A Call to Integrate Neuroscience and Translational Research in Psychopathology: A literature review of the RDoC and substance abuse disorder

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Introduction

In general medicine, and much more in the treatment of psychiatric illness, one size does *not* fit all. Expansive breakthroughs in science and medicine have given scientists insight into the biological causes of diseases and disorders heretofore unimaginable until the past several years. Moreover, the field of neuroscience has begun to unravel the complicated networking systems of the human brain, and scientists are slowly beginning to comprehend how humans process the world around them. This has allowed for personalized treatment and improved results in physical health. But what of emotional and mental health? The focus of this review is to call for the integration of neuroscience and translational research in psychopathology, a field concerned with the malfunctioning of those processes. The Research Domain Criteria (RDoC), a project launched by the National Institute of Mental Health in 2009, is the basis for this literature review, due to its transdiagnostic nature and focus on integrating neuroscience into mental health research and treatment. The limitations of the current classification system of mental disorders will be reviewed in chapter 1, followed by an overview of the RDoC format. Chapters 2 and 3 will cover genetic and neuroscientific research, including the concept of endophenotypes which the RDoC matrix is structured upon, and chapter 4 will focus on the reward system and its abnormal functioning in substance use disorder (also known as addiction).

In attempts to move past using specific DSM diagnoses, it may seem counterintuitive to focus on one particular disorder, such as substance use disorder. However, substance use disorder can be especially useful as a template for a transdiagnostic mechanism when studying the underlying biology of psychopathology. Substance use disorder is frequently co-diagnosed with other mental disorders. Statistically, according to the US Department of Health and Human

Services, 41-65% of those suffering from a lifetime substance use disorder also have a history of at least one serious mental illness, and 50% of those with a lifetime serious mental illness also have a history of at least one substance use disorder (Perron, Bunger, Bender, Vaughn, & Howard, 2010, p. 1263).

Moreover, substance use passes through several stages of differing patterns of behaviors, employing different neural circuits, affective states, cognitive functions, and behavior patterns. The "downward spiral" of the addiction cycle can actually mimic different disorders as it progresses through these various stages, which allows researchers specific targets for research during this process (Everitt, Belin, Economidou, Pelloux, Dalley, & Robbins, 2008). For example, the competing processes of what the addict "wants" vs. "does" (self-reported desire to stop yet the inability to do so) provides researchers a dense subject matter of neurological dysfunction. By focusing on the underlying circuitry involved, rather than on the illness itself, substance use disorder casts a wide net when searching for dysfunctional processing of neural circuits.

It is time to redefine the understanding of mental disorders, and change the ways of research and treating them. The current literature review seeks to illumine this new approach in psychopathology.

Chapter 1- Classification System

In his State of the Union address in 2015, President Obama proclaimed the new Precision Medicine Initiative (PMI), a dramatic shift in healthcare and medicinal research that will be centered on the patient rather than the disease. Far too many diseases go untreated, or ineffectively treated, because of a lack of understanding of their underlying biology. This new

initiative seeks to change that. The goal of the PMI is to incorporate a patient's genetic and environmental information, as well as the molecular manifestations of a disease, into treatment efforts. The $215 million investment in the PMI will aid researchers in discovering biomedical innovations for prevention, treatment, and even cures for medical diseases and conditions. Rather than focusing efforts toward the "average patient" of a specific diagnosis, the goal is to clarify specific illnesses and target interventions for treating and preventing them.

With an increased comprehension of the biological underpinnings of diseases, scientists can help improve the health of millions of people by using a more clear-cut approach to treatment as well as improving prevention efforts. The PMI uses an interdisciplinary approach ranging from genomics, epigenomics, proteomics, and bioinformatics, so clinicians will be able to specify not just what disease a patient has, but what *type* of that disease and how it is uniquely manifested in their specific condition. Moreover, due to large-scale data collection, a prominent factor of the PMI, scientists will have a more complete knowledge network of the molecular and genetic causes and risks for heritable and infectious diseases.

Great strides have already been made with this initiative for some medical conditions such as cancer. Distinct types of genomic signatures for several types of cancers have already been discovered because of this approach (Collins & Varmus, 2015, p. 794). Improved research efforts toward molecular diagnoses will continue to address certain problems in precision oncology, such as unexplained drug resistance and genetic variances between tumors.

The PMI is possible because of vast technological and scientific progress in recent years. Due to continuous breakthroughs in fields like molecular, cellular, and systems neuroscience, there is an ever-increasing understanding of the human body and its inner workings (for further review see Insel & Landis, 2013).

In just one example, the National Institute of Health has seen incredible developments in this area by funding the Human Connectome Project (HCP), an effort that has set out to map the brain's neurological wiring in its entirety (Van Essen et al., 2012). Until now, neuroscientists have only been able to infer conclusions based on studying different areas of the brain. The HCP, however, will collect data and images from the brain as a whole. This is a fundamental paradigm shift toward understanding mental processing, especially related to complex disorders such as schizophrenia, substance use disorder, and bipolar disorder. Researchers involved in the project are optimistic about the use of the project's data, believing that the benefits resulting from the HCP will include: more precise charting of brain parcellations, brain networks, and their dynamics; improved specificity of measurement of individual brain network variation; and increased understanding of the relationship between phenotypes and neural networks (Van Essen et al., 2013, p.77). The advantages of the clinical utility of this type of data are self-explanatory, and researchers are understandably very hopeful.

Sadly, the progress for the treatment of mental disorders is far less impressive. Neuropsychiatric illness is the leading cause of disease burden in the developed world, and is the largest source of years lived with disability; furthermore, mental illness is highly correlated with suicide--rates are over 38,000 per year in the US--and most of those involved a mental disorder (Insel & Landis, 2013, p. 563). The societal burden is substantial as well, in 2010 the cost of lost earnings due to psychiatric illness was estimated to be $200 billion per year (Akil et al., 2010, p 1580). Moreover, treatment advances in this field are sorely lacking. There have been no significant breakthroughs in treatments for schizophrenia in over 50 years, and none for treatment of depression in the last 20 years (Akil et. al, 2010, p. 1580).

The method of diagnosis for mental disorders is the clinical observation of symptoms. Currently, clinicians rely on categories of clustered signs and symptoms to diagnose and treat mental disorders. The NIMH challenges this approach by highlighting the lack of neurologically-based criteria as the reason for the gap in progress in this field, compared with the improvements seen in the medical health profession (Pemberton & Wainwright, 2014, p. 218). In other words, we are relying on outdated observational methods when the expanse of neuroscience has given us new and exciting insight into brain functioning.

Scientists have recognized for some time that psychological disorders are not just behavioral problems, but involve dysfunction in the brain. What we are seeing now, however, is that these disorders are not limited to one site in the brain, but involve many areas. Psychiatric disorders, then, would be better thought of as "brain circuit problems"—what researchers have called 'connectopathies', rather than straight neurological disorders that damage a specific part of the brain (Collin, Turk, van den Heuvel, 2016, p. 1). These circuits can be identified using the new technological developments of functional imaging.

Yet, even with all the excitement surrounding methods for viewing brain connections in vivo, as well as advances in electrophysiology and functional neuroimaging, skepticism abounds. Many psychologists fear that clinicians will be swept away by biological approaches, restricting their ability (or willingness) to include psychological, behavioral and social dimensions of a disorder. Proponents of the biopsychosocial model argue that, despite proclamations of coming closer to significant treatments for mental disorders, the biomedical model has produced little progress toward this end. In fact, while cases of patients suffering from mental disorders have increased, cures seem just as far off as they did decades ago; citing lobotomies, electroconvulsive

therapy, and insula coma treatments, many critics think the disease model of mental disorders has caused more harm than good (Deacon, 2013, p. 848).

