularly decreased amygdala volume (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). The amygdala has also been shown to play a role in identifying emotionally significant stimuli, as well as the recollection of emotionally meaningful events; depressed individuals show greater amygdala reactivity to emotional stimuli (Gotlib & Hamilton, 2008). Accordingly, dysfunctions in the prefrontal cortex, as well as common pathways of the amygdala may account for an individual's susceptibility to depressive disorders.

Substance Use Constructs. According to the DSM-5 (2013), the critical facet of a substance use disorder (SUDs) is a constellation of cognitive, behavioral, and physiological symptoms indicating that the individual continues to use the desired substance despite significant substance use consequences. A cardinal trait of SUDs is the "excessive pursuit and use of a substance that is disproportionate to the hedonic impact derived from it" (Baskin-Sommers &

Foti, 2015, p. 230). Different types of substances have different pharmacological and pharmacokinetic properties, but all substances share a common neural dysfunction, reward circuitry (Baskin-Sommers & Foti, 2015). In addition to cardinal feature of decreased sensitivity to reward, SUDs are also related to impaired emotional regulation, and inhibitory control (Franken & van de Wetering, 2015; Gorka, Chen, & Daughters, 2015) and much research has focused on brain reward systems and altered circuity functioning to better understand the etiology of SUDs (Lindberg, Fugett, & Carter, 2015). Specifically, SUDs neuroimaging findings should be organized with respect to key reward constructs within the Positive Valence and Cognitive System Domain.

Recently, key neural circuitry associated with SUDs (Baskin-Sommers & Foti, 2015) has been identified, including the frontal-limbic system, specifically the orbitofrontal cortex (OFC), and amygdala (Brady & Sinha, 2005), suggesting that an interactive networks of neural circuitry underlies substance use disorders.

Substance use disorders are associated with reduction in reward responsiveness, particularly to pleasant stimuli that are not drug related, which may be associated to anhedonia in depression (Gearhardt, Boswell, & Potenza, 2014). Traditionally, neuroimaging has focused on dysregulation in frontal-limbic systems associated with reward pathways in substance use disorders; including reduced frontal metabolism and hypoactivity in the amygdala, which have also been purported in depressive disorders (Brady & Sinha, 2005). In regards to reward pathways, the importance in the PFC has increased; specifically the OFC, which is involved in inhibitory decision making, especially in reward-related behaviors; decreases in the PFC are also implicated in deficits in inhibitory control, also a key clinical trait of SUDs (Dom, Sabbe, Hulstijn, & Van Den brink, 2005). Withregard to emotional regulation and inhibitory control,

reduced activity in the amygdala, dPFC, and vmPFC is associated with substance misuse (Gearhardt et al., 2014). In sum, dysfunctions in the prefrontal cortex and limbic systems may account for the vulnerability to development a substance use disorder.

Shared Transdiagnostic Constructs. The clinical symptoms of anxiety, depressive, and substance use disorders are extensive, involving emotional, motivational, cognitive and neurophysiological domains. Depression frequently co-occurs with anxiety, and it has been estimated that over half of individuals with a depressive or anxiety disorder also meet diagnostic criteria for a substance use disorders and, conversely, approximately half of individuals suffering from substance use disorders have co-occurring depressive or anxiety disorders, which suggests a significant degree of overlap among specific brain regions (Russo & Nestler, 2013). From a neurophysiological perspective, individuals with these disorders display dysfunctions in the cortical-limbic system and reward circuity.

Differential activation patterns in the brain's reward circuitry have been associated with negative emotional symptoms that often accompany clinical symptoms of depression, anxiety, and substance use disorders. More precisely, associations between self-reports of emotional states and metabolism in limbic regions have been identified across disorders (Volkow, 2004). The brain areas and neural circuitry most frequently identified as dysregulated across disorders are cortical regions of prefrontal cortex and the amygdala (Ressler & Mayberg, 2007; Peters, Kalivas, & Quirk, 2009). In general, a dysfunction in the cortical-limbic system and reward circuity could conceivably predispose an individual to an anxiety, depressive, and substance use disorder. For this reason, it is likely that current clinical nosology of psychopathological phenomena is not identifying the more "authentic" phenotypic clusters of overlapping disorders, and, in turn, may not be most useful system to move psychopathology forward.

