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On The Future Of Antidepressant Treatments: Targeting Neurotrophic Factors And Plasticity

Stephen W. White
University of Mississippi

ON THE FUTURE OF ANTIDEPRESSANT TREATMENTS:

TARGETING NEUROTROPHIC FACTORS AND PLASTICITY

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Stephen W. White

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ABSTRACT

For 60-plus years the explanatory model for Major Depressive Disorder (MDD) has been the monoamine theory, which states that low levels of monoamine neurotransmitters or alterations in their post-synaptic receptors are responsible for depressive symptoms. Drugs designed to elevate synaptic monoamine levels have remained the first line of pharmacotherapy prescribed by clinicians for MDD patients. However, these drugs have shortcomings. Despite evidence that current antidepressants elevate synaptic monoamine levels within hours of administration, these drugs require four to six weeks of daily administration before symptom relief appears. Furthermore, approximately half of patients taking typical antidepressants never achieve full symptom relief. The therapeutic lag time and low response rates associated with typical antidepressants suggests that elevation of monoaminergic activity may not be their true mechanism of antidepressant action and brings into question the validity of the monoamine theory. As a result, novel biological targets have been investigated for development of more reliable and faster-acting antidepressants. Recent work has shown that low doses of ketamine, a glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist, can provide depressive symptom relief within hours of administration. What is interesting about these findings is that ketamine works on a completely different biological system than typical antidepressants. Moreover, a number of non-drug treatments, such as electro-convulsive therapy, psychotherapies, and exercise have proven efficacious in treating depressive symptoms. Understanding the biological mechanisms that underlie all of these various treatment modalities may provide evidence for a more valid explanatory model of MDD. In a review of relevant

literature examining biologic alterations produced by monoaminergic antidepressants, ketamine and other glutamatergic agents, psychotherapies, electroconvulsive shock therapy, or exercise a commonality was identified: all of the treatments promote the growth of new synapses (synaptogenesis) and the growth of new neurons (neurogenesis). This finding prompts support for the developing Stress-Neurogenic Theory of depression. This theory suggests depressive symptoms are due to chronic, unpredictable stressors which stimulate the production of stress hormones leading to cell death in major brain areas and treatment for depression is dependent upon stimulating the brain's natural processes responsible for the growth of new connections and new cells in affected brain regions.

LIST OF ABBREVIATIONS AND SYMBOLS

MDD	Major Depressive Disorder
TRD	Treatment-Resistant Depression
FDA	Food and Drug Administration
NMDA	*N*-methyl *D*-aspartate
DSM	Diagnostic and Statistical Manual
HDRS	Hamilton Depression Rating Scale
CDC	Center for Disease Control
5-HT	Serotonin
NE	Norepinephrine
ECT	Electro-convulsive Therapy
MAO	Monoamine Oxidase
VMAT	Vesicular Monoamine Transporter
MAOI	Monoamine Oxidase Inhibitors
TCA	Tricyclic Antidepressants
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Selective Norepinephrine Reuptake Inhibitor
BDNF	Brain-derived Neurotropic Factor
mRNA	Messenger Ribonucleic Acid

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
PFC	Prefrontal Cortex
mGluR	Metabotropic Glutamate Receptor
CSF	Cerebrospinal Fluid
MRS	Magnetic Resonance Spectroscopy
LTP	Long-Term Potentiation
EPSP	Excitatory Post-Synaptic Potential
AP-5	(D,L)-2-amino-5-phosphono valeric acid
FST	Forced Swim Test
TST	Tail Suspension Test
AP-7	2-amino-7-phosphonoheptanoic acid
CMS	Chronic Mild Stress
PCP	Phencyclidine
IQ	Intelligence Quotient
NBQX	2, 3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2, 3-dione
mTOR	Mammalian Target of Rapamycin
NIMH	National Institute of Mental Health
HNK	Hydroxynorketamine
Trk-B	Tyrosine Receptor Kinase - B
CRH	Corticotrophin-Releasing Hormone
HPA	Hypothalamic-Pituitary-Adrenal
IPT	Interpersonal Therapy