Some critics go so far as to reject the notion of mental illness altogether, such as Thomas Szasz, a vehement opponent of psychiatry despite being a psychiatrist himself. Szasz claimed that mental disorders were not real because illness requires the presence of a physical lesion, and since the mind is not an organ, it cannot be afflicted in such a way (Vatz & Schaler, 2008, p. 60). Thus, he argued mental disorders were "metaphors" and "problems of living" rather than medical conditions; furthermore, he criticized psychiatry's view of symptoms *as* the disease, rather than a *sign* of disease (Vatz & Schaler, 2008, p. 58, 60). He also thought that mental health diagnoses were a form of social control, to impose moral values and/or attempt to mitigate responsibility from those who were guilty of criminal behavior.

Though Szasz's theories are misguided, mainly due to his anachronistic belief in mind/body dualism, there is a point he makes that must not be overlooked. Essentially, Szasz was not belittling the suffering experienced by individuals with these illnesses, nor was he invalidating the empirical evidence of symptoms; rather he was suggesting that until biological etiology could be accounted for, clinicians were grasping at classifications based *solely* on symptoms. Szasz maintained that when these biological causes were discovered, they would not reveal disorders of the mind—but disorders of the brain. This is an important distinction, and has since been recognized by many clinicians and researchers alike.

Take schizophrenia, for example. Many decades ago, physicians viewed schizophrenia as a disorder of the mind, with no discernable physical abnormalities (Aftab, 2014, p. 20). Thanks to neuroscience, however, scientists are now aware of many abnormalities in the brain that

underlie this disorder; including, but not limited to, impaired synaptic connectivity, decreased cortical volume and thickness, and compromised neuronal and axonal integrity (Darrick & Joseph, 2011). Further, disturbances in the dopaminergic and glutamatergic neurotransmitter systems have been detected (Falkai, 2012). Nevertheless, the vast complexity of this disorder leaves the discovery of a specific biological cause well outside the grasp of current understanding. It is the opinion of most scientists that different discoveries about this disorder should not be regarded as mutually exclusive, but that each could provide further insight into the connectivity of neural circuits and the impact of many biological factors present in one disorder.

The limitations of the present diagnostic criteria prevents expanded research into this disorder, mainly because of the nature of criteria necessary for schizophrenia diagnoses. The functional and chronological criteria is unclear and applied very inconsistently (Maj, 1998, p. 459). Moreover, the symptomatological criteria confuses the heterogeneity of symptoms of schizophrenia because several schizophrenic symptoms can also be found in major depressive disorder, mania, and dementia (Maj, 2011, p. 21). Due to these complications, scientists are beginning to suggest the redirection of research attention; perhaps the focus should be towards organic causes of symptomatology, rather than starting with rigid disorder categories.

Current diagnoses stem from the highly relied up Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Statistical Classification of Diseases and Related Health Problems (ICD). The DSM and ICD have been incredibly useful and widely respected, but they are not without their flaws. These tools were designed to provide a consensus on what constitutes a mental disorder with common language and standards that could be used by clinicians, researchers, health and pharmaceutical companies, etc. This focus on inter-rater reliability was well-intentioned, but many argue that high reliability should not be a substitute for

validity (Hagan & Guilmette, 2015, p. 2). In other words, the agreement between scientists as to what constitutes a mental disorder is a veneer of actual scientific legitimacy, as majority agreement does nothing to get us closer to actually *understanding* these disorders.

As medicine and scientific research have progressed, DSM/ICD revisions have been made, yet they still garner hefty criticism and controversy. Among these criticisms are the lack of biological validity, the superficial reliance on subjective observation and self-reports, and the lack of validity of the diagnostic categories themselves; furthermore, many of these diagnostic categories arbitrarily define disorders and ignores the overlapping symptoms between them, which leads to an overabundance of co-morbid diagnoses (Lilienfeld, 2014).

The latest revision of the diagnostic manual, the DSM-5, does attempt to incorporate biological findings in its assessment of mental disorders, highlighting validators such as genetic traits, similar neural substrates, and possible biomarkers, yet the emphasis is still focused on clinical usefulness among clinicians rather than successful treatment options for individual patients (Hofman, 2014, p. 578). Even the switch from roman numerals to the decimal system reflects an openness to allow for revisions when new empirical evidence become available (Wakefield, 2013, p. 140). However, this new addition of biological component did not prevent vehement scrutiny and denigration. First among the concerns is the discontinuation of the multiaxial system found in previous DSM editions, most notably eradication of Axels IV and V (Raines, 2014, p.2). These Axels addressed the psychosocial and environmental factors that contribute to or cause mental disorders, and the strengths of the individual being diagnosed, respectively (Raines, 2014, p.2). The inclusion of biological factors is a step in the right direction for the DSM-5, but swinging the pendulum so far towards *only* the biological side of these disorders leaves no room for the psychosocial factors that contribute to their complexity. By

narrowing the criteria to focus *solely* on biological factors, the DSM-5 misses the mark for adequately understanding the nature of mental disorders. There have been no single biological causes identified in psychiatric disorders, so the elimination of possible environmental factors in diagnosis is premature at best, and irresponsible and misleading at worst.

Other controversy was stirred by the inclusion of several more disorders to the DSM-5 manual. Of the 94 suggestions of new diagnostic categories, the DSM-IV added only two; yet the DSM-5 has added *several* more diagnoses such as grief disorder and somatic symptom disorder, and further blurred the lines of existing diagnostic categories by loosening criteria for certain disorders like the already overused diagnosis of adult ADHD (Frances, 2013, p 221.). Critics worry that this will lead to an inflation of assumed prevalence of mental disorders in the general population, and lead to a "medicalization of normal human distress" that is only beneficial for pharmaceutical companies looking to recruit more pharmacological customers (Kinderman, Read, Moncrieff & Bentall, 2013, p. 2). Also among the concerns is the apparent reduction in reliability estimates from DSM-5 field trials, which suggest that "reliability of psychological diagnosis may be lower than commonly believed" (Chmielewski, Clark, Bagby, & Watson, 2015, p. 768). Allen Frances, professor at Duke University and previous chairman of the DSM-IV task force, points out that previous editions of the DSM required a disorder to show a significant kappa reliability of about .6 to be considered acceptable; the DSM-5 allowed for a kappa as low as .2 in some cases (Chimielewski et al., 2015, p. 765).

In contrast, the RDoC is a formative new way of studying mental disorders. The RDoC aims to be a biologically-valid, neuroscientifically-informed framework for understanding mental disorders. Because behavioral symptoms are multidetermined, diagnoses based on presenting complaints are unavoidably heterogeneous in terms of pathophysiology (Insel, 2014).

Therefore, the NIMH has conceptualized a way to incorporate neuroscience and genomics into current research methods and clinical observations to ultimately help inform a better way of classifying mental disorders in the future (Insel et al., 2010, p. 748).

The RDoC urges scientists to study "fundamental biobehavioral dimensions that cut across heterogeneous disorder categories…from genes to circuits to clinical behavior" (Østergaard, 2014, p. 409). Advances in DNA sequencing and neuroimaging can give us new insight into psychological disorders not yet seen in medical and clinical practice. This new integrated approach is able to cover the entire spectrum of human functioning, rather than being limited to a diagnostic category. So many mechanisms are at play in mental disorders, many of which are still poorly understood at a basic level, much less at the level of complexity seen in psychopathology. Many disorders share the same symptoms, and many symptoms vary wildly within the range of each diagnostic category.

The RDoC project was created as a possible solution to the predicaments encountered by the current nosological system. The NIMH Strategic Plan 1.4 states the Institute's goal is to, "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" (Casey, Craddock, Cuthbert, Hyman, Lee & Ressler, 2013, p. 812). Moreover, the RDoC seeks to study the complete spectrum of functioning, from normal to pathological (Casey, et. al, 2013, p. 812). Critics of the nature of the "well" versus "ill" concept of the DSM will rejoice over the inclusion of a spectrum for mental disorders, such as those seen in diabetes and hypertension; this concept was also most recently applied to autism, the first real revision in the right direction for the DSM.

