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A Biological Review of Mental Illness: An Overview of Genetics and Pathophysiology of Schizophrenia, Major Depression, and Addiction

Christopher R. Angerhofer
South Dakota State University, christopher.angerhofer@jacks.sdstate.edu

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South Dakota State University

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PREFACE

There are a lot of issues in the United States but the stigmatization of the mentally ill is one often overseen. In writing this review, I hope to shine a spotlight on the current situation of mental illness research and treatment, and how it is in desperate need of reform and funding. Research has progressed to a point where biological etiology and pathophysiological explanation can be made for many disorders.

ABSTRACT

Christopher Angerhofer: A Biological Review of Mental Illness: An Overview of Genetics and Pathophysiology of Addiction, Major Depression, and Schizophrenia
(Under the direction of Greg Heiberger)

Novel approaches in understanding mental illness present solutions to current issues in treatment and diagnosis. With advancements in genetics and neurology, the etiology and pathophysiology of mental illness is slowly unwrapping. In discovering biomarkers for depression, addiction, and schizophrenia, the precision for preventing, diagnosing, and treating these disorders increases. The aim of this paper is to review current research for addiction, major depression, and schizophrenia in genetics and physiology, while also clarifying the need for reclassifying mental illness as diseases with a pathophysiological basis, not syndromal, idiopathic disorders. Mental illness is dynamic in that it encompasses both environmental and biological factors, but research emphasis on the latter has potential to improve the treatment of disorders, and possibly prevent them.

INTRODUCTION

MENTAL ILLNESSS & SOCIETY

Despite the advances in modern medicine over the last century, understanding and treatment for mental illness has remained rather stagnant[5]. Other areas of medicine have adopted a proactive approach to deter the onset of serious illnesses and disorders, while developments in psychiatry have remained primarily therapeutic. With recent advances in genetics and neurology, research in mental illness has progressed faster than ever although, the dynamic nature of mental illness has made this progress difficult. Mental illness is not characterized by biology alone and the influence of environmental variables can make them unpredictable[6].

Although research in this field has progressed significantly, the burden of mental illness is still present. Psychiatric disorders require extensive care due to their severity and frequency. Mental illness is socially, economically, cognitively and behaviorally detrimental. These illnesses don't affect just the individual, but also their families and communities. In the United States alone, nearly fifty percent of people will be diagnosed with a mental illness in their lifetime[7]. Without significant changes in how mental illness is viewed and treated, this is unlikely to change anytime soon[8].

Mental illness is expensive to both the individual and the community. In the United States alone, the combined annual costs of substance abuse and anxiety disorders is estimated to be around $542 billion. This accounts for the cost of criminal justice, medical, accidents, and loss of earnings. In total, psychiatric illness accounts for approximately 6.2% of the nation's health care expenditure. The economic impact in the individual has been difficult to determine, but in a door to door survey conducted by the National Comorbidity Survey Replication (NCS-R), there is an estimated earning loss of $16,306 per individual with a serious mental illness that accumulates to approximately $193.2 billion annually. This estimate is very conservative in that it does not account for a multitude of other factors. When including factors such as disability benefits, public housing, food stamps, etc. the actual estimate is closer to $317 billion annually, and this still doesn't account for incarcerated persons, comorbid conditions, or early mortality related costs[8, 9].

Stigmatization plays a significant role in the issues plaguing mental illness in healthcare. The diagnosed contend with both the disorder itself and the negative connotation society has place on it[10]. There are two separate parameters to this prejudice wherein stigmatization is self-inflicted as much as it is socially imposed. Western and European cultures are infamous for their stigmatization of mental illness which often extends to even medical professionals. Benevolence, fear and exclusion, and authoritarianism are three distinct traits that individuals diagnosed with a mental illness often express due to this stigmatization[6]. Insofar, the most effective method in combatting this issue has been, and will continue to be, education and awareness[10].