CBT	Cognitive Behavioral Therapy
DLPFC	Dorsolateral Prefrontal Cortex

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1.0 INTRODUCTION

According to the National Institute of Mental Health, major depressive disorder (MDD), or major depression, is characterized by a combination of symptoms that interfere with a person's ability to work, sleep, study, eat, and enjoy once-pleasurable activities. Some people may experience only a single depressive episode within their lifetime, but more often a person will experience multiple depressive episodes. According to the DSM-5, five of the following criteria must be met in the same two week period to diagnose someone as suffering from a major depressive episode: 1) depressed mood most of the day, nearly all day; 2) diminished interest or pleasure in all, or almost all activities most of the day nearly every day; 3) significant weight loss when not dieting or significant weight gain, or a decrease or increase in appetite nearly every day; 4) insomnia or hypersomnia nearly every day; 5) psychomotor retardation or agitation nearly every day; 6. Fatigue or loss of energy nearly every day; 7) feelings of worthlessness or excessive or inappropriate guilt nearly every day; 8) diminished ability to think or concentrate, or indecisiveness, nearly every day; 9) recurrent thoughts of death other than fear of death, recurrent suicidal ideation, or a suicide attempt, or a specific plan for committing suicide (Diagnostic and Statistics Manual-5).

A 2003 study using 9090 participants found that 16.2% suffered from an MDD episode during their lifetime and that 6.6% of the participants experienced a major depressive episode

during the 12 months before the study. If those sample numbers were extrapolated to the general population, the study suggests that between 33-35 million U.S. adults experience a major depressive episode in their lifetime and between 13-14 million U.S. adults experience at least one depressive episode during a 12-month period (Kessler et al, 2003). In a 2005 follow up study designed to estimate 12- month prevalence, severity, and comorbidity of DSM-IV anxiety, mood, impulse control, and substance abuse disorders found that 6.7% of the subjects experienced a major depressive episode in the preceding 12 months, findings consistent with the 2003 study (Kessler et al., 2005). The estimated economic cost of MDD in 2000, which includes the cost of treatment and loss of work productivity, was estimated at $83.1 billion in the United States alone (Greenberg et al. 2003).

While the economic impact of MDD is staggering, major depressive disorder is not the only type of depressive disorder. Other common depressive subtypes are treatment-resistant depression, bipolar depression, and dysthymic disorder. Although it is not recognized by the Diagnostic Statistical Manual (DSM) used by clinicians for diagnosis of mental disorders, treatment- resistant depression, or TRD, is relatively common in MDD cases as only 50% of MDD patients respond to typical pharmacotherapies for depression (Papakostas, G. I., & Fava, M. 2010). Currently the FDA defines treatment-resistant depression as the failure of depressed patients to respond to adequate dosing and regimen of pharmacotherapies from two distinct classes of traditional antidepressants. This diagnostic criteria can only be made post-treatment thus leaving patients to continue to suffer from depressive symptoms. A 2010 study by Fostick and colleagues revealed that patients diagnosed with TRD suffer from more severe MDD symptoms as scored on the Hamilton Depression Rating Scale (HDRS). In this study 107

patients diagnosed with MDD were interviewed by a psychiatrist who was blind to the purpose of the study and to the treatment history of the patients and scored the severity of depressive symptoms using the HDRS. The study reported that non-TRD patients had a mean score of 9.8 versus a mean score of 18.6 for TRD patients (Fostick et al., 2010). This same study also found a positive correlation between depression severity and economic impact. Patients with more severe depression had increased direct costs, such as blood and imaging tests, physician visits, and hospitalization costs, as well as increased indirect costs, such as lower worker productivity and higher worker absenteeism. In a recent meta-analysis of the cost of MDD patient care from 2001 to 2009, it was found that the medical expenses for TRD patients was almost 30% higher than normal MDD patients (Olchanski et al., 2013). The association of increased expenses and TRD was confirmed in an analysis by Gibson and colleagues who found that, on average, depressed patients deemed treatment resistant had 40% higher medical costs compared to respondent MDD patients (Gibson T. et al., 2010).

While the economic impact of depressive disorders is significant, not only to the sufferer but to the general public as well, the more troubling symptom of these depressive disorders is suicide ideations and attempts. According to the Center for Disease Control (CDC) website, suicide is defined as "death caused by self-directed injurious behavior with intent to die as a result of the behavior." (see www.cdc.gov). The CDC also lists suicide as the tenth leading cause of death in 2015 and the third leading cause of death among people between the ages of 10 and 14 and the second leading cause of death among people between the ages of 15 and 34 in that same year. Furthermore, the CDC reports that there were 44,193 suicides in 2015 compared to 17,793 homicides.

The economic and personal impact of depressive disorders make the need for effective therapies for MDD paramount. Identifying and developing more effective and faster acting antidepressants requires our full understanding of the etiopathology associated with the disorder. The purpose of this paper is to review the development of the monoamine theory of depression, examine the validity of the findings that prompted it, and identify any common mechanisms shared by all forms of efficacious treatment for depression. If any commonality in biological alterations exists between the various treatment modalities, it may prove useful in developing a more valid explanatory model for MDD, which would promote a new avenue in development of more effective and faster acting antidepressant pharmacotherapies.