The NIMH stresses the notion of the RDoC as a framework for research, rather than a replacement of the DSM/ICD diagnostic tools. The ultimate goal *is* toward a new classification system, or perhaps just an improvement of the old one, but that is way down the line. Rather, the RDoC will attempt to move psychiatry forward by examining what the brain actually does, then seek to determine malfunctions within those systems. Beginning with the neural circuitry of the brain in healthy function, researchers will be able to better map out what goes wrong in an entire network of the brain instead of just one or two areas. This is no small feat, and the NIMH is well aware of the tremendous workload that awaits this new approach. Nevertheless, the disentanglement of intricate circuitry within the brain could be the most promising revolution in both psychology and mental health science has seen yet.

The RDoC created a matrix to use as framework for research. This grid is comprised of rows that contain domains and constructs, and columns which specify units of analysis. The research is blind to diagnostic categories; rather, the heuristic is guided by current knowledge about neural circuits and their associated genes, molecules, physiological signals, and behaviors as well as by gaps in that knowledge (Morris, Rumsey, & Cuthbert, 2014, p. 9). The five domains include: negative valence systems (fear, anxiety, loss), positive valence systems (reward learning, reward valuation), cognitive systems (attention, perception, working memory, cognitive control), systems for social processes (attachment formation, social communication, perception of self, perception of others), and arousal/modulatory systems (arousal, circadian rhythm, sleep and wakefulness; Kozak & Cuthbert, 2016, p. 289). The constructs within these domains were decided upon through workshops where experts were consulted to discover what similar systems are known about that cut across many disorders.

These domains will be studied by seven different units of analysis. These units include: genes, molecules, cells, circuits, physiology, behavior and self-reports; also included will be a unit of analysis titled "paradigms", which will include different lab tasks used to study these constructs (Kozak & Cuthbert, 2016, p. 289). Contrary to some concern, one can see the inclusion of behavior and self-reports do not narrow the focus of the RDoC to biology alone. Instead, the goal is to provide a comprehensive understanding of both phenomena, which are neither exclusively biological nor psychological, thus resulting in more dynamic and compelling theories in the end (Cuthbert & Kozack, 2013, p. 931). The focus on brain-behavior relations incipiently, then connecting them to clinical phenomena, is a revolutionary way to study these brain disorders.

The opponents to the RDoC and reappraisal of mental disorders as brain disorders are numerous, many citing that there is no scientific basis for such a claim (McLaren, 2013). However, if human processing occurs in the brain, then it would behoove every scientist to know more about the organ of interest. This is the basic reasoning behind the call for neuroscience to inform the arena of clinical practice. Indeed, this concept is the very foundation of translational research.

Translational research is defined as "the transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing, or treating disease" (Hall, 2002 p. 235). In many other areas of medicine, the approach of studying the genetic, cellular, and molecular aspects of diseases has led to increasingly more specific and efficacious treatment options. The interdisciplinary fields in academia also reflect the recognition of the paradigm shift toward translational medicine and research. Areas such as behavioral neuroscience, biological psychology, neurophysiology, and other programs are designed to integrate the disciplines of the

life and physical sciences, mathematics, engineering, psychology, and medicine. Some universities have developed programs to span the breadth of these disciplines to prepare students for a career in translational research.

This need for collaboration among disciplines is not meant to imply that the work done by basic research or clinical practice alone are thus far are without merit. However, this bench-to-bedside approach will enable scientists to bridge the gaps that single disciplinary research has left in the field. We are in need of scientists that are willing to venture beyond their "comfort zones" in terms of their areas of expertise and embrace insights discovered outside of these domains (Chiccetti & Toth, 2006, p. 621).

Chapter 2- Genetics

The latter part of the 20th century began a shift, with new discoveries in molecular biology leading to increased knowledge of the structure and function of DNA. The completion of the human genome in 2003 was a huge step toward a new understanding of human biology. With greater understanding of human functioning at the genetic, molecular, and cellular level, came a realization that dysfunction occurs at these levels as well. Psychiatric disorders are no longer thought to be simply behavioral or environmental, as once assumed, but have biological components that must be included in our overall understanding of psychopathology.

Though trait inheritance was speculated and assumed long before the technology to study it was created, the scientific discipline of genetics was founded by the late 19th-century scientist, Gregor Mendel, who used pea pods to test his theory that organisms pass down certain traits to their offspring (Garlick, 2006, p. 53). Mendel's pioneering work set the stage for much of what geneticists still do today, investigating trait and molecular inheritance passed down through family lines. It is now established that every human child inherits half of their genes from their father, the other half from their mother, resulting in specific traits that are expressed. Some of these are physical, such as hair and eye color, and many other traits have been found to be genetic as well, such as personality traits, behaviors, and risk for certain diseases (Vukasović & Bratko, 2015, p. 780; Adams et al, 2015, p 12,81).

The field of genetics led to large discoveries for disease etiology. Many diseases, such as Rett's syndrome, cystic fibrosis, and sickle-cell anemia, were found to be caused by mutations in a single gene (Chial, 2008, p. 192). These disease are appropriately termed "Mendelian", or single-gene, disorders. Unfortunately, *most* diseases were found to be much more complex. The

term "polygenic" is used to describe disorders with at least two (but usually many more) genes that work together to influence phenotypic (observable) expression. The task of geneticists dealing with the etiology of these types of disorders, including psychiatric disorders, was now to differentiate between what portions of the disorder were due to the genotype (the information carried in an individual's genes) and what portions were due to other factors. This is the reason scientists are often interested in the heritability estimate of each disorder.

Heritability is the ratio of variation due to differences between genotypes and the total phenotypic variation for a characteristic or trait in a population (For a full review, see Urbanoski & Kelly, 2012). Heritability estimates determine how strongly a characteristic is shared in a family by evaluating the prevalence rate of that characteristic among family members, so that the percentage rate of that characteristic shared among family members can be attributed to biological factors (Garrett, 2015, p. 112). Consequently, it has been well-established that mental disorders aggregate in families, with high heritability estimates for schizophrenia (.80-.84), bipolar disorder (.60-.70), autism (.90) and moderate estimates for all anxiety disorders (.30-.40) and major depression (.28-.40) (Merikangas & Risch, 2003, p.626).

Another way to research heritability is by comparing twins and adoptees. Adoption studies compare the similarities between children and their biological parents (heredity) and their adoptive parents (environment), whereas twin studies compare the similarities between identical (monozygotic) and fraternal (dizygotic) twins (Garrett, 2015, p. 113). Twin studies are able to be more specific when determining genetic factors because monozygotic twins share 100% of their genetic material, while dizygotic twins share 50%. The studies comparing twins and biological children reared apart from their parents such as in adoption studies, are very beneficial for genetic research because they allow scientists to separate genetic and environmental factors.

Results from twin and adoption studies have shown that substance abuse disorders are highly heritable, with alcohol abuse heritability estimates ranging from .50 to .60, and estimates from .30 to .80 for other substances; moreover, first-degree relatives of individuals with a substance abuse disorder show a 4-8 fold increase in the risk of those relatives developing the disorder themselves (Urbanoski & Kelly, 2012, p.61).

Unfortunately, high heritability estimates like these are somewhat misleading. Though discovering the heritability of psychological and behavioral traits was helpful in determining a genetic element to these traits (as opposed to a strictly environmental causality, as was once the primary assumption), it does little to explain their origin or explain their pathology in individuals. One reason is because heritability estimates are reflections of aggregation of variance in *populations*, not individuals; thus, the expression of many genetic polymorphisms for any given trait will show increasingly higher heritability rates across populations, which broaden the possible functioning of each gene rather than narrowing our understanding of what each gene actually does (Johnson, Penke, & Spinath, 2011, p. 256). Another reason that heritability is misleading is that genetic factors alone do not properly incorporate the prominent role of environment in determining phenotypic causality. Innovations in behavioral genetics are discovering more and more that genes and environment both have significant contributions in the development of phenotypes, and the assumption that genetics and environmental influences are independent (the underlying assumption when determining heritability) is simply inaccurate (Johnson et al, 2011, p. 258).

