Review Article

Exploring Mouse Models and Optogenetics to Probe Bipolar Disorder

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ABSTRACT

Bipolar disorder is a neuropsychiatric disease affecting 1-4% of the worldwide population; characterized by spontaneous depressive and manic episodes, very little is known about the pathology of bipolar disorder, and there is no known cure. Theorized pathologies of bipolar disorder include genetic and environmental factors, the dopamine hypothesis, and the role of gut microbiota. This paper reviews several pieces of scientific literature pertaining to these theories, integrating optogenetics as a research tool to more accurately examine and manipulate relevant cellular activity. The reviewed literature draws clear connections from the HPA axis, gut microbiota, circadian rhythms, and dopaminergic expression to the pathology and manifestation of bipolar disorder. However, despite this, there is simply not enough information about the disease itself for researchers to come to a sound conclusion. The disparity is mentioned at least once in each piece of literature and is attributed to both the ambiguity of the disease, and the variability in symptoms between patients. Not only does this affect the current theories surrounding bipolar disorder, but also makes studying the disease incredibly difficult, as without a pathology, ideal animal models are nearly impossible to identify. Literature rooted in the use of optogenetics present results which express increased specificity in both data and conclusions, cementing its potential in future studies concerning bipolar disorder. From this, this paper proposes a new behavioral experimental design in mouse models, integrating optogenetics with the most prevalent theories of the pathology of bipolar disorder.

Keywords: Bipolar disorder; dopamine; optogenetics; gut- brain axis; mouse models

INTRODUCTION

Bipolar disorder is a neuropsychological disease characterized by spontaneous behavioral episodes, commonly manifesting in young adults, ages 19-30. It affects over 6 million people in the US every year, with healthcare costs amounting to over $30 billion USD annually (1). The three behavioral episodes consistent with BD are depression, mania, and euthymia. Depressive episodes present with decreased energy, motivation, and serotonin expression, and elevated behaviors of helplessness. Manic episodes typically include increased energy, irritability, and dopamine expression, and decreased anxiety and depression (2). Finally, euthymic episodes are the baseline, or "normal" behavior exhibited in humans. The switch between these episodes is

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spontaneous, and the triggers are often unknown (3). Bipolar disorder is also associated with consistent, low-grade inflammation in the body and brain that can lead to additional health complications, such as premature death from cardiovascular or respiratory events, and suicide (4). The average life expectancy of individuals with BD is 10-13 years shorter than that of control patients. The etiology (cause) of the disease is a combination of genetics and environmental factors. A patient could be genetically predisposed or experience a traumatic event which triggers the manifestation of bipolar disorder. Currently, the only available treatments are mood stabilizers such as lithium or valproic acid to mediate the symptoms of behavioral episodes (1). The function of such medications is primarily observed in animal models, mainly mice.

Ideal mouse models of any neuropsychiatric disorder are notoriously difficult to identify. This is due to the nature of the diseases themselves, with subjective, varied symptoms, and complex, often incomplete pathologies. However, the complexity of neuropsychiatric diseases allows them to be broken down into increasingly streamlined symptoms, for which there are well- known models. Bipolar disorder is no different, with much of the research grounded in models of depression and mania (3). These models can be broken down into three subcategories: environmental, pharmacological, and genetic models. Environmental models are exposed to various extreme conditions, observed in trials involving sleep deprivation, resident-intruder paradigms, and open field tests (OFT). Pharmacological models are administered psychostimulants such as amphetamines or cocaine, which simulate manic episodes, with observed response to common mood stabilizers. Genetic models are often modified or bred to have a specific gene mutation which will render the model prone to symptoms of BD.

Each of these models go through a meticulous vetting process including three forms of validity: face, predictive, and construct validity. Face validity centers around the presentation of symptoms in a model, and their likeness to that of a human patient. Predictive validity concerns a model's response to typical treatments of a disease, comparing various aspects of responses from both model and patient. Finally, the most credible form of validity, construct validity, emphasizes the molecular happenings of diagnosed patients, and compares them to potential models (3). If a potential model satisfies validity, they are then utilized to examine the various theories of the causes of BD.