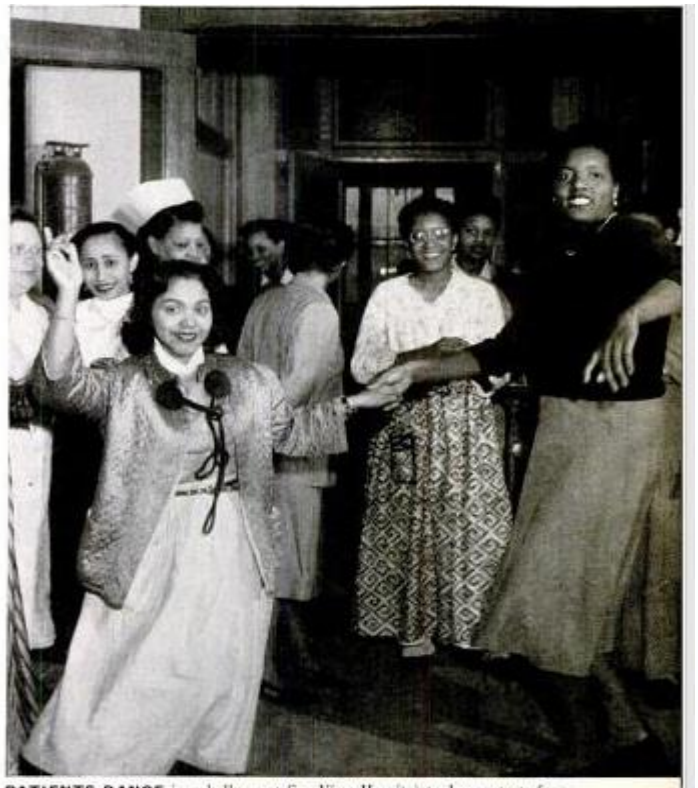
2.0 BACKGROUND

2.1: Development of the Monoamine Theory of MDD

For the past 60-plus years, the etiology of MDD has been explained through the monoamine theory which proposes that MDD is caused by deficiencies in the monoaminergic neurotransmitters, specifically serotonin (5-HT) and norepinephrine (NE), or by some dysregulation of their post-synaptic receptors. Evidence in support of this theory originates from two discoveries that occurred in the 1950's: 1) the ability of drugs that elevate monoaminergic activity to improve mood and 2) drugs that deplete synaptic monoamine levels induce depression.

Prior to the 1950's, the use of electro-convulsive shock therapy (ECT) developed by Ugo Cerletti was the most successful treatment option for depressive disorders, but due to the invasiveness of the procedure, it was only used as a last resort after traditional therapist-client psychiatric methods failed. The development of the first pharmacotherapies for depression in the 1950's occurred by chance. In 1951, pre-clinical researchers began investigating the anti-tuberculosis properties of a class of compounds called hydrazines. After testing in animals proved successful, clinical trials with the most promising hydrazine, isoniazid, took place in hospitals across the state of New York. The antitubercular effects on isoniazid in these hospitals offered hope for patients, doctors, and researchers and opened an avenue for the development of

structurally similar drugs, such as iproniazid which was much more effective in humans than isoniazid. As a side note of interest, introduction of these drugs to treat tuberculosis caused the death rate in the United States to fall from 188 deaths per 100,000 persons in 1904 to just 4 in 1952. In that same year, doctors using iproniazid to treat tuberculosis patients at Sea View Hospital on Staten Island in New York noticed that tubercular patients treated with iproniazid showed increased vitality and an increase in their social interactions with other patients and staff and even led to some patients engaging in dancing in the hospital, the event immortalized in the picture "*The Patient's Dance*." (see image below).



PATIENTS DANCE in a hallway at Sea View Hospital to demonstrate for a newspaper photographer how miraculously the drugs have restored their energy.

Image 1: Tubercular patients at Sea View Hospital dancing after treatment with hydrazines.