Kendler (2013) astutely illuminates that a stunning amount of traits are heritable, from hours spent watching television (Plomin, Corley, DeFries, & Fulker, 1990) to church attendance (Kendler & Meyers, 2009); thus, claims that heritability provides insight into biological causality

of psychiatric disorders are an over-simplification. Rather, brains are wired from genetic instructions, so essentially everything that makes up one's brain is created from genetic information. Kendler (2013) also remind us that "individual psychiatric disorders are clinical-historical constructs, not pathophysiological entities" (p.1059). As we have already noted, the DSM and ICD diagnostic categories are constructs created to provide consensus among clinicians and are not based in biology, which means they do not map on to any physiological pathology. Therefore, approaching the biology of psychiatric disorders with the current diagnostic categories might complicate, or worse *prevent*, discovering the biological etiology of psychopathology.

The advent of molecular genetics has allowed scientists to study the structure and function of specific genes. Hyman (1999) explains, "The goal of modern molecular genetics research is to identify the genetic loci (a locus is literally a place in the genome, which may range from a single DNA nucleotide to a deletion of a large chromosomal segment) that contribute to a trait, such as vulnerability to a mental illness," (p. 518). However, he goes on to report, "…it appears that multiple alleles found at multiple loci within the genome interact to produce vulnerability to a mental disorder" (Hyman, 1999, p. 518).

Complexity notwithstanding, there are two approaches that have been largely utilized in determining genetic factors of psychopathology: linkage gene mapping and association studies. "Linkage has highlighted specific chromosomal regions; association studies have suggested specific genes implicated in the predisposition to, and protection from, addiction" (Ball, 2006, p. 448). In other words, linkage studies are concerned with *where* the implicated genes are located. Association studies are concerned with *which* genes are implicated. The idea behind these methods is that if the specific locations of genes or alleles that are involved in disorders are

discovered, it will lead to a discovery of causality. Progress has been made with these approaches, but once again the incredible complexity was not anticipated. Studies on alcoholism produced genetic linkage to *several* chromosomal regions, and identified even more candidate genes, which are discussed below.

Linkage studies for alcohol dependence showed possible connections to chromosomes 1, 2, and 7, with protective factors found on chromosome 4, and possible linkage to chromosome 16 (Reich et al., 1998, p. 211-213; Reich, Culverhouse, & Beirut, 1999, p. 600). Since these studies were conducted, the use of wider genome scan availability has led to the identification of 41 chromosomal regions that may contribute to polysubstance use vulnerability (Kreek, Nielsen & LaForge, 2004, p. 88). The vast number of possible loci for specific genes in a given disorder, coupled with the lack of sensitivity to smaller effects of important genes in a given disorder, have left a lot to be desired from linkage study results (Ball, 2008, p.364). Linkage studies have proven disappointing in the quest for discovering the pathophysiology of complex disorders because "the effects of the underlying genes are not strong enough to be detected by linkage…Therefore, genome-wide association studies have been offered as a more powerful approach" (Merikangas & Risch, 2003, p. 626).

Association studies, however, have implicated at least 1,500 genes affiliated with risk for substance abuse (Urbanoski & Kelly, 2012, p. 62). Kreek, Nielsen, and LaForge (2004) highlight a few selected genes that are involved in susceptibility to addiction, some of which are drug specific (i.e. alcohol dehydrogenase (ADH) in alcoholism, kappa and delta opioid receptors in opiate addiction) while others within the dopamine, serotonin, and GABA systems have shown to be involved in addiction across several different substances, as well as in polysubstance addiction (for review see Kreek, Nielsen & LaForge, 2004). It is well established that these

systems are also implemented in a wide range of psychiatric disorders, implying risk genes most likely overlap between substances use disorders and co-morbid psychiatric diagnoses.

In just one example, a study using data from the Psychiatric Genetics Consortium determined shared genetic etiology across five psychiatric disorders, with significant correlations between schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) (Lee, Ripke, Neale, Faraone, Purcell,….Asherson, 2013, p. 989). As we can see, though the findings of association studies have been promising, they still cast too wide a net to provide specific, accurate detection of the underlying biology of any of the complex psychiatric disorders mentioned. Moreover, we must remember that genes are not the *only* factors that contribute to psychopathology.

The complex interplay between genes and environment is of particular importance in psychiatric disorders. Kremen, Panizzo, and Cannon (2016) highlight the difference between two different phenomena: gene-environment correlation and gene-environment interaction (p. 3). Gene-environment correlation is where one's genotype will influence the environment they inhabit, and these effects can be passive, evocative, or active (Kremen, Panizzo, & Cannon, 2016, p. 3). This is especially important for externalizing psychiatric disorders, such as substance use disorder, in which individuals shape their own environments often leading to undesirable behavior. Gene-environment interaction, however, refers to the phenomena whereby a person's *response* to environmental factors will influence genetic expression (or mutability) based on their genotype (Kremen, Panizzon, & Cannon, 2016, p. 3).

Glatt, Montalvo-Ortiz, Gelertner, Hudziak, and Kaufman (2016) discuss gene-environment interaction and their involvement in stress-related disorders citing that maltreated children are at risk for a host of psychiatric illnesses such as major depression, post-traumatic

stress disorder, anxiety disorders, aggressive behavior, and substance abuse (p. 81). Glatt et al. (2016) also state that each candidate gene associated with stress-related disorders were also associated with a variety of phenotypic traits, emphasizing the pleiotropic effects of a number of risk genes for several psychiatric disorders, which can lead to exacerbated comorbidity diagnoses (p. 82). Glatt et al. are therefore enthusiastic supporters of the RDoC efforts to study specific clinical phenotypes, rather that multifaceted clinical syndromes (p. 87).

Building upon the concept of the interplay between genes and environment, Glatt et al. (2016) also turn their attention to the field of epigenetics. The term epigenetics refers to "changes in the genetic material that leads to phenotypic changes without altering the DNA sequence" which include DNA methylation and modifications to the DNA packaging material, chromatin (Umesh & Haque Nizamie, 2014, p. 124). Methylation in the promoter region of a candidate gene is associated with gene silencing, and is directly affected by environmental exposure to things like trauma and early life stress; moreover, 97% of epigenetic functioning occurs in the intergenic regions and between gene bodies which can affect transcription binding sites that influence gene expression close *and* far from the epigenetic activity (Glatt et al. 2016, p. 85). Furthermore, epigenetic mechanisms such as DNA methylation and histone modification have been associated with brain regions that are implemented in many stress-related psychiatric disorders, such as the ventral tegmental area, nucleus accumbens, and the hippocampus (Glatt et al, 2016, p. 85, 86).

Revolutionary research done by Meaney and colleagues (2004) showed that "maternal behavior (licking, grooming, etc.) could produce stable alterations of DNA methylation and chromatin structure, providing a mechanism for the long-term effects of early adversity on gene expression in the offspring" of rats (Weaver et al., 2004). In other words, exposure to

environmental stress (maternal neglect, for example) in the early life of offspring actually changed the biological expression of genes in the offspring of rats, and these changes persisted into adulthood. Studying epigenetic mechanisms, then, could possibly help bridge the gap between environmental risks and biological pathophysiological risks for psychiatric disorders (El-Sayed, Koenen, & Galea, 2013, p. 610).

Epigenetics is particularly meaningful for substance abuse disorders, since long-term use of psychoactive drugs is known to affect neuronal structures and functions of certain brain regions (McQuown & Wood, 2010, p. 145). Moreover, epigenetic factors may influence the initiation of drug seeking behaviors. In other words, epigenetic changes highly influence addictive behavior, and addictive behaviors influence epigenetic changes, thus it is an important area for researching substance use disorder. The following section will highlight two transcription factors that are prime targets research due to their prominent role in addiction pathology. Without the field of epigenetics, these contributing factors to addictive behaviors might have been overlooked.