Purpose

The National Institute of Mental Health's Research Domain Criteria Initiative (RDoC) calls for systematic efforts to integrate neurobehavioral traits into dimensional models of psychopathology (Nelson et al., 2016). Current RDoC findings suggest that common neural etiologies underlie traditionally distinct forms of psychopathology and should be better conceptualized as transdiagnostic (Insel & Cuthbert, 2010; Lilienfeld, 2014). Yet additional empirical examples are needed to link biobehavioral constructs to clinical symptoms (Nelson et al., 2016). Thus, the current study will evaluate two domains proposed by the RDoC model, Positive and Negative Valence System, to further provide empirical evidence for the extent to which depression (DEP), anxiety (ANX), and substance use disorders (SUDs) share underlying neurobehavioral constructs by using a dimensional approach to psychopathology. Our dimensional approach, the MMPI-2-RF, will allow us to accomplish our goal using the most empirically-validated and reliable measure of psychopathology in the literature.

Hypotheses

The present study will explore the associations of the RDoC's neurobehavioral constructs of Positive Valence, Negative Valence, and Cognitive Systems with clinical symptoms of frequently co-occurring syndromes identified by the DSM-IV. Specifically, we will examine the extent to which depressive symptoms (DEP), anxiety symptoms (ANX), and symptoms of substance use disorders (SUDs) share these underlying neurobehavioral constructs using the dimensional approach of the MMPI-2-RF. We will measure relevant MMPI-2-RF subscales, RC2 (Low Positive Emotion), RC7 (Negative Emotionality), and DISC-r (Disconstraint), from an archival data set comprised of veteran and non-veteran inpatients. In line with recent theory advocating a transdiagnostic approach to conceptualizing

psychopathology, we expect to see overlapping clinical symptoms across our three groups, and we also expect these overlapping symptoms will reflect the neurobehavioral domains of positive and negative valence, and cognitive systems from the RDoC model. Results from this investigation may provide greater support for building a bridge between neurobehavioral constructs derived from neurophysiologic research (i.e., RDoC model) with core features of co-occurring psychopathology using a dimensional approach (MMPI-2-RF).

Specifically, the following hypotheses will be examined in our sample:

Hypothesis 1: Researchers will demonstrate that SUDs overlap with DEP on core underlying neurobehavioral trait constructs of positive affect (PA), as set forth by the RDoC approach and measured by the MMPI-2-RF Restructured Clinical Scales RC2. We expect that:

PA, as measured with reversed directionality by RC2, will not differ between DEP only and DEP and SUD

Hypothesis 2: Researchers will demonstrate that SUDs overlap with ANX on core underlying neurobehavioral trait constructs of negative affect (NA), as set forth by the RDoC approach and measured by the MMPI-2-RF Restructured Clinical Scales RC7. We expect that:

NA, as measured by RC7, will not differ between ANX only and ANX and SUD

Hypothesis 3: Researchers will demonstrate that SUDs overlap with DEP and ANX on core underlying neurobehavioral trait constructs of INH, as set forth by the RDoC approach and measured by the MMPI-2-RF PSY-5 Scales DISC-r. We expect that:

A: INH, as measured by DISC-r, will not differ between DEP only vs. DEP and SUD.

B: INH, as measured by DISC-r, will not differ between ANX only vs. ANX and SUD**.**

C: Patients who score higher on DISC-r, may be more likely to also have SUD.

CHAPTER 3: METHOD

Participants

The data set that will be used for analyses is comprised of 2,873 inpatients and outpatients from the Minneapolis Veterans Affairs (VA) Medical Center and the Hennepin County Medical Center who completed the MMPI-2, which was converted into MMPI-2-RF, and received DSM-III or DSM-IV diagnoses as part of their comprehensive psychological assessment. The majority of are males (75.5%) with a mean age of 40.13 (*SD* = 4.018) years. The ethnic composition of the data set is as follows: 78.6% were Caucasian, 15.4% African American, 1.8 Native American, 1.1% Asian American, 1.0% Hispanic, and 1.3% other.

Measures. *MMPI-2-RF*. The 338-item Minnesota Multiphasic Personality Inventory-2-Restructured Form is a true/false, self-report inventory that was developed conceptually and empirically to assesses an individual's psychological functioning across several domains (i.e., personality, psychopathology, and social/behavioral functioning) (Tellegen & Ben-Porath, 2008) .The MMPI-2-RF contains a total of 51 scales, 9 Validity Scales, and 42 substantive scales, and for the purposes of this study we will focus on RC2; Low Positive Emotion, RC7; Dysfunctional Negative Emotions, and DISC-r; Discontraint-Revised. Reliability of the proposed RC Scales include: RC2; .84 for men and .82 for women in outpatient community mental health centers, .86 for men and women in psychiatric inpatient community hospitals, and .84 for men in psychiatric inpatient VA hospitals, RC7: .87 for men and women in outpatient community mental health centers, .90 for men and .89 for women in psychiatric inpatient community hospitals, and .89 for men in psychiatric inpatient VA hospitals (Tellegen & Ben-Porath, 2008). Reliability of the MPPI-2-RF Personality Psychopathology five (PSY-5) Scale, DISC-r, is .72 for men and .70 for women in outpatient community mental health centers, .73 for men and women in psychiatric

inpatient community hospitals, and .75 for men in psychiatric inpatient VA hospitals (Tellegen & Ben-Porath, 2008). Specifically, the MMPI–2-RF technical manual offers extensive reliability and validity data for this instrument (Tellegen & Ben-Porath, 2008). Higher scores on DISC-r indicate greater disinhibitory control, or INH-. Higher scores on RC2, or PA-, represent a lack of positive emotion, and RC7 (NA-) indicates a tendency to be worried or anxious (Ben-Porath, 2012).