While stigmatization poses a significant social issue, cognition deficits are typically more of an issue with severe

disorders like schizophrenia, though problems are noted in more common disorders as well[11]. These affects are noted by a decline in working memory, executive function, and attention and information processing. Initial illness coupled with lethargic medication compound this issue. Thus, a major obstacle for those with disorders is job retention and the need for cognitive treatment and rehabilitation to live normal lives[12].

Unfortunately, mental illnesses are rising in adults, young adults and adolescents, with significant increases in the latter two[13] . The increasing incidence and prevalence of mental illness will amplify the issues discussed above. This is further justified by figure one that shows emergency department visits due to mental health have increased as well[14]. Another ongoing issue promising to heighten the severity of this situation is the opioid epidemic that plagues the United States. Comorbid addiction is fairly common in serious mental illnesses, with studies showing nearly 50-60% of individuals with schizophrenia also having a substance abuse issue[15]. Each year, opioid related deaths increase in both accidental overdosing and suicide related deaths[16]. This trend shows a need to increase research and funding in addiction and depression to directly combat this national epidemic. Though the main culprit in this situation is the painkiller hydrocodone, other psychoactive drugs have been implicated as well. A new method of treating addiction, depression and schizophrenia is desperately needed. Traditional pharmaceutical therapeutic approaches work to some extent, but antipsychotics can have severe side effects with some long term use leading to neurological issues like tardive dyskinesia[17]. Through novel genotyping and neuroimaging practices, precision medicine can be practiced with psychiatric diagnosis and care [5].

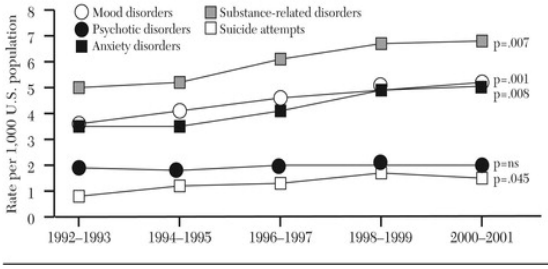

Figure 1. National trends in mental health-related emergency department visits per 1,000 U.S population, by disorder category, 1992 to 2001[14].

DIAGNOSTIC ISSUES

Diagnosing mental disorders has traditionally been done using the Diagnostic and Statistical Manual of Mental Disorders (DSM), which originated as a variant of the International Classification of Diseases (ICD), of which diagnose using a primarily symptom-based approach. As of this review, the manual stands on its fifth edition (DSM-V) which was recently constructed in 2000 and published in 2013, has improved immensely since its fruition in 1952[18]. Developed by the American Psychological Association (APA), it is a classification system that currently holds diagnostic for 297 conditions[18]. Significant changes from the DSM-IV to the DSM-V include nomenclature, a reworking of the multiaxial system and the introduction of dimensional assessments which is aimed at diagnosing subtypes of disorders[19].

As science and research have advanced, the DSM has been highlighted with major criticisms with its nosology.

Until the most recent edition, diagnostic criteria had been primarily description based, almost entirely ignoring an etiology-based approach to mental illness. A major criticism in development of the current DSM structure is that the disorders it defines were developed with little validity[20, 21]. Though the defining characteristics of illness and disorders were developed with an objective, empirical method of observation, they stem from an almost entirely psychoanalytic perspective and many fail to account for the biological nature of mental illness[22].

This leads into the issue of a lack of a disease progression system in psychiatric healthcare. Most clinical pathologies are defined and treated according to their clinical stage of development. This works to judge the severity of disease and provides a better baseline in developing an effective treatment strategy. This method of evaluation has remained mostly absent in psychiatric medicine to this day[23]. The importance of such a structure comes into play when attempting to prevent either disease progression or regression. By denoting a stage of severity in mental illnesses, treatment strategies can be developed that deter disease progression through both biological and environmental means. The prevention of regression in more severe stages is another issue the current diagnostic model fails to account for. In the process of effective psychiatric treatment, theses constructs are just as important as they would be in other medical pathologies[23].