In an exemplary review of epigenetic mechanisms in addiction, McQuown and Wood (2010) elucidate the role of two important transcription factors: ΔFosB and cyclic adenosine monophosphate response element–binding (CREB) protein. CREB is induced rapidly after drug exposure, then returns to baseline after a few hours, while ΔFosB accumulates slowly after drug each drug exposure, and remains highly stable for months after cessation; both are shown to mediate distinct aspects of drug addiction (McQuown & Wood, 2010, p.147). Studies conducted on rodents show activation of CREB "leads to a negative state of decreased reward and increased drug tolerance and dependence"; furthermore, rodents with decreased CREB showed more sensitization to cocaine and cocaine-related cues (McQuown & Wood, 2010, p. 148).

Conversely, ΔFosB is shown to increase drug-induced locomotion, drug sensitization, and motivation for self-administration (McQuown & Wood, 2010, p. 148).

McQuown and Wood (2010) also explain that drugs of abuse enhance histone acetylation (HDAC) activity, where cocaine self-administering rats had increased histone acetylation, which increases drug intake (p. 150). Most interesting of all, HDAC inhibitors are shown to enhance synaptic plasticity and long-term memory, by consolidating learning events into long-term memory formation, when otherwise the formation of long-term memories would not occur; moreover, such memories outlast the longevity of normally formed long-term memories (McQuown & Wood, 2010, p. 151). So, epigenetic effects might be the cause of, or at least contribute to, some of the abnormal learning processes seen in the cycle of drug addiction. Addicts that have learned to assign value to drugs and other stimuli related to drugs of abuse may have formed these memories with the assistance of these epigenetic changes.

Because of its role in learning and memory, HDAC has been a target for novel drug therapies in fear-related disorders such as anxiety and PTSD, with striking results on fear-extinction learning in preclinical translational research (Whittle & Singewald, 2014, p. 570). In regards to substance abuse, the application of HDAC inhibitors could facilitate a reduction of relapse behaviors due to increasing the extinction of learned behaviors associated with drug use and drug-seeking; these changes would also persist over longer periods of time than behavioral re-learning alone. Studies have also shown that chronic administration of HDAC inhibitors have an antidepressant effect on rodents (Fuchikami, Yamamoto, Okada, Yamawaki, & Yamawaki, 2016, p. 322). These epigenetic mechanisms have vast implications for clinical utility that are applicable for more than just substance abuse disorders, as seen in a review by Tsankova et al.

(2007) on the epigenetic effects of several psychiatric disorders such as depression and schizophrenia.

Since the complexity of psychiatric disorders is no longer underestimated, there are some exciting research prospects ahead. Genetic research efforts should continue to focus on new avenues based on innovations in the field of psychiatric and behavioral genetics, such as gene-environment interactions and epigenetics. However, without a clear gene-to-disorder pathway, as in the case of Mendelian disorders, researchers suggest looking at psychiatric disorder biology not as direct etiological pathways, but as intricate networks (Miller & Rockstroh, 2013, p. 180). Therefore, the first priority in these continued efforts will be to redefine phenotypes of interest during research, rather than attempting to prove biological causality of existing psychiatric diagnoses. By evading heterogeneous symptom clusters, researchers will be able to study specific targets, which is precisely the goal of the RDoC matrix.

Chapter 3- Endophenotypes

It is becoming clear that it is incredibly difficult, perhaps impossible, to find genes that "code for" psychiatric illness. The hope of finding simple Mendelian casual pathways for psychopathology is a distant memory. The brain is far too complex an organ to be able to trace a disorder from an observable symptom, down a biological linkage chain, to a single point of origin. Psychiatric disorders are multifactorial and polygenetic. Moreover, because one's environment and genome shift over time, how a person's genome is operationalized is a moving target (Miller, Clayson, & Yee, 2014, p. 1329). Realizing the difficulty of this endeavor, the search continues for alternative ways of researching psychopathology without merely attempting to match specific genes to broad, complex symptom clusters.

While studying schizophrenia in the 1970's, Gottesman and Shields (1973) realized that instead of trying to connect complex behavioral symptoms with individual genes, it would be beneficial if they could identify an intermediate target that was easier to measure, but involved both the schizophrenic genotype *and* phenotype (p. 15). Gottesman and Shields proposed "endophenotypes as a vital link in discovering and understanding genetic contributions to psychopathology" (Miller & Rockstroh, 2013, p. 178).

The endophenotype concept lay dormant for decades, until an invited review by Gottesman and Gould (2003) increased attention for this crucial theory due to growing disillusionment with the DSM and ICD, and now momentum is rallying behind the endophenotype concept and dimensional constructs of psychopathology that integrate psychological and biological phenomena like the RDoC initiative (Miller & Rockstroh, 2013, 178-179).

Essentially, endophenotypes are ways of reducing complex phenotypes into more feasible ways of measuring them. Gottesman and Gould (2003) conceptualize endophenotypes as "measurable components unseen by the unaided eye along the pathway between disease and distal genotype" (Gottesman & Gould, 2003, p. 636). The idea is that endophenotypes will be "more defined and quantifiable measures that are envisioned to involve fewer genes, fewer interacting levels and ultimately activation of a single set of neuronal circuits" (Gould & Gottesman, 2006, p. 115). Though these claims have been challenged by many researchers who suggest that endophenotypes are no less genetically complex than clinical psychiatric diagnoses, many remain who are optimistic about their potential as alternatives, to add to the growing "big data" collection efforts, and to improve the current methods of genetic research (Cuthbert, 2014, p. 1206).

Conceptually, an endophenotype suggests that there is an internal deviation in processing in those with mental illness. Indeed, "endo" (from the Greek "within") eludes to inner disturbances, perhaps before external symptoms even begin to manifest (Lenzenweger, 2013, p. 1351). At the time when this was suggested, these concepts were "hidden" within the individual and simply assumed or inferred by the researcher. Luckily, many of these theoretical constructs can now be evaluated with 21st century technological tools.

Most endophenotypes cited in the psychiatric literature thus far are neuroimaging, electrophysiological, and cognitive variables (Glahn et al., 2014, p. 123). However, endophenotypes could potentially be any type of measurement, from neurophysiological, biochemical, endocrine, neuroanatomical, cognitive or neuropsychological (Gould & Gottesman, 2006, p. 114). The criteria set forth for a biological marker to qualify as an endophenotype include qualities such as it should be associated with the illness, and found in higher rates of

unaffected relatives of affected individuals than in the general population; furthermore, the marker should be heritable indicating a genetic contribution (Dick et al., 2006, p. 113).

Though the use of endophenotypes has been mostly applied in schizophrenia research, there have been several studies on substance abuse and alcoholism where endophenotypes were employed. One such study used electrophysiological endophenotypes to measure genetic predisposition to alcoholism. Abnormalities in the central nervous system (CNS) have been shown to be a marker for those susceptible to alcoholism as well as other externalizing disorders, and also among their relatives, which can be seen in the human electroencephalogram (EEG), with event-related potentials (ERPs) such as the P300 response (Begleiter & Porjesz, 1999, p. 1130). Event-related potentials can be explained as the measurement of electrical activity of neural networks in response to a stimulus, and the P300 is a positive wave that reflects the time (in milliseconds) in which the subject detects the stimulus (Landa, Krpoun, Kolarova, & Kasparek, 2014, p. 17, 18). Reduced P300 amplitude, which can reflect cognitive decline and brain dysfunction, is associated with the risk for alcoholism and other psychiatric disorders (Rangaswamy et al., 2004, p. 245). Differences in the P300 signify that a dysfunctional frontoparietal circuit may be responsible for the reduced P300 found in subjects at high risk for alcoholism (Dick et al., 2006, p. 113). Increased beta wave power (which is associated with anxious thinking) in the EEG bands has been reported at higher levels at resting state among alcoholics compared with controls, and has also been observed in the offspring of male alcoholics; moreover, it is also highly heritable, with heritability estimates of 86% (Beijsterveldt, Geus, Boomsma, 1996, p. 568).

Dick et al. (2006) used the beta wave frequency and the known chromosomal regions of potential candidate genes for alcoholism to attempt to provide linkage evidence for this disorder.