As with most neuropsychiatric disorders, information regarding the pathology of the disease is strikingly incomplete, however there are several solid theories. The dopamine hypothesis states that hyperdopaminergia underlies mania and has been one of the foremost theories of the pathology of bipolar disorder for nearly five decades (5). The expression of dopamine in bipolar patients has long been a focal point of the study of this disease. Depressive episodes are characterized by a drop in dopamine levels, while dopamine transporter and knockout genetic mutation mice have been used as models of bipolar disorder on numerous occasions. The role of dopamine is significant in all aspects of BD and thus warrants vigorous investigation.

Another theory that has come forward more recently is the role of the gut microbiome in brain function. The gut microbiota (bacterial ecosystem of the human gut) consists of thousands of bacteria, phages, and fungi, which are constantly shifting according to changes in daily activities (4). Many of these molecules are also either instigators or byproducts of low-grade inflammation consistent with bipolar disorder, making it relevant to the pathology of the disease. However, the most reliable mode of observing and manipulating the microscopic events responsible for these potential pathologies is optogenetics (6).

Optogenetics is a relatively new technique of cellular manipulation and observation, but has been fruitful in the study of neuropsychiatric disorders. The two functions of optogenetics are distinguished by the type of tools being used: sensors or actuators (7). Actuators are genetically encoded to be responsive to certain wavelengths. In neuropsychiatry, the main type of actuators used are microbial opsins: light- responsive ion channels embedded in cell membranes. These ion channels– located in the cell body (membrane) of a neuron– produce nerve impulses by moving ions across the cell membrane to alter its overall charge. When opsins are inserted into the cell, its ability to produce new impulses can be regulated by turning on and off a corresponding wavelength of light being shone onto the targeted cells. There are four main opsins used for cellular manipulation. Channelrhodopsins 1 and 2 are both blue light activated and allow for cations (positively charged atoms) to flow into the cell, although ChR2 is often preferred, as it has higher conductance. Halorhodopsins are yellow light activated and allow for chlorine influx into a cell when opened, causing hyperpolarization (increased negative charge) of the neuron, inhibiting its function. Finally, Archaerhodopsins and Wild- Type Mac opsins are a green/yellow and blue/green light activated, proton efflux channels, also used for inhibiting neuron function (Table 1). This literature review discusses animal models of BD, the dopamine hypothesis and gut-brain axis,

Table 1. Types of microbial opsins used for cellular manipulation in optogenetics

Microbial Opsins	Light Activators and Purpose
Channelrhodopsins	Blue light activated, opens cation channel into cells
Halorhodopsins	Yellow light activated, opens chlorine channel into cells, results in hyperpolarization of the cell
Archaerhodopsins	Green or yellow light activated, opens proton channel into cells, results in neuron inhibition
Wild- Type Mac	Blue or green light activated, opens proton channel into cells, results in neuron inhibition

environmental and genetic factors of bipolar disorder, and how optogenetics have already been used to assist in this research.

EXISTING ANIMAL MODELS OF BIPOLAR DISORDER

The goal for Nestler and Hyman is to explore the generation, identification, and validation of potential animal models for three different neuropsychiatric disorders, including bipolar disorder (9). It does so by examining three forms of validity, and how they manifest in BD. Face validity measures the model's ability to mimic symptoms of bipolar disorder displayed by human patients. A key drawback of face validity is that symptoms are often not exclusive to one psychiatric disorder, and many are subjective, and can vary from patient to patient. As a result, face validity is often the most contested out of the three types. Predictive validity tests a potential model's response to established treatments of a psychiatric disorder. In the case of BD, the most common and long-standing treatments are lithium and valproic acid. Like face validity, predictive validity has its limitations– mostly pertaining to the varied responses of patients– making it contested as well. The least contested form of validity is constructing validity. It combines the criteria of face and predictive validity, utilizing various behavioral and molecular tests to prove or disprove a potential model's ability to present markers of a psychiatric disorder (9).

There is little information regarding the role of the genetic basis of BD. While it is known that the cause of bipolar disorder is a combination of genetic and environmental factors, this remains the broadest consensus. While there are numerous identified possibilities, the complex genetic makeup in models makes identifying the exact mutations responsible for BD. To up the ante, researchers are tasked with generating models which display symptoms and treatment responses to all three episodes associated with BD. Nester and Hyman argue that, while there is much potential for the generation of models for neuropsychiatric disorders, there is not yet enough information about the pathophysiology for diseases such as bipolar disorder to generate truly accurate models yet (9).