Another significant issue with the DSM is the “box canyon problem”[24]. This problem analogizes that psychiatric diagnosis has dug itself into an inescapable hole, the box canyon, and criticizes that the criteria for diagnosis has been systematically built upon instead of developing a new, independent diagnostic tool. This method of revision is in and of itself unscientific in that it assumes the previous model of diagnosis was correct. This evolutionary method of nosology has constricted the understanding of mental illness. The development of the DSM-III in the 1980’s marked a noted significant increase in the reliability of diagnosis from both the DSM-I and DSM-II, but it’s reliability has remained mostly unchecked since[25].

This is all not to say the DSM should be completely discarded, but that a new approach should be researched that can improve the efficacy of diagnosis and treatment. A more pragmatic approach that utilizes current scientific and clinical technology to define mental illness should be integrated into the current model. To fix the box canyon problem, a new framework must be built. The DSM is a starting point and with the addition of genetics and pathophysiology, treating mental illness can be more effective[1].

MATERIAL AND METHODS

In writing this review, Web of Science - All Databases and Google Scholar were used for searching relevant research articles. Wikipedia pages were used to gain a basic understanding of some subject material and to acquire additional references and primary literature articles. To ensure that the information this review provides is accurate and relevant to the scientific community, the vast majority of sources are no older than the year 2000.

Keywords used in finding research articles were; biomarkers, genetics, and

pathophysiology. Each of these was searched in conjunction with the respective disorders evaluated in this review. Schizophrenia, depression, and addiction were chosen as the three disorders in this review due to promising research and shared pathophysiological traits[26].

GENETICS

IDENTIFICATION METHODS

With the significant progression in genotyping technology in the twenty-first century and the completion of the Human Genome Project in 2003, a new era of medicine was born[27]. This new technology has the potential to correlate genetic variants with various psychiatric disorders. Not only does this show promise in a diagnostic capacity, but in therapeutic one as well. Identification of common markers for specific disorders can denote which forms of treatment may be most effective in a particular case. Medications for treatment can then also be personalized based on the individual's genetic architecture[27].

Psychiatric disorders presented many issues in the first attempts to correlate genes with illness. One of the first genotyping methods using high-throughput sequencing studied single nucleotide polymorphisms (SNPs). Researchers quickly realized that there could be a multitude of SNPs in one gene and this method was abandoned as technology wasn't advanced enough to provide timely results. Fortunately, the concept of linkage disequilibrium (LD) solved this issue in that only a portion of SNPs need be mapped to determine common structural variants (SV). This led to linkage analyses that could test for rare mutations with high penetrance and heritability in a small population of alleles. Most linkage analyses results reveal Mendelian inheritance patterns[28].

As genotyping methods improved, Genome-Wide Association Studies (GWAS) became an invaluable tool that made possible the mapping of millions of SNPs in a genome of large populations of individuals. Microarrays, and other genotyping arrays, have allowed the identification of common SV in association with many mental disorders today. The main drawback of GWAS is the phenomenon that it is unable to prove strong heritability of gene[29, 30].

Beyond the specific types of genomic sequencing, a vital aspect to this research is the methods by with the information is obtained and interpreted. Genetic research designs fall under two categories; case-control or pedigree studies. The first, which is most often utilized in GWAS, looks for how many genetic variations are present in a specific population and then compares that number to an appropriate control. This type of design is simple and is efficient at eradicating possible bias. The primary limitation of case-control studies is the lack of Mendelian genetics, and thus no ability to discern *de novo* mutations[29].

Pedigree studies, following a specific phenotype through family ancestry, can achieve what case-control cannot and are divided into the subcategories of simplex and multiplex[31]. Simplex pedigree studies compare an affected individual with unaffected relatives. This case design has

been typically associated as the best method of studying *de novo* mutations that correlate with mental illness. Multiplex pedigree studies are the most common form of pedigree study and consist of phylogenic study with multiple affected individuals of relation. The primary reason for widespread use is that high-penetrance mutations within a family are can be linked for causation[29].