Using a multidisciplinary program called COGA, they compared peaks in the EEG recordings and genetics analyses and found significant linkage peaks with the ERPs; this technique successfully led to the identification of correlations between endophenotypic markers and *GABRA2* and *CHRM2* as genes associated with alcohol dependence (Dick et al., 2006, p. 123). Dick et. al. point out that alcohol dependence diagnoses had previously placed susceptibility at chromosomes 4 and 7, where these genes can be found, but never so narrow as to locate these genes specifically, until using the electrophysiological measures used here. The genes implemented are summarized below.

The *GABRA2* gene is located within a tight cluster of $GABA_A$ receptor genes on chromosome 4p; GABA is involved in many of the behavioral effects of alcohol including motor incoordination, sedation, ethanol preference, and withdrawal signs (Dick et al., 2006, p. 117). GABA is believed to play a role in CNS disinhibition related to the predisposition to alcoholism, and thought to be involved in the beta brain rhythms measured by the EEG (Dick et al., 2006, p. 117).

The *CHRM2* gene is a muscarinic cholinergic receptor gene, which influences the effects of acetylcholine on the central and peripheral nervous system; therefore they are thought to have a direct influence on the P300 generation (Dick et al., 2006, p. 119). They are also thought to have a role in cognition and memory, and recently, significant deficits in behavioral flexibility, working memory, and hippocampal plasticity were observed in *CHRM2* knockout mice (Dick et al., 2006, p. 119). Dick et al. (2006) also reported an association between the *CHRM2* gene in alcohol and major depression, which is often a comorbid diagnosis (p. 121).

Another proposed endophenotype cited in the psychiatric literature is impulsivity. This construct is heritable and multifaceted, including tendencies for poorly planned, premature and

risky actions (Belin, Belin-Rauscent, Everitt, & Dalley, 2016, p.79). Impulsivity has been implemented in a host of psychiatric disorders, such as ADHD, conduct disorders, pathological gambling, intermittent explosive disorder and substance abuse. Not only can its symptoms manifest in the context of disorders such as ADHD, schizophrenia, or depression, but the lack of self-regulation in reward-related behaviors seen in drug addiction is directly affected by this construct (Belin et al., 2016, p. 79). Impulsivity's generalizability highlights the practicality and importance of researching it as an endophenotype (Jonas & Markon, 2014, p. 661).

Ersche, Turton, Pradhan, Bullmore, and Robbins (2010) compared the personality traits of impulsivity and sensation-seeking, both of which are largely prevalent as risk factors for, and consequences of, drug addiction between drug users and their non-affected siblings. Studies of drug addiction have shown that decreased inhibitory control can lead to the out-of-control drug seeking behavior seen in addiction. Desensitized response to natural rewards has been shown to lead to risky behaviors such as drug taking (Ersche et. al, 2010, p. 770). Ersche et al. (2010) surmised that impulsivity and sensation-seeking may be viable endophenotypes for a genetic predisposition to drug addiction.

The results of Ersche, Turton, Pradhan, Bullmore, and Robbins (2010) study confirmed their assumptions: both drug users and their siblings reported significantly higher trait-impulsivity than their control counterparts, with drug users more impulsive than their siblings (p. 771). For sensation-seeking, drug users reported significantly higher desire for sensation than their siblings and the controls, with no significant differences between the other two groups (Ersche et al., 2010, p. 772). Ersche et al. (2010) found that impulsivity could possibly be an endophenotype for addiction, a predisposition in brain circuitry long before one ever touches a drug. Long term drug use involves neuroadaptive changes in large scale striato-thalamo-

orbitofrontal networks implemented in natural reward processing and behavior regulation, which may exacerbate a biological predisposition to impulsivity (Ersche et al., 2010, p. 772). Though sensation-seeking did not prove to be an endophenotype in this study, it does not rule out its presence in the initiation in drug seeking, and perhaps served as a protective factor in the siblings that did not pass the threshold into substance use or abuse (Ersche et al., 2010, p. 772).

The endophenotype concept is incredibly valuable for research into psychopathology. To break down complex behaviors that overlap diagnostic categories and study them across interdisciplinary levels will no doubt provide greater depth of understanding into the tangled webs of psychiatric illnesses. However, this teasing out of complex phenomena can also aid in researching single complex phenomena.

As one example, Ray, Bujarski, and Roche (2016) suggest initial subjective response to alcohol as a predictive endophenotype for alcohol dependence. The behavioral and pharmacological effects of alcohol are dichotomously dispersed between stimulant and sedative effects; when blood alcohol levels are rising, alcohol produces intensely stimulating, rewarding effects and when blood alcohol levels are declining, sedative and unpleasant effects are felt (p. 8). Importantly, as seen in several studies, both recent and over decades, those with a family history of alcohol abuse are more sensitive to the rewarding effects of alcohol, and less sensitive to the negative effects (Ray, Bujarski, & Roche, 2016, p. 8).

For the treatment of alcoholism, a few medications have been approved by the FDA to supplement attempts to terminate addictive behaviors, including nalmafene, acamprosate, and naltrexone; yet the most efficacious of these medications are sometimes only effective for 30% of the individuals who take them (Helton & Lohoff, 2015, p. 122; Ray, Bujarski, & Roche, 2016, p. 12). Ray et al. (2016) point out, however, that in genetic studies on the subjective response of

alcohol, even though they implemented well-known genes related to alcohol (including the aforementioned *GABRA2*), studies focused specifically on the stimulating subjective effects of alcohol found differences in the carriers of a single nucleotide polymorphism (SNP) in the mu opioid receptor gene (*OPMR1*) called the Asn40Asp SNP (p. 10). Carriers of the Asp40 showed varying tandem repeats of the dopamine transporter gene (*SLC6A3*), which has been shown in behavioral and neuroimaging studies to respond to naltrexone (Ray et al., 2016, p. 10). In another study, carriers of the Asp40 who were treated with naltrexone were less likely to relapse than those with the Asn40 allele, showed longer periods of abstinence if they *did* go back to relapse, and drank less when they resumed drinking than the Asn40 group, as well (Helton & Loff, 2015, p. 124). Interestingly, Asp40 carriers reported greater subjective experiences of alcohol effects and self-administered more alcohol than their Asn40 counterparts, both in the laboratory and naturalistic settings, yet this subjective response was not reported when alcohol was administered intravenously (Ray et al., 2016, p. 10). This discovery has large implications regarding the ability to predict the effectiveness of naltrexone, and other pharmacological treatments, based on personalized medicine (Ray et al., 2016, p. 10).

Ray, Bujarski, and Roche (2016) poignantly address the urgency and practicality of a framework like the RDoC to increase consilience across studies. In their article, Ray et al. (2016) highlight the single endophenotype of subjective response to alcohol that spans a breadth of studies across many units of analysis. Moreover, they highlight many other factors that this one concept encompasses not expressly covered in this review, such as administration methods, clinical vs subclinical populations, and stages of progression of alcohol consumption: light vs heavy drinkers, heavy drinkers vs alcohol-dependent drinkers, early-stage alcoholism vs. late-

stage alcoholism, etc., as well as reviews of other genetic and imaging studies and suggestions for future research (Ray et a., 2016, p. 12).

The relationship between biology and psychology, genes and environment, nature versus nurture, is one of the most fundamental issues in the history of psychology. Scientists, however, must acknowledge the equally important contribution of both genes and environment, in much more complex ways than even once imagined. Miller and Rockstroh (2013) explain that the notion of a causal chain has been misleading, as demonstrated by progress in such fields as epigenetics, which is why a network model and Cuthbert's assertion of "brain circuit disorders" are more appropriate (pp. 178-203).

The benefit of the endophenotype concept--the use of intermediary markers of maladaptive phenotypes that will aid in the identification of the genes that contribute to those phenotypes--in psychopathology research. The greatest strength of the endophenotype approach is that is dimensional; it does not limit itself to strictly clinical populations and it transcends categorical diagnostic boundaries, which is also a defining feature of the RDoC matrix (Miller & Rockstroh, 2013, p. 202).