The goal of McClung and Logan is to examine recent findings in genetically modified mouse models of bipolar disorder, with the aim of utilizing validity to identify ideal models (1). Researchers note that there are few known biomarkers of psychiatric diseases, especially BD, which are inconsistent and complex; therefore, construct validity is more highly contested than it normally would be in a disease with a clear genetic cause. McClung and Logan also criticized face validity, noting its reliance on diagnostic criteria outlined in guides such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IVTR), which does not contain enough verified information specific to BD (1). However, it does introduce the potential of pathological validity, in which the pathology of both human and model postmortem tissues are examined and compared to one another. A drawback of this form of validity is the uncontrollable variables associated with postmortem studies.

McClung and Logan thoroughly discuss three versions of potential models for bipolar disorder (1). Pharmacological models are those generated via the administration of psychostimulants- mainly amphetamines- with the goal of inducing mania-like behaviors and symptoms. This state can then be mediated with common treatments of BD, such as lithium or valproic acid (VPA). It is noted that while amphetamines are mostly successful in eliciting some manic symptoms, a few (including neuroplasticity) are not replicable in models. In addition, researchers note that the amphetamine and lithium treatments are acute, unlike bipolar mania itself, which is chronic and therefore could have altered long term effects. Finally, it is noted that the acute administration of quinpirole- a dopamine D2 receptor agonist- which induced manic-like behaviors, is exclusive to McClung and Logan (1).

Environmental models of mania are produced by

inducing significant disruptions in daily activities and circadian rhythms. These include sleep deprivation, resident-intruder paradigms, and isolation. To induce sleep deprivation, models were placed on a small platform surrounded by water for 72 hours. It was found that for the first 30-40 minutes following placement back into their home cage, models exhibited extreme manic symptoms, often past the point considered normal in human BP patients. However, the models were receptive to mood-stabilizing treatments. The model's response to resident- intruder trials were mitigated with lithium and exaggerated with antidepressants. However, it is noted that most of the observed behaviors overlap with anxiety disorders, therefore limiting predictive validity of these experiments (1).

McClung and Logan examined potential genetic models in great detail, focusing on the effects of several different genetic mutations associated with bipolar disorder (1). BD is thought to result from a combination of several gene mutations; however, studying them collectively would be complex. Therefore, McClung and Logan reviewed each mutation separately, on a molecular level (1). The CLOCKΔ19 gene mutation is associated with the regulation of circadian rhythm, affecting the frequency of manic episodes, insomnia, and the sleep-wake cycle. The cause of these symptoms is affected by excess dopamine from VTA (ventral tegmental area) neurons, as demonstrated through optogenetics. The Cholecystokinin (Cck) gene governs peptide release with dopamine which inhibits further expression. It is associated with a reduction of CLOCK mutation in mice and found in human postmortem VTA tissue. The GSK-3β gene regulates amplitude and period of circadian rhythms, and overexpression results in hyperactivity and reduced food intake. The SHANK-3 protein is essential to synapse function and maintenance. When overexpressed, it results in sensorimotor deficits and altered locomotor activity but is respondent to VPA treatment. The ANK3 gene is strongly associated with bipolar disorder and also considered a risk factor of schizophrenia, as it is a significant mediator of mood- related behaviour. Finally, Myshkin mutant (Myk/+) models commonly present with hyperactivity, exaggerated locomotor response, sleep pattern disruption and reduced anxiety (Table 2).

To conclude, McClung and Logan discusses the lack of models of mood switching (the spontaneous switch of bipolar episodes), and information concerning the seasonal element of BD (1). McClung and Logan state that the recent developments of new technologies will be incredibly beneficial to neuropsychiatric research, and making strides towards identifying the pathophysiology of bipolar disorder (1).