GENE ASSOCIATIONS

To date, there have been many genetic associations made with various mental illness. An important concept in this research is that in identifying candidate genes with mental illness associations, the results are not going to lead to single variant on one gene[29]. The interplay between phenotype and genotype denotes that a multitude of genes contribute to phenotype, and this is especially true in the case of mental illness. Therefore, early research that yielded results in gene associations, especially with schizophrenia, was met with significant criticism because of the complexity of genetics[2].

In the search for a genetic association to mental disorders, Schizophrenia has essentially stood as the poster child for promising research. With a heritability of approximately 80%, a genetic component of schizophrenia was almost certain[32]. Early results in this research were met with criticism as duplication efforts were seemingly unsuccessful due to the presence of multiple alleles and

Table 1. *Schizophrenia susceptibility genes and the strength of evidence in four domains.* Most of the identified loci are a result of linkage analyses[2].

		Strength of evidence (0 to 5+)			
		Association with schizophrenia	Linkage to gene locus	Biological plausibility	Altered expression in schizophrenia
COMT	22q11	+++	++++	++++	Yes, +
DTNBP1	6p22	+++++	++++	++	Yes, ++
NRG1	8p12-21	+++++	++++	+++	Yes, +
RGS4	1q21-22	+++	+++	+++	Yes, ++
GRM3	7q21-22	+++	+	++++	No, ++
DISC1	1q42	+++	++	++	Not known
DAOA (G72/G30)	13q32-34	+++	++	++	Not known
DAAO	12q24	++	+	++++	Not known
PPP3CC	8p21	+	++++	++++	Yes, +
CHRNA7	15q13-14	+	++	+++	Yes, +++
PRODH2	22q11	+	++++	++	No, +
AKT1	14q22-32	+	+	++	Yes, ++
GAD1	2q31.1	++		++	Yes, +++
ERBB4	2q34	++			Yes, ++
FEZ1	11q24.2	++		+++	Yes, ++
MUTED	6p24.3	++++	++++	+++	Yes
MRDS1 (OFCC1)	6p24.3	++	++++	+	Not known

Table 2. *Alcohol and nicotine addiction susceptibly genes, and their functions, identified in a Genome Wide Association Study(GWAS)[3].*

Gene	Summary
Alcohol	
ALDH2 Glu504Lys (rs671)	Decreased capacity to metabolize acetaldehyde to acetate leads to high concentrations of acetaldehyde, and the 'alcohol flush reaction',[33] which decreases alcohol use and the risk of alcohol dependence (e.g.[187–189])
ADH1B Arg48His (rs1229984)	Increased rate of conversion of ethanol to acetaldehyde leads to slightly higher concentrations of acetaldehyde, with similar deterrent effects on alcohol use and alcohol dependence risk (e.g.[188–190]).
GABRA2 (rs279858, rs279826, rs279871)	Repeatedly associated with alcoholism (e.g.[36]) although non-replications also exist (e.g.[39,191]). Also associated with impulsivity and alcohol-related endophenotypes. SNPs are not functional but α2 subunit expression has been associated with binge drinking.[138]
DRD2/ANKK1 (Taq1A, rs1800497)	Recognized as a risk factor for alcoholism.[192] Meta-analyses find odds ratios ≈1.2 ($P<0.001$)[193] –1.4, ($P<0.00001$),[194] for the A1 allele. Considerable across-study heterogeneity exists.
Nicotine	
CHRNA5/A3/B4 (rs16969968/rs1051780)	Meta-analyses of GWAS[88–90] and candidate gene[91,177] data show replicated association with cigarettes/day. Involved with receptor modification,[195] sensitization and desensitization.[196] Additional evidence for rs578776 as an independent signal[177]
CHRNB3-CHRNA6 (rs6474412)	Evidence from a large GWAS but not as widely replicated.[89]
CYP2A6 (rs1801272)	Impairs metabolism of nicotine to cotinine.[197] Associated with cotinine levels and associated at genomewide significance with smoking in one study, with other studies yielding inconsistent results (e.g.[89]).

haplotypes[2]. As research and technology progressed though, table one shows that over a dozen genes have been implicated in increased susceptibility for schizophrenia[2]. Fortunately, linkage analysis studies have revealed that schizophrenia has a strong genetic component. This has mostly been attributed to the fact that multiple susceptibility genes are found in linked regions[2]. The high genetic heritability of schizophrenia has made link analyses particularly successful.