CHAPTER FOUR: RESULTS

Hypothesis 1: Researchers will demonstrate that SUDs overlap with DEP on core underlying neurobehavioral trait constructs of positive affect (PA), as set forth by the RDoC approach and measured by the MMPI-2-RF Restructured Clinical Scales RC2. We expect that:

PA, as measured with reversed directionality by RC2, will not differ between DEP only and DEP and SUD

An independent-samples t-test was conducted to compare RC2 in co-occurring DEP and SUD and DEP only. There was not a significant difference in the scores for DEP and SUD (M = 69.94, SD = 15.52) and DEP only (M = 69.58, SD = 16.35); $t(1319) = -.40$, $p = .687$

The DEP and SUD (n = 613) group was comprised of 79.1% males and 20.9% females with a mean age of 38.6 and the DEP (n = 708) only group was 68.6% male and 31.4% female with a mean age of 41.4.

Hypothesis 2: Researchers will demonstrate that SUDs overlap with ANX on core underlying neurobehavioral trait constructs of negative affect (NA), as set forth by the RDoC approach and measured by the MMPI-2-RF Restructured Clinical Scales RC7. We expect that:

NA, as measured by RC7, will not differ between ANX only and ANX and SUD

An independent-samples t-test was conducted to compare RC7 in co-occurring ANX and SUD and ANX only. There was not a significant difference in the scores for ANX and SUD (M = 65.11, SD = 14.22) and ANX only (M = 63.67, SD = 15.06); $t(82) = -.45$, $p = .657$

The ANX and SUD (n = 36) group was comprised of 75% males and 25% females with a mean age of 40.3 and the ANX (n = 48) only group was 75% male and 25% female with a mean age of 44.1.

Hypothesis 3: Researchers will demonstrate that SUDs overlap with DEP on core underlying neurobehavioral trait constructs of INH, as set forth by the RDoC approach and measured by the MMPI-2-RF PSY-5 Scales DISC-r. We expect that:

A: INH, as measured by DISC-r, will not differ between DEP only vs. DEP and SUD.

An independent-samples t-test was conducted to compare DISC-r in co-occurring DEP and SUD and DEP only. There was a significant difference in the scores for DEP and SUD (M = 61.02, SD = 11.47) and DEP only (M = 53.65, SD = 11.41); $t(1319) = -11.68$, $p < .001$

B: INH, as measured by DISC-r, will not differ between ANX only vs. ANX and SUD.

An independent-samples t-test was conducted to compare DISC-r in co-occurring ANX and SUD and ANX only. There was a significant difference in the scores for ANX and SUD (M = 60.67, SD = 12.46) and ANX only (M = 52.23, SD = 9.54); $t(82) = -3.52$, $p < .001$

C: Patients who score higher on DISC-r, may be more likely to also have SUD.

An independent-samples t-test was conducted to compare DISC-r in SUD and no SUD. There was a significant difference in the scores for SUD (M = 61.28, SD = 11.49) and no SUD (M = 53.99, SD = 11.21); $t(2871) = -17.021$, $p < .001$

The SUD (n = 649) group was comprised of 78.9% males and 21.1% females with a mean age of 38.7 and the no SUD (n = 756) only group was 69% male and 31% female with a mean age of 41.5.

CHAPTER FIVE: DISCUSSION

The purpose of this study was to provide systematic efforts to integrate neurobehavioral traits into dimensional models of psychopathology that correspond to constructs of Positive and Negative Valence, and Cognitive Systems as set forth by the NIMH's RDoC initiative.More specifically, this study attempted to demonstrated that core neurobehavioral traits overlapped with clinical symptoms with regards to depression (DEP), anxiety (ANX), and substance use disorders (SUDs) using the most empirically-validated and reliable measure of psychopathology in the literature, the MMPI-2-RF. These findings did not provide evidence for viewing SUD as transdignostic. However, and with regards to the current findings, limitations, and future research is discussed in order to further advance research and shift current categorical taxonomies to a more empirically and etiologically based nosology of psychopathology.