Beyer and Freund outlines exact requirements for ideal models of bipolar disorder, as well as the role that circadian rhythms, dopaminergic pathways, environmental stressors, and the immune system play in the pathology of BD (2). Beyer and Freund state that ideal models of BD must display disease- specific behavioral abnormalities, be able to emanate the cyclical nature of bipolar disorder, and respond to current treatments, among other requirements (2). It also introduces the deletion of exon 19 or VTA knockdown as being exact mutations of CLOCK that result in behaviors of BD, observing increased dopamine in both models. However, Beyer and Freund notes that sleep deprivation alone is enough to elicit symptoms of bipolar disorder, without the need for genetic manipulation (2).

The discussion of sensitization models and

Table 2. Biological effects of genetic mutations on models used in trials concerning bipolar disorder

Genetic Model	Associated Biological Functions
CLOCKΔ19	regulates circadian rhythm, affects frequency of manic episodes, insomnia, and the sleep-wake cycle, results in elevated dopamine levels in the VTA
Cholecystokinin (Cck)	governs peptide release with dopamine, inhibiting expression, reduces CLOCK mutation
GSK-3β	regulates amplitude and period of circadian rhythms, overexpression results in hyperactivity and reduced food intake
SHANK-3	essential to synapse function and maintenance, overexpression results in sensorimotor deficits and altered locomotor activity
ANK3	mediator of mood- related behaviour, strongly associated with both bipolar disorder and schizophrenia
Myshkin (Myk/+)	regulates hyperactivity, exaggerated locomotor response, sleep pattern disruption and reduces anxiety

neurotransmitters is unique to beyer and Freund and mainly concerns depressive states of bipolar disorder (2). Situations such as increased daytime periods and withdrawal from psychostimulants increase depressive behaviors, as well as the activation of the cholinergic system. Additionally, it is noted that sensitization models are among the few to exhibit both depressive and manic behaviors in the same model. However, a major limitation of sensitization models is the inability of psychostimulants to elicit symptoms exclusive to bipolar mania. Instead, researchers recommend conducting focused neurotransmitter/ psychostimulant experiments, as they yield more conclusive results (2).

It is known that the cause of BD is a combination of genetic and environmental factors. Beyer and Freund focused on the environmental manipulation and trauma of juvenile models, exploiting undeveloped brains in the womb (2). Pregnant maternal models were periodically placed into stress environments, while the fetal development was closely monitored, in the hopes of observing manic or depressive behaviors in the offspring post- birth. Other trials focused on young or adolescent mice– whose cognition was still developing– and subjected them to the same conditions. It was found that early life stresses can manifest in depressive behaviors and phenotypes in adult mice, similar to humans.

Another aspect of bipolar disorder examined in mouse models is the consistent, low-grade inflammation in the immune system. Beyer and Freund discuss this in a process similar to that of environmental models, utilizing maternal mouse models that had been exposed to pathogens such as influenza while pregnant (2). It was found that maternal models who contracted viral diseases gave birth to pups with an increased risk of developing bipolar disorder. Additionally, models with similar immune activations in early development presented behavioral alterations associated with bipolar depression and mania. These connections are a key takeaway of Beyer and Freund, concluding that these risk factors are deeply intertwined, and contribute to the study of BD (2). Finally, researchers suggest that the relationship between the length of daytime periods and mood cycling may be worth examining further.

Einat states that the current animal models of bipolar disorder remain limited due to an incomplete understanding of the pathology and biology of the disease (8). Echoing sentiments expressed in Beyer and Freund and McClung and Logan, Einat states that there are no current animal models that emanate the cyclical aspect of BD, and suggests new methods for developing such models (8). While it is known that there is no single ideal model for any psychiatric disorder, there are models which express significant aspects of a disease, such as depression and mania in bipolar disorder. As demonstrated by these studies, utilizing existing models for the major aspects of bipolar disorder will contribute to the goal of a single model. This includes bred models, selective mutation models, and standard mutation models, as previously explored by Beyer and Freund and McClung and Logan (1, 2).

USE OF OPTOGENETICS TO AFFECT BEHAVIOR RELATED TO BIPOLAR DISORDER

Hsueh *et al*. is aimed to construct noninvasive optogenetic pacemakers to control cardiac rhythms of model mice, and examine the effects of cardiac rhythms on emotional state through whole brain scans (7). This particular structure required the use of Channelrhodopsin Chmine to gain cell-type specific control of cardiac pacing, activated by an LED light fixed to the model's chest. The model's behaviour was then observed in both an elevated plus maze (EPM) and an open field test (OFT), and compared to that of control mice (models without pacemakers). No significant disparity was found between either set in those tests, nor in baseline anxiety and mobility for both groups. However, it was found that increased use of optical pacemaking in models also increased insular activity (cellular activity in the insular region of the brain), which governs the interoceptive process in the brain.