In studies attempting to discern gene associations for major depression, results have been slow and inconsistent. Very few studies have actually been conducted, and where they have, the sample sizes have not been large enough to hold external validity[33]. Despite these setbacks, recent research has yielded promising results. In a 2010 study conducted in a Swedish population-based cohort, four candidate genes have been identified that show a suggestive association with depression[34]. Use of the terminology "suggestive association" is used by the authors to imply that further research of these four candidate genes is necessary to confirm their genetic associations with major depression.

The epidemiology of depression has always suggested that a strong genetic component is involved[35]. As more research is conducted on the genetics of depression, results are indicating a high percentage of heritability in nearly every study[36]. Many recent studies have begun to report a heritability of just under 80%, which is similar to schizophrenia's heritability, while others have reported lower stating that major depression involves a genetic component of ~ 40%[36]. The discrepancy in this research is most likely attributed to the associated genes being undetectable in linkage studies due to their

low effect size[33]. These results have strengthened the assertion that major depression is not solely based on one gene, but interplay of several different loci.

Another obstacle in the quest to delineate genes associated with major depression is the heterogeneity of the disorder. The polygenic nature of major depression has commonly led to an overlap in findings associated with the identification of genetic determinants for other disorders. These results indicate that formulating specific subtypes of depression may yield more accurate results when attempting to search for associated genes[37].

Addiction encompasses a broad category of mal-adaptive behaviors signified by compulsive and uncontrollable substance abuse or activity[3, 38, 39]. As one of the most significant mental illness in society, identifying associated genes is of utmost importance in combating it. Addiction can be further subdivided into the two categories of behavioral addictions (e.g. gambling, sex, shopping, etc.) and substance abuse addictions. Both are relevant in this context as genetic associations have been made in each category[3].

Numerous candidate genes have been identified for the various forms of addiction. Table two outlines candidate genes that have been identified in alcohol and nicotine dependence[3]. The genes listed above have shown the highest association with these two types of substance abuse, as confident replication in identifying associated genes in other forms of addiction has been notably lacking. Currently, identified genes can also be divided into two separate categories as well. The first consists of substance specific genes, and the second category consists of genes identified with high risk behaviors, such as impulsivity[3].

The heritability of addiction has been extensively studied and results have provided interesting insight into this disorder. Rates of heritability differ from substance to substance, but each hover around 50%[40]. In further assessing the genetic influence of addiction, stages of this disorder show differing heritability. When addiction is broken down into three stages of initiation, chronic use, and addiction, the effects of heritably are dependent on the stage of the disorder. It is found to be weakest during initiation and strongest in last two stages[3].

A significant issue in researching genetic associations of addiction is the high amount of comorbidity present in this disorder. Addiction is commonly comorbid with other forms of addiction, as well as, other mental illnesses[39]. An explanation for high comorbidity is derived the from the second category of associated genes, discussed above, in that high-risk behavior genes correlate with further maladaptive behavior. As a result of this issue, research into specific genetic associations in relation to individual substances has been limited[3].

PATHOPHYSIOLOGY

ALTERED GENE EXPRESSION

Discovering genes associated with psychiatric illness is important research but knowing what those genes transcribe for is the next step in making this research clinically relevant. Genome wide gene expression (GWGE) studies are a research

method similar to GWAS. Instead of focusing on solely genetic architecture, and the SVs therein, GWGE studies offer a method of observing both DNA and RNA in a hybrid model[28]. This method of research is important in discerning the etiology of diseases by comparing the expression of mRNA between a control and experimental group[28].