However, these behavioral changes were seen as side effects assumingly produced by iproniazid's stimulatory effects to the central nervous system and were not initially recognized

by the doctors as alterations to patients' mood. In an effort to determine exactly how these hydrazines worked biologically, in 1952 a team at Northwestern Medical School in Chicago discovered that iproniazid was more effective than isoniazid at inhibiting monoamine oxidase (MAO), the enzyme responsible for enzymatic degradation of the monoamine neurotransmitters dopamine, norepinephrine, and serotonin. As a result of inhibiting this enzyme, iproniazid increases the amount of the monoamine neurotransmitters in the synaptic cleft and thus increases the activation of their post-synaptic receptors. In 1957, researchers at the National Institute of Health (NIH) led by Sydney Udenfriend observed that administration of iproniazid, but not isoniazid, in animals resulted in rapid elevation in brain levels of the monoamine neurotransmitter serotonin, an important discovery in iproniazid's effect on the central nervous system. These findings led to iproniazid being the favored choice in trials for anti-tubercular properties.

However, iproniazid was eventually abandoned as a treatment option for tuberculosis due to a poor safety profile, except in extreme cases, though some researchers concluded that the stimulatory side effects of iproniazid could be a primary effect if used as treatment for certain psychiatric disorders. Researchers and practitioners in the United States began to use and report the mood altering effects of the hydrazine compounds isoniazid and iproniazid. In 1952, Jean Delay reported that two out of four patients (50%) treated with isoniazid showed depressive symptom improvements (Delay, Lainé, & Buisson, 1952). In 1953 a two to three week trial with iproniazid in 11 psychiatric patients suffering from various disorders reported that two of the 11 (18%) "appeared improved" in opinion of themselves, interest in general activity in the ward, and general appearance (Smith, 1953). And also in 1953, Salzer and Lurie used isoniazid to treat

a group of 40 depressed patients and reported that approximately 70% showed improvement in mood (Salzer and Laurie, 1953). In the publication of findings from this last study, the psychiatrist Max Lurie, a private practice psychiatrist in Cincinnati, along with Harry Salzer first used the term "antidepressant" to describe the mood enhancing effects of the hydrazine isoniazid in depressed patients.

Together, the discovery of the hydrazine's effect on mood and their biological mechanism of action (inhibition of monoamine oxidase resulting in increased synaptic activity of the three monoamines) was an important step in developing a biological explanation for depression. The second piece of evidence in the development of the monoamine model of depression came from reserpine's ability to induce depressive states. Reserpine is the primary active compound from the Indian snakeroot plant (*rauwolfia serpentine*) and is capable of blocking the storage of monoamines into vesicles in the pre-synaptic terminal. By blocking the vesicular monoaminergic transporter (VMAT), reserpine reduces the amount of monoamine neurotransmitters stored in presynaptic vesicles. While normal exocytosis processes remain uninterrupted, the vesicle is empty and releases very little, if any, monoamines into the synapse, thus reducing activity at their post-synaptic receptors. The behavioral and physiological effects of reserpine had long been known to the people of India. It was commonly used to treat snake bites, provide a calming effect to infants and mental patients, and was later determined to lower blood pressure and was marketed as an antihypertensive drug in India in the 1930's. Reports from India on the use of *Rauwolfia* and/or its primary compound reserpine in calming patients with mental disorders prompted its trial in treating schizophrenic patients at Rockland State Hospital in New York in 1954. While it failed to provide psychotic symptom relief, it was noted

to produce behavioral sedation as measured by a reduction in both assaults and the need for patient restraint (Kline, N., 1954). However, reserpine still proved useful in treating hypertension and a number of early trials in patients suffering from psychiatric illnesses and/or hypertension reported reserpine's depressionogenic effects (Fries E., 1954; Harris T., 1957).

Together, the two discoveries 1) that early anti-tubercular drugs improved mood and elevated synaptic monoamine levels and 2) that reserpine reduces synaptic monoamine levels and is depressionogenic, led to the development of the Monoamine Theory of Depression.

Today there are a number of different classes of drugs that increase synaptic monoaminergic activity through various mechanisms. As described above, early antidepressants attempted to increase synaptic monoamine levels by inhibiting their enzymatic degradation via monoamine oxidase (i.e. monoamine oxidase inhibitors or MAOI's), thus prolonging monoamine availability in the synapse and increase activity on their post-synaptic receptors. However, MAOI's proved to have potentially deadly dietary interactions and have fallen out of use. More recent drugs utilized to treat MDD comprise three separate classes of drugs, each with its own mechanism of action of increasing synaptic levels of serotonin and/or norepinephrine and include 1) tricyclic inhibitors (TCA's) of both NE and 5-HT reuptake transporters, such as imipramine, 2) selective serotonin reuptake inhibitors (SSRI's), such as fluoxetine, and 3) newer selective NE reuptake inhibitors (SNRI's), such as maprotiline. However, the Monoamine Theory of MDD and the drugs designed to treat depression based on that theory are not without their issues.

Firstly, the