Brain regions involved in interoception (awareness of the internal processes of one's body) include the prefrontal cortex, anterior singulate area, and brain stem. Interception is the body's process of identifying and reacting to cellular changes in any given area. Similarly, these brain regions are activated by optically evoked tachycardia. However, insular inhibition trials resulted in decreased anxiety response to optical cardiac control, which is otherwise increased in environments with perceived risk factors. Overall, Hsueh *et al*. was a success, as it produced a functioning, noninvasive, optogenetic pacemaker, which allowed for precise cardiogenic alteration (7).

Recently, optogenetics has been identified as an essential new method of cellular observation and is expected to revolutionize fields of research in neuropsychology. However, as thoroughly discussed by Sidor and McClung, one aspect of optogenetics that has yet to be examined is the effect of timing (6). Most biological functions occur

on a 24 hour cycle, regulated by the circadian rhythm. The coordinated neural activity across all involved regions (hippocampus, amygdala, ventral tegmental area, central nervous system) is crucial to ensure that all daily activities occur smoothly. Throughout the day, the behavioral state evolves according to the circadian clock, which can affect results obtained from optogenetic stimulation. The disparity is dramatically increased when stimulation is carried out in opposite stages of the day (light and dark cycle), during specific behavioral high and low points.

CLOCKΔ19 mice (mutated to disrupt the circadian rhythm) are used to study effects of chronic alteration of daily activities on reward and mood related behaviors. It is noted that tests aimed to alter amplitude, phase or period of neural activity rhythms which require significantly longer periods of time to examine. With these chronic alterations, abnormalities such as reduced anxiety behaviors, increased depressive behaviors, hyperactivity, and reduced sleep occurred. Overall, CLOCKΔ19 mutant mice exhibited alterations of timed neural events and dopamine system function, although the mechanisms driving these remain unclear. Sidor and McClung found that sustained optogenetic manipulation led to long-term plastic neural changes when observed over a minimal period of three days (6). Stimulation itself lasted five minutes or less, however it is noted that any stimulation intended to last upwards of ten minutes requires opsins sensitive to lower wavelengths of light (such as blue or green sensitive opsins).

Although Sidor and McClung themselves are considered successful, it is noted that repeated reinjection of opsins required for optogenetic stimulation is not the most efficient method of chronic stimulation (6). Instead, Sidor and McClung recommend chronic fiber implants, which last longer and require significantly less physical handling of models, utilizing wireless technology for noninvasive, chronic stimulation (6). Although still somewhat underdeveloped, a head-mounted LED combined with radio frequencies to produce optogenetic stimulation was provided as an example.

Kong *et al.* also utilized optogenetics to examine brain function in mouse models, focusing on changes in the frontal limbic system of the brain (3). It proposes dysfunction of the suprachiasmatic nucleus (a circadian rhythm dictator located in the hypothalamus) and circadian rhythms as pathologies of bipolar disorder. The frontal limbic system is strongly linked to the pathophysiology of BD, as it involves many of the same cognitive structures, including the hippocampus and amygdala. The many subsections of the frontal lobe contribute to the challenge of identifying which structures are most prevalent in bipolar disorder, although there are a few that stand out immediately.

The amygdala is known to have heightened activity during manic episodes and is therefore a target of optogenetic manipulation. In addition, dysregulated dopamine receptors are associated with the pathophysiology of BD, and could be targeted through optogenetic tools to either replicate or reverse emotional abnormalities. Kong *et al*. also noted that gut microbiota (GMB) interact with the brain through epigenetic and genetic regulation, contributing to the theory of a link existing between emotional states in the brain and gut health (3).

Although the exact mechanisms connecting biological rhythms and emotional states had yet to be identified, the synchronization and regulation of circadian rhythms is a proven therapy for bipolar disorder. Similarly to Sidor and McClung, researchers also note here that the rhythm state of the body– the stage of the circadian rhythm it is currently in– should always be considered when attempting optogenetic stimulation (6). To conclude, Kong *et al*. recommends future studies to place greater emphasis on clinical models of BD (3).