BIOMARKERS

Current research has been focused on developing various novel methods to diagnose psychiatric disorders[41-44]. While currently there is no certainty in biological markers for diagnosis, progress is being made and shows promise. Research is taking multiple approaches in identifying psychiatric disorders utilizing proteins markers in easily accessible fluids, genetic markers, and inflammatory markers such as cytokines or hormones[41]. This type of diagnosis allows for specific and individualized care and has started to redefine what is known about current disorders. A prime example of this is the use of motion-related Blood-oxygen-level dependent (BOLD) signal effects in defining subtypes of depression[45]. The symptomatic diagnostic approach currently in practice has led to a generalization of symptoms that can defined by one or more disorders, while research is showing that mental illness can be more precisely defined by pathophysiological abnormalities[46].

Due to the debilitating nature of schizophrenia, there has been a significant amount of research done in diagnosing this disorder. The field of transcriptomics, identifying genetic variations associated

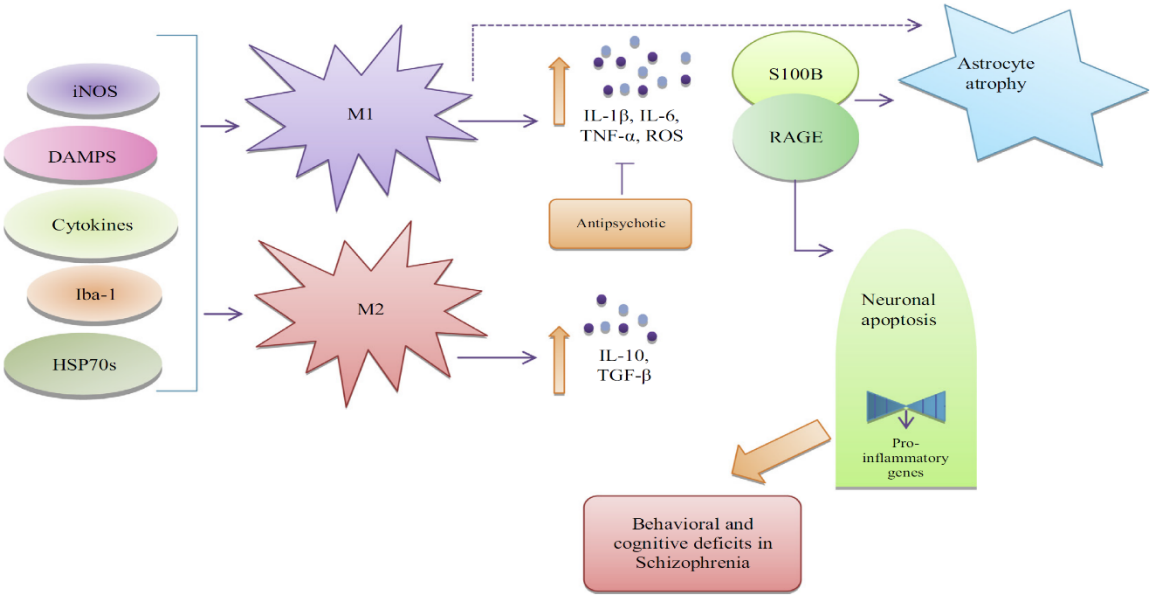

Figure 2. *Microglial activation hypothesis in the pathophysiology of schizophrenia.* The left most column, iNOS, DAMPS, Iba-1, and HSP70s, are examples of increased pro- inflammatory cytokines commonly seen in schizophrenia. They activate M1 and M2 microglial cells, which in turn upregulate immune system effectors, IL-1β, IL-6, TNF-α, and ROS, responsible for symptoms and pathophysiology associated with schizophrenia. DAMPS=damage-associated molecular patterns; Iba-1=ionized calcium binding adaptor molecule 1; iNOS=nitric oxide synthase; HSP70s=shock 70-kDa proteins; RAGE=glycation end-products receptor; ROS=reactive oxygen species; TNF-a=tumor necrosis factor-a[4].

with pathological illness, has shown immense success in cancer research and therefore, has taken the lead role in identifying biomarkers associated with schizophrenia[47]. Using gene ontology enrichment studies, gene association to function can be derived. Consistent with other research, these studies have revealed a relationship between altered metabolism, neural development/function, and immune response with schizophrenia pathology. Figure two reveals a pathway in which the immune system may play in the pathogenesis of schizophrenia[4].