Understanding how the brain works is still in its infancy, and as such, researchers must broaden their scope of researching the brain's processing capabilities by viewing not just isolated sections, but whole network processes at a time, both functional and dysfunctional. The next section will examine one of these circuits, the brain's reward system.

Chapter 4- Reward Systems

Neural circuitry is arguably one of the most important concepts in understanding human behavior. The human brain is made up of trillions of cells, all interconnected into a vast network. The circuits that connect these cells are the way this network communicates within itself to produce the perception of the world. The field of neuroscience, together with many other disciplines, is beginning to investigate how these processes work. Subsequently, the field of mental health is concerned with pinpointing when these processes begin to function abnormally.

This is a grand undertaking, and the NIMH is not taking it lightly. When organizing the RDoC matrix, the workgroups assigned to create the domains had two requirements that constructs in the matrix must meet: they must be valid, as evidenced by many studies from many different laboratories, and they must show previous evidence of linkage to a neural circuit or system (Kozak & Cuthbert, 2016, p. 289). As covered earlier, the workgroups settled on five domains: positive valence systems, negative valence systems, cognitive systems, systems for social processes, and arousal/modulatory systems, each with corresponding sub-constructs to further elaborate on each domain (Kozak & Cuthbert, 2016, p. 289). The positive valence system domain for reward circuitry, because of the well-known relevance of reward in drug addiction, will be the focus of this chapter. Following this, a demonstration of how reward circuitry can be studied across multiple diagnostic boundaries will be presented.

Substance use disorder

Addiction is characterized by the transition from voluntary, impulsive drug consumption to compulsive, habitual substance abuse and the inability to limit intake even in the face of negative consequences (Koob & Volkow, 2010, p. 217). Koob & Volkow (2010) also point out

the severely negative affective state that results when access to the drug is prevented; these stages are classified as 1) Binge/Intoxication 2) Withdrawal/Negative affect 3) Preoccupation/Anticipation (p. 217, 219).

When it comes to drug addiction, "reward" is the beginning of the end. Many addicted individuals report no longer feeling pleasure from using drugs; it is no longer a choice for them, it is a *need*. The shift from cognitively-informed behavioral choices to habit-based, sensory-driven behaviors reflects the progressive dysfunction of the interconnected reward and motivation/control circuits that become increasingly deficient as addiction continues (Karoly, YorkWilliams, & Hutchinson, 2015, p.2074). Once substance use progresses into addiction, the dysfunction of other neural circuits become more pronounced, such as the fear circuits during acute and sustained threat. It is beyond the scope of this article to elaborate further into these domains, but further research into substance abuse across the constructs of the RDoC matrix would be warranted.

Reward

The brain's "reward circuit" has been a central focus of research for decades. Any number of stimuli can be rewarding and reinforcing for humans and animals, and therefore elicits motivation to seek continued consumption of the reward, which in turn allows the organism to learn to assign value to the stimulus and prioritize what resources to devote to obtaining the reward (Hyman, Malenka, & Nestler, 2006, p. 567). This circuit, and its dysfunction, has been found to be associated with many psychiatric disorders, including schizophrenia, obsessive-compulsive disorder, autism, attention deficit/hyperactivity disorder, depression, and substance abuse (Pujara & Koenigs, 2014, p. 82).

The discovery of the brain responding to reward can be traced back to Olds and Milner (1954), who realized rats would repeat behaviors that elicited electrical stimulation of electrodes placed on certain brain areas because the rats found the effects to be pleasurable (Pujara & Koenigs, 2014, p. 82). This subjective feeling of pleasure experienced by the rats is what most people attribute to the term "reward". In reality though, this hedonic experience is but one component of reward. Scientific progress has since delineated three dissociable components of reward: "liking" (hedonic impact); "wanting" (incentive salience); and learning (predictive associations), all of which have their own underlying neural circuitry and differ in their psychological and biological functioning (Berridge, Robinson & Aldridge, 2009; Baskin-Sommers & Foti, 2015, p. 228). "Liking" refers to the hedonic response to reward and is generally, but not always, associated with an experience of subjective pleasure (Baskin-Sommers & Foti, 2015, p. 228). "Wanting" refers to the motivation of approach toward, and consumption of, rewards (Berridge et al., 2009, p. 68). Learning is the ability to build knowledge about specific relationships between cues, behaviors, and reward outcomes (Baskin-Sommers et al., 2015, p. 229). Learning processes are varied and complex; associative learning usually refers to Pavlovian or instrumental conditioning which typically results in procedural (habitual) responses, while cognitive learning refers to the knowledge obtained by an individual and generally results in declarative (conscious) responses (Berridge & Robbinson, 2003, p. 507). Though these processes are dissociable, they function as part of an interactive network; sometimes these circuits work together, sometimes they contend with one another, and at times they are expressed implicitly beneath the conscious awareness of the individual (Berridge et al., 2003, p. 508).

The disentanglement of reward components has fascinating ramifications. It is often assumed that what one likes, one wants—and vice versa, yet neuroscience has determined that they do not occur as simultaneously as once believed. If "liking" typically represents the subjective feeling of pleasure or euphoria one experiences from a reward, then "wanting" can be described as the component of the reward that makes the reward attractive and desirable to the individual—thus "wanting" is motivational rather than emotional (Berridge & Robinson, 2003, p. 510). So, for a person addicted to drugs, it is highly plausible that they can report not "liking" the drug, but still "wanting" to use drugs. The term "incentive salience" is used to describe this component because of its descriptive nature of the function of "wanting", since it has both perceptual and motivational value, and that value is evidenced by the effort willing to be put forth by the animal in order to obtain the reward (Berridge & Robinson, 1998, p. 313). An addicted individual has ascribed motivational value to the drug of abuse, therefore the abnormal desire they feel toward that drug has nothing to do with "liking", but with an abnormal or dysfunctional attribution of incentive salience.

The studies done by Berridge, Robinson, and Alridge (2009) highlight the separate components of the reward and their independent functioning. Berridge and his colleagues sought to isolate areas of a specific brain structure that elicits a "liking" response in rodents; for example, they injected a mu opioid agonist in a small region of the nucleus accumbens (NAc) suspected to increase the "liking" response, to which the subsequent "liking" reaction to sucrose was tripled (p. 66). That same microinjection produced a double increase in the "wanting" response as well, shown by the stimulation in eating behavior and amount of food intake by the rodents (Berridge et al., 2009, p. 66). Berridge et al. named these small areas "hedonic hotspots", because outside of these "hotspots", the same injections, even in the same brain structures,

showed no increase in the "liking" response, though it maintained the increase in the "wanting" response (p. 66). This shows the dissociable nature of these two components. They found similar results for an overlapping endocannabinoid "hedonic hotspot" in the NAc, which is a substructure of the ventral striatum (VS), activated by a different substance called anandamide, that more than double both the "liking" and "wanting" responses (Berridge et al., 2009, p. 67). This result has interesting implications for the pharmacological endocannabinoid antagonists for treating obesity and addiction; because of the role of endocannabinoids in appetite and craving, as well as increasing fatty tissue storage, and lab studies conducted to block the activation of this system were shown to reduce these effects, making this system a model target for drug therapies (Kirkham, 2008, p. 1100).

To display the separate role of "liking" and "wanting" further, in a study by Lamb et al. (1991), the reinforcing effects of morphine were measured and shown to increase self-administration, even at very small doses, before ever reaching the threshold for self-reported "euphoric", drug-liking experiences; the self-administration of the placebo, however, dropped markedly after a few sessions. The study determined the best predictor of increased self-administration was discovered to be the physiological pupil constriction the morphine solution produced, more so than the subjective experience of pleasure (Lamb et al., 1991, p. 1169). This study concluded that even though the addicted individuals reported no pleasure from the injections of morphine, they were still willing to work by pressing a lever to self-administer very small doses of morphine as compared to a saline injection, thus still responding to the reinforcing effects of the incentive salience ascribed to the drug, without feeling the pleasurable effects (Lamb et. al, 1991).