THE DOPAMINE HYPOTHESIS OF BIPOLAR AFFECTIVE DISORDER

The dopamine hypothesis states that dopaminergic transmission is disturbed depending on mood phase (5). It is currently one of the most promising hypotheses for identifying the pathophysiology of bipolar disorder. Currently, the aspects of the dopaminergic system that interact the most with pathologies of BD are the D2/3 receptors. Although they have been used in several trials related to bipolar disorder, DAT knockout or knockdown mutations only elicit behaviors of bipolar mania, and not depressive states. General dopamine mutated models only exhibit increased dopamine expression, mania, and depressive behaviors upon termination of manipulation, further clouding the significance of these mutations.

Ahsok *et al*. discusses the hypothesis that hyperdopaminergia underlies mania, and the failure of certain dopamine receptors could underlie the pathophysiology of BD (5). It presents post mortem and pharmacological examinations, functional magnetic resonance, and molecular imaging studies as proof. Using optogenetics, researchers linked model hyperlocomotion (an excessive amount of movement or activity) to a spike in dopamine in the VTA during the daytime, and use the

manipulation of those same neurons to reverse depressive behaviors. Although Ahsok *et al*. utilized the comparison of postmortem tissue from patients and models, it also outlined several limitations of this particular form of examination (5). These limitations include postmortem interval (length of time since the patient's death), cause of death, and the patient's medication status– variables often out of the control of the researchers– which could produce tainted results.

Ahsok *et al*. discusses several studies concerning dopamine imaging in living models and patients, coming to surprisingly few conclusions (5). Only two of the studies examined focused on dopamine expression in the euthymic state of bipolar disorder, and their results are inconsistent with one another. Similarly, there is a sizable lack of information pertaining to dopamine release in depressive states of BD. Ahsok *et al*. discusses two trials, one of which examines models of both depressive and euthymic states, not exclusively depressive states (5). The results of these experiments are mostly inconclusive, aside from the confirmation that the D2/3 receptor plays a role in the pathology of bipolar disorder- though its exact function is still unclear. Functional magnetic resonance imaging studies utilized reward experiments to examine responsive behaviors of depressive, manic, and euthymic models in comparison to control groups. Unfortunately, many of these results are also contradictory, showing varied responses to reward behaviour in euthymic models and no difference between responses from depressive and control groups. However, it is noted that hyperactivity in the reward circuits of the brain is higher when models are in a manic state. Pharmacological trials were significantly more successful than the previous two, utilizing tyrosine to inhibit manic behaviors. Ahsok *et al*. found that not only does tyrosine mediate mania, it also increases depressive behaviors (5). Conversely, these trials also conclude that stimulants meant to mediate depressive behaviors can increase mania.

Imaging studies and pharmacological evidence both support that hyperdopaminergia leads to mania. They also project that in addition to the existing monotherapies and adjunctive treatments of bipolar disorder, both dopamine agonist and blocking drugs have potential benefits against bipolar depression. Ahsok *et al*. concludes by suggesting additional studies of similar content focused on the mixed states of BD (5).

Scott and McClung echoes the sentiments of Ahsok *et al*., stressing the importance of circadian rhythms and the HPA (hypothalamic- pituitary- adrenal) axis in bipolar disorder, aiming to introduce the significance of circadian abnormalities in mood disorder treatments (5, 11). However, in contrast to such reviews, Scott and McClung states that abnormalities of the molecular clock pathway going beyond gene alterations contribute more significantly to the pathophysiology of BD, and to mood disorders in general (11). The study continues on to discuss the relationship between stress, dopamine, the HPA axis and circadian rhythm, stating that the latter two (the HPA axis and circadian rhythm) are known to regulate each other, while the former (stress and dopamine) are byproducts of them. Scott and McClung also introduces chronotherapeutics– treatments designed to target circadian rhythm regulators– to control antidepressant responses, including manipulations of sleep, light, and melatonin processes (11). To conclude, Scott and McClung reiterate the significance of the relationships between circadian rhythms and the HPA axis to monoaminergic transmission, and its potential to further research for treatments of BD (11).