Like schizophrenia, inflammation has also been indicated in major depression[43]. When compared to individuals without depression, both healthy and unhealthy depressed individuals show signs of inflammation. Symptoms of depression appear to be side effects of the upregulation of pro inflammatory which have various effects on neurotransmitter metabolism, neuroendocrine function, and neural plasticity[43]. Notably, dopamine synthesis and serotonin availability are compromised in depressed individuals[43]. Another approach in identifying depression has been using resting state fMRI (rsfMRI) to recognize abnormalities in frontostriatal and limbic brain networking[45]. Using this method, researchers have been able to define four subtypes of depression based on abnormal connectivity[45]. This type of research provides an additional avenue to diagnosing and treating depression beside the symptomatic descriptive method currently used.

Research in identifying biomarkers in addiction has been mostly concerned with

Table 3. *Example of RDoC organization[1].*

	Units of analysis							
Domains/constructs	**Genes**	**Molecules**	**Cells**	**Circuits**	**Physiology**	**Behavior**	**Self-reports**	**Paradigms**
Negative valence systems								
Active threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive valence systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for social processes								
Imitation, theory of mind								
Social dominance								
Facial expression identification								
Attachment/separation fear								
Self-representation areas								
Arousal/regulatory systems								
Arousal and regulation (multiple)								
Resting state activity								

the dopamine pathway[48, 49]. The most consistent finding in addiction imaging is the reduction of striatal D2 receptor binding in individuals with addiction problems, though reductions in D1 receptors have been indicated also[48, 49]. The decreased binding of dopamine in the striatal region effects the circuitry of the prefrontal cortex and therefore dysregulating impulsivity control[49]. Therefore, mutations or modifications to D2 receptors can actually be predictive of addictive behavior[48].

PROSPECTIVE RESEARCH

NOVEL DIAGNOSTIC METHODS

A recent initiative to modify current mental illness diagnosis has been dubbed the Research Domain Criteria (RDoC), which aims to take a more dynamic approach in identifying mental illness by focusing on biology-based criteria[1, 6]. The two current diagnostic methods for identifying mental illness are the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD), both of which were developed before modern neuroscience and thus do not coincide nicely with some new findings in this field[6]. Therefore, the National Institute of Mental Health (NIMH) initiated the RDoC to design a more comprehensive diagnostic system that include genetics, physiology, and neuroscience alongside behavioral dimensions[1].

The RDoC, in its current state, is more of a research database rather than a diagnostic tool to be used in a clinical setting[6, 50]. It is different from the currently used diagnostic manuals in that it is a matrix of information that can continuously be modified as research advances, similar to how the National Database for Autism Research (NDAR) is currently being used[6]. Table three shows how the RDoC relates Domains/Constructs to different measurable units where the intersecting points will be filled with research in that particular area[1]. The goal of this research is to enter a new stage of precision medicine for psychiatric illnesses[50].

Clinical staging of mental illness aims to adapt the same model of disease progression associated with other clinical pathologies to develop more specific treatment regimens[23]. Using tools such as the RDoC, psychiatric medicine can engage in precision medicine that can specifically target various stages of mental illness progression. Staging is quite common in other areas of medicine such as in cancer and heart disease, yet this same ideology is rarely applied to psychiatric illness[23, 51]. Disease staging has immense therapeutic and preventative potential. By identifying and utilizing biomarkers, mental illness can be mapped into different stages of disease progression based off of brain structure, inflammation levels, and neuroendocrine markers[52].

GENE & STEM CELL THERAPY

Discovering genetic and physiological biomarkers for mental illness opens the door for new treatment methods. Moving beyond conventional pharmacological remedies for mental illnesses, both gene therapy and stem cell therapy have had success in mouse models treating different forms of mental illness. In one study, researchers were able to reduce depression-like behavior in mice with the

administration of an adeno-associated virus (AAV) into the nucleus accumbens to restore p11 protein expression[53]. Humans diagnosed with depression show low rates of p11 expression and mice with a p11 knockout mutation show depressed behavior, making this biomarker a good candidate for gene therapy in treating depression.

Researchers may have also discovered a treatment for alcohol addiction. Neuroinflammation, caused by chronic ethanol intake and indicted as the cause for perpetual alcohol use, was abolished in mice with the administration of human mesenchymal stem cells (hMSCs) into a brain lateral ventricle[54]. The result of this stem cell therapy is that within a 24hr period, chronic alcohol consumption was reduced by 70% and relapse-like alcohol use was reduced by 80%. This study is another example showing the potential effectiveness of novel mental illness treatment strategies.

CONCLUSIONS

IMPLICATIONS

As research in psychiatry advances, the etiology and pathophysiology of mental illness clarifies. With this comes the ability to develop prevention strategies based on genetic heritability or provide specific therapy to stop disorders from worsening. Personalized medicine can be developed based on the genotype of an individual and this medicine can be used in a stage specific manner depending of the severity of the disorder. The biological component of psychiatric medicine will benefit immensely from this research, and combined with proper psychotherapy, the goal lifelong remission is one step closer for many.

While these medical advances in psychiatry show promise, they may not be welcome in some respects. The ethical implications of a biological-based approach to mental illness has many pros and cons to take into consideration. Unexpected issues that may arise are testing costs, reliability, and discrimination[41]. As research in genetics advances, the idea of genetic existentialism often accompanies it, which is the idea that we are simply nothing more than what are genes code for[5]. This ideology has both positive and negative consequences. Genetic existentialism beliefs can take responsibility off the patient for having a mental illness, but at the same time, studies have shown that it can lead to public discrimination and self-stigmatizing [5].

LIMITATIONS

Small sample size is a consistent issue in most genetic studies on mental health. Finding a sample size that holds external validity is difficult when researching disorders that have low incidence and prevalence, such as schizophrenia.

When considering the etiology of mental illness, environment plays much too large of a role to be ignored. The complexity of translation and transcription is further multiplied due to the influence that environmental stressors can have on gene expression. Concentrating solely on one or the other is not what this review endorses, but to instead understand the various influences that cause the manifestation of mental illness.

APPENDICIES

APPENDIX A

References are in APA format with numbered citations. The majority of this review's style is based off UNC's Graduate Thesis/ Dissertation Guide, that can be found at; https://gradschool.unc.edu/academics/thesis-diss/guide/. A two-column format was selected for consistency to coincide with the other dissertations from the Human Biology M.S. cohort of 2018.

APPENDIX B

Reviewer Feedback;

Like you, my prayer is that one day we will understand the biological underpinnings of schizophrenia, which has like 17 different subtypes and proposed etiologies, depression, my own personal demon, and addictions...C.S. Lewis described alcohol or gambling manias as problematic by society, but we turn a blind eye to golfing or shopping manias...yet the neurobiological circuitry is the same...only societies condemnation of one and blessing of other determines need for research dollars.

DSM is not perfect, and we need biological understanding of mental illnesses...but...until you new minds solve this for us, the DSM has improved our ability to talk, research, and accurately...mostly, analyze the myriad of symptoms afflicting our patients, and find the constellation of symptoms best matching a diagnosis...which accurately treats current symptoms.

While I have whole heartedly embraced pharmacogenomic testing and use it regularly in my practice, it only provides presently liver metabolic level information and not molecule receptor specifics, still remains a game changer in my practice. I still hold out for germ line change of target SNP's through viral vectors in my life time...but one can only hope...and keep researching.

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