The division of these two components of reward led to one of the most sensational discoveries about the neurochemical understanding of our pleasure system—the function of the neurotransmitter dopamine. When it comes to reward, the mesolimbic dopamine system has been the central focus of research. Wise (1980) was the first to postulate the "dopamine hedonia/pleasure hypothesis", to which other researchers built upon, even coining the loss of pleasure the alternative "dopamine anhedonia hypothesis". It was well understood that dopaminergic projections were the cause of the subjective experience of pleasure.

When it comes to drug addiction, there is a clear relation between the rewarding effects of drugs of abuse and the continued self-administration of these substances. Most studies investigating drugs of abuse find that the experience of drug-induced pleasure is due to the release of dopamine in the VS, (Franken, Booij, & van den Brink, 2005, p. 200). The mesolimbic dopamine pathway, which involves dopaminergic projections from the ventral tegmental area (VTA) into the NAc, is a crucial pathway in drug reward (Volkow, Wang, Fowler, Tornasi, & Telang, 2011, p. 1503).

However, contributing to the "liking" aspect of rewards may not be dopamine's most prominent role, after all. Berridge and Kringelbach (2015) point to translational research done on rats that shows even almost complete destruction of mesolimbic dopamine neurons, reduced to 1% of normal levels by neurotoxic lesions, left all "liking" facial responses to sweet rewards intact (p. 656). Similarly, patients with severe dopamine depletion due to Parkinson's disease do not show any sign of decreased "liking" responses to sweet tastes, in fact some actually show increased pleasure responses to sweet foods (Meyers, Amick, & Friedman, 2010, p. 91). Thus, the summary of these studies, and a large body of supporting literature, concludes that the

function of dopamine is not a mechanism of the appetitive value of rewards, but of the "wanting" aspect of reward (McClure, Daw & Montague, 2003, p. 423).

In addition to the abnormal processing of incentive salience, the dysfunction of many other circuits are implemented in drug addiction, such as the mesostriatal and mesocortical pathways--circuits involved in condition/habits, motivation, and executive functions such as inhibitory control and decision making (Volkow, Wang, Fowler, Tomasi, & Telang, 2011, p. 15037). Reduced morphological volume of the prefrontal cortex (PFC), the area of the brain responsible for higher order cognitive functioning, and decreased connectivity between the PFC and subcortical structures such as the VS and amygdala—both of which lead to altered learning and deficient behavioral control--are among the most consistent neuroimaging findings in patients with substance abuse disorders (Baskin-Sommers & Foti, 2015, p. 231).

Both animal and human studies have shown lack of adaptive association learning in reward-related tasks for substance-dependent subjects. Rats with lesions in the NAc showed preference for smaller, immediate rewards rather than larger, delayed rewards which suggests the NAc must be intact for discrimination learning (Wilson, Sayette, Fiez, 2004; Pujara & Koenigs, 2014, p. 85). Volkow, Fowler, and Wang (2003) explain that surges of dopamine by drugs of abuse result in changes in brain functioning to increase the motivational salience of drug-related stimuli and decreases sensitivity to natural reinforcers, essentially causing an anhedonic response similar to that seen in major depressive disorder and schizophrenia (p. 1447). This results in a hypoactivation of the memory and prefrontal control circuits, resulting in impaired learning. Disruptions in the prefrontal cortex can be seen by neuroimaging studies during drug-related, cue-reactivity tasks confirming the impairments in cognitive abilities of drug addicted individuals (Wilson, Sayette, Fiez, 2004).

Now that we have established how the reward components of liking, wanting and learning are disordered in substance abuse disorder, we will discuss a study that displays the effects of how a dysfunctional reward system can manifest across diagnostic boundaries. Hägele and colleagues (2015) used functional magnetic resonance imaging (fMRI) and a monetary incentive delay (MID) task to research disordered reward anticipation between a host of psychiatric disorders, including alcohol dependence (AD), schizophrenia, major depressive disorder (MDD), bipolar disorder (acute manic episode), attention deficit/ hyperactivity disorder (ADHD), and healthy controls. They assumed that blunted ventral striatal activity would be most pronounced in those illnesses with depressive symptoms, as evidenced by the drop in dopamine projections known to occur in these states (Hägele et al., 2015, p. 332). As hypothesized, Hägele et al. observed reduced right VS activation during reward anticipation in the schizophrenic patients, AD patients, and patients with MDD, as compared to the healthy controls, but no difference in those with symptoms of anxiety disorders (p. 339). It is the conclusion of this study that reward expectation is significantly correlated with striatal dopamine projections, and the dysfunction of learned reward-prediction/anticipation errors directly influences the severity of depressive symptoms regardless of clinical diagnosis (Hägele et al., 2015). The similar behavioral and neurobiological data obtained from the patients of this study confirm the presence of comparable symptoms across a range of psychiatric diagnoses, substantiating the urgency for a research framework such as the RDoC initiative.

In this section, the construct of reward to was highlighted to display the complexity of its dysfunction in substance use disorder. The field of neuroscience must continue in its efforts to tease apart the many components and contexts in which this and many other constructs function, and at what point these processes begin to operate abnormally. The RDoC has begun this process

by creating a framework that studies the disentangled elements of constructs such as reward, and provides a large-scale, collaborative effort between different disciplines. This is the next step toward innovative discoveries for treating mental illness and advancing toward an understanding of human cognitive processing and behavior.

Conclusion

This review presents the need to integrate neuroscience and translational research in the treatment of psychopathology. Substance use disorder was used as a template, because it is frequently co-diagnosed alongside other mental disorders in the mental health field, and it progresses in stages from voluntary substance use to compulsive addiction, thus it is a useful target for studying the biological underpinnings for psychopathology. Chapter 1 displayed the shortcomings of the current classification system, and surveyed the intentions of the RDoC research framework. Chapter 2 reviewed the limitations of the conventional methods for genetic research into mental illness and highlighted the promising future of epigenetics in mental health. In chapter 3, the possibility of using endophenotypes as research targets for psychiatric disorders, rather than diagnostic categories, was discussed because they are believed to be more viable options for discovering etiological causality at the genetic, molecular, and cellular levels. Chapter 4 examined the reward system, and the dysfunction of this system that can occur in substance use disorder and across diagnostic boundaries.

The goal of personalized medicine is to customize healthcare and tailor medical decisions, procedures, and prognoses to the individual patient. The Precision Medicine Initiative, Human Connectome Project, and now the Research Domain Criteria project, all point to the dramatic paradigm shift in researching the etiology and pathophysiology of diseases and disorders. Translational research incorporates aspects of both basic science and clinical research, in order to connect fundamental research findings to people and practice in the real world clinical setting. This translational research approach is the future of neuroscientific progress.

This literature review was intended to some light on the state of our mental health care treatment for individuals suffering from debilitating illnesses such as addiction, and the devastating impact it can have on them, their families, and society at large. The colossal breakthroughs in technology and traditional medicine have yet to graze the field of psychiatry and mental illness; some disorders have not seen treatment improvement in over 50 years (Akil et al., 2010, p. 1580). The shift toward integrating neuroscience and translational research in psychopathology can change that. The RDoC is a huge step in that direction, and the NIMH and other institutions such as the National Institute of Drug Abuse that have begun to implement these types of research approaches in practice and are leading the way toward real progress for this field. The utility of the translational approach is also being recognized at the educational level. Emerging fields such as behavioral neuroscience and neuropsychology are already being implemented, and will give burgeoning scientists and clinicians a wide curricula of knowledge with which to draw in order to understand human behavior at multiple levels of processing.

The field of mental health has long been in need of a redirection, and initiatives such as the RDoC are possibly the solution to the many problems encountered in the research and treatment of psychiatric disorders. Researchers are optimistic for the future of the integration of neuroscience in this field and are eager to see an increase of funding and positive results. It is time to give those suffering from psychiatric disorders hope of a better outcome and new successful treatment options that they are not only in desperate need of, but of which they are rightly deserving of, as well.

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