With regards to PA, as measured with reversed directionality by RC2, the relationship was as predicted; individuals diagnosed with a depressive disorder alone did not differ from co-occurring depressive and substance use disorder on measures of positive affect. Individuals diagnosed with a depressive disorder did not score lower on levels of PA than individuals with co-occurring DEP and SUD. This is in line with neuroscientific work showing that depressive symptoms may not be discrete emotional states from substance use disorders.

Researchers demonstrated that the association between individuals diagnosed with an anxiety disorder alone and co-occurring anxiety substance use disorder on measures of negative affect was not significant. That NA showed no differential relation between ANX and ANX and SUD is not surprising in light of pervious neurophysiological research which purports that individuals with these disorders display dysfunctions in the cortical-limbic system and reward circuity, and high co-occurrence rates (Russo & Nestler, 2013).

However, differential patterns of association were evident for two constructs in relations to INH; individuals diagnosed with a depressive disorder differed from individuals with a co-occurring depressive and substance use disorder, this pattern of associations was also seen with anxiety disorders versus co-occurring anxiety and substance use disorder. Research has established that dysfunctions in the connectivity between amygdala and the vmPFC may increase susceptibility to anxiety and depressive disorders (Motzkin et al., 2014). However, the exact processes by which the vmPFC influences affective processing are not entirely understood. Yet, it is proposed that the vmPFC serves to regulate negative affect by "top-down inhibition" of brain regions involved in processing negative emotion, mainly the amygdala. Thus, clinically elevated levels of negative affect in depressive and anxiety disorders develop due to dysregulations in the vmPFC and interconnected amygdala activity (Motzkin et al., 2014). As mentioned before, the vmPFC has been implicated as a critical component of decision making. It is well documented in neuropsychological research that areas of the brain implicated in decision making influence levels of inhibitory control (Boes et al., 2009). Hence, patients with dysregulated vmPFC display an impaired ability to weigh risks and benefits effectively. And recent advances in neuroimaging techniques have shown that substance use has been shown to further impair the vmPFC (Boes et al., 2009), thus exacerbating weak inhibitory control. Consequently, when a patient lacks vmPFC regulation of the amygdala as a result of co-occurring substance use, there is an increased activation in the amygdala possibly accounting for the differences in co-occurring SUD and DEP or ANX. In line with this inhibitory model of vmPFC function, SUD, ANX, and DEP symptoms may share common circuity, yet the extent to which the vmPFC modulates amygdala function may differ. Hence, the exact processes by which the vmPFC influences the amygdala across disorders is warranted before conceptualizing

SUD as "transdiagnostic." Considering INH showed differential patterns of associations across clinical symptoms with regards to depressive, anxiety, and substance use problems.

Some limitations of the present study should be addressed when considering the implications of the findings. First, variables were based on self-reports and DSM-III or DSM-IV diagnoses. It will be important in future research for clinicians and researchers to replicate these findings based on clinical presentation and symptomology in order to provide information beyond DSM diagnoses. This will aid in providing more ideal treatments modalities for 'disorders' that may share common neural circuitry. It will be important to operationalize INH in other ways, not only by self-report measures, or clinician rating, but in physiological (EEG), neurological measures (fMRI), and other behavioral measures (Go-NoGo task) as well. Comparing self-report assessments and/or clinician rating to fMRIs findings may provide even more fruitful information to better understand the gap between DSM categories and emerging neuroscience. Also given the number of statistical tests performed, it will be important to see if findings differ in new samples. It is important to note that this sample is comprised of mostly middle age, white males, and thus a sample with broader demographics would further provide generalizability.

Aside from the limitations, the current findings have important implications diagnostically and for neuroscientific research that focuses on understanding the extent to which neurobehavioral constructs are shared across depressive, anxiety, and substance use. These findings suggest that inhibitory control plays a critical role in patients that pathologically use substance. Lower levels of INH could denote a distinct pathophysiological process in patients who are diagnosed with a substance use 'disorder.' Moreover, research postulates that the cardinal feature of a SUD is the decreased sensitivity to reward, however behavioral

dysregulation related to unconstrained behavior (poor inhibitory control) may play a more vital role in clinically elevated substance use. With regards to treatment, impaired inhibitory control leads to using more of a substance than intended, and failed attempts to control one's use. Clinically elevated levels of inhibitory control have also been correlated with a significant risk for treatment noncompliance and an unlikelihood that the patient will be internally motivated to seek treatment (Tellegen & Ben-Porath, 2008). Hence, inadequate impulse control as the target of treatment may increase attempts in controlling substance use, preventing relapse, and increase overall noncompliance. It will be important to continue to explore the role of INH as well as other possible transdiagnostic traits with regards to DEP, ANX, and SUD given the common neural circuitry. Globally, systematic efforts that integrate neurobehavioral traits can move psychopathology toward a more etiological based conceptualization of psychopathology that assess across clinical symptoms.

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