MICROBIOTA-GUT-BRAIN AXIS MECHANISMS IN BIPOLAR DISORDER

Ortega *et al*. focuses entirely on the function of the gut microbiota in bipolar disorder, including the microbial ecosystem of the gut, bacteria translocation, and neuroinflammation and the HPA axis (10). The microbiota ecosystem is an ever-changing environment that contains bacteria, viruses, fungi, and amoebozoa and archaea. It is constantly adapting, affected by factors such as diet, exercise, psychological and physical stress, sleep restrictions, drugs, and body temperature, just to name a few. It is closely associated with low grade inflammation in many psychological conditions (10). Despite this, proven information on the microbiome is limited. It is known that some bacteria present in the microbiota are linked to specific brain functions, and that the composition organisms present in the gut microbiota differ from control models to bipolar patients.

Bacterial translocation in models is an indication of a weakened intestinal barrier, allowing a greater range of cells to pass through it (10). Altered levels of intestinal cytokines are observed in bipolar patients, possibly linked to systemic inflammation as well as intestinal inflammation, though current evidence is limited. Abnormalities have been observed such as elevated proinflammatory cytokines in models of manic and depressive states. This disrupts intestinal integrity and causes additional systemic inflammation and gut dysbiosis, which contributes to neuroinflammation (10).

These factors can lead to immunological response from the brain– including blood- brain barrier dysfunction– which is associated with BD. The immune response from the brain can lead to neuroplasticity and inflammation, contributing to the development of bipolar disorder (10). Additional factors, such as sleep disruption, early life traumas, HPA axis alteration, and elevated cortisol levels can also further aggravate neuroinflammation. Furthermore, short fatty acid chains– also present in the gut microbiota– are linked to neural alterations observed in several psychiatric disorders, including bipolar disorder (10).

In addition to examining the gut microbiota itself, Ortega *et al*. also details various treatments for BD, and the behavioral states they most appropriately address (10). For instance, researchers state that mania should be treated with lithium, divalproex, or atypical antipsychotics, and mixed episodes should be treated with divalproex or atypical antipsychotics. However, depressive episodes have less available treatment options. As a response, the exploration of pharmacomicrobiomics– a field of study examining the effect of the GMB on human response to drugs– for antidepressants is a promising course of action for treatment of bipolar disorder. As for additional ways to improve gut microbiota composition, consistent administration of VPA has been shown to alter composition, as well as several lifestyle changes, including diet or immune-based approaches. Ortega *et al*. concludes by suggesting future trials focusing on additional depressive states, as well as trials considering type I and II bipolar disorder (10).

The complexity of bipolar disorder is unsuitable for easily identifiable pathologies or genetic makeup. The thorough examination of current models of depression, mania, and mood switching, is instrumental to identifying a more ideal model for BD overall. By examining genotypes and phenotypes of environmental, genetic, and pharmacological models, researchers can begin building a more accurate model. This includes any models that can reliably replicate key aspects of bipolar disorder, although it should be noted to keep this list as concise as possible, as the identification of pathologies and ideal models of BD are heavily reliant on one another.

The dopamine hypothesis holds promise for identifying an etiology of mania, although more conclusive testing is needed to prove it. The study of dopamine expression and suppression in BD is most often observed in environmental and genetic manipulation models. It is examined in models of dopamine transmitter or knockout mutation genes, as well as models in extremely low or high stress environments. Dopamine can regulate mood swings, follow the circadian clock and HPA axis cues, and is well established in studies of depression and mania.

The human gut microbiota is an extensive field of research within itself, but also holds special significance in neuropsychiatry. It considers the symptoms of bipolar disorder from another angle. Low levels of systemic and neurologic inflammation and HPA axis dysregulation are common symptoms of BD. Such symptoms can often lead to major health complications as well. Not only does the study of the gut microbiota offer an examination of gut bacteria known to affect brain function, but also a potential mode of transmission of risk- associated genes and inflammatory bacteria between a mother and child.

Despite its somewhat recent arrival to neuropsychiatric research, optogenetics has quickly become a revolutionary tool in this field. The ability to manipulate systemic functions on a cellular level is an exciting concept, especially in diseases like bipolar disorder, where existing information is limited. The technique allows researchers to observe interoception in real time, as well as examine the events of the circadian cycle on a molecular level, in any area of the body. These developments are especially important for diseases of the brain, which are notoriously difficult to identify and treat accurately.

Between each review —McClung and Logan, Beyer and Freund, Kong *et al*., Ahsok *et al*., Sidor and McClung, Hsueh *et al*., Eniat, Nestler and Hyman, Ortega *et al*., and Scott and McClung— the overall experimental processes and conclusions are the same; there is no ideal animal model of bipolar disorder due to a lack of proven mechanisms responsible for it. This in turn impedes further research for early diagnosis, improved treatments, and cures. While this is true for a number of neuropsychiatric disorders, the multi- episodic, cyclical characteristics of BD pose a unique hurdle in the pursuit of these goals. While it is accepted that there is no ideal model for neuropsychiatric disorders, and current research is far from one (1, 8, 9), reviews agreed on the use of existing models of depression and mania, as well as proven behavioral experiments to be the basis for further research. While very few used optogenetics — considering its novelty in neuropsychiatry — Kong *et al*. and Hsueh *et al*. endorsed its potential for the future of neuropsychiatric research (3, 7). Despite the absence of an ideal solution, the reviews did not reveal any major contradictions. The trials examined in each review were similar, utilizing the most common tests for depression and mania: EPM, OFT, sleep deprivations, and resident-intruder paradigms. The trials also had similar outcomes, supporting some conclusions– such as the significance

of animal models– and weakening others that did not have clear outcomes. Replacing inconclusive trials– such as reward paradigms– with different approaches is a potential course of action where the methods of inducing certain behaviors are edited or switched out entirely. The further integration of optogenetics into neuropsychiatry- considering its suitability to exploring chemical pathways of the brain- could accelerate the process of deciphering the elusive mechanisms behind BD. Similarly, a greater investigation of the gut- brain axis, with the integration of optogenetics, could bear additional improvements. If these goals are attained, they could lead to the development of advancements in diagnosis and treatment of bipolar disorder, potentially reducing suicide rates in patients, and extend average life span of individuals living with the disease.

CONCLUSION

As highlighted in the literature review of this paper regarding bipolar disorder (1-11) , the lack of information on the pathology of BD is a significant limitation to any new or ongoing research. While there are several known connections between various biological systems, (circadian rhythms, dopaminergic transmissions, the HPA axis, and the gut- brain axis) there are not enough proven specifics about these relationships to allow them to provide significant assistance in the curation of new treatments. The lack of essential animal models from this limitation creates yet another challenge for the research of BD. However, while the pathology of bipolar disorder continues to elude researchers, this won't be the case forever.

In agreement with McClung and Logan, this paper further endorses the use of optogenetics to examine mood switching models (1). Mood switching is a somewhat underdeveloped aspect of bipolar disorder and has much potential. Using optogenetics to monitor brain cell activity during mood changes could be an incredible contribution to the study of BD. This paper proposes a combination of reliable behavioral tests and mouse models, observed with an emphasis on dopamine and microbiota alterations as a potential new paradigm. Reliable behavioral tests would include elevated plus mazes, open field tests, and resident- intruder trials. Reliable mouse models would include Madison mice, CLOCKΔ19 mice, and D-protein knockout mutated mice, as they are the species most genetically similar to bipolar human patients. Such trials would employ optogenetics as a means to alter and monitor brain cell activity, in addition to dopamine expression and HPA axis alterations. These manipulations would be most ideal using neural- inhibiting actuator opsins –such as halorhodopsins or archaerhodopsins – in the VTA. The goal of these proposed paradigms is to clarify the interactions of these variables, which have each been studied extensively as isolated topics, but very rarely examined together. It will do so by clarifying previous inconclusive trials, isolating and re-testing each variable with reliable models and paradigms and creating connections between successful trials and their previously drawn conclusions.

Bipolar disorder continues to be a prominent disease today, affecting over 80 million people, and continues to lack a cure. Continuing exploration of the topics discussed in these studies, and implementing new tests– such as the one proposed here– will contribute to the final goal: improved treatment and prognosis for the millions of people living with bipolar disorder.

DECLARATION OF CONFLICT OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this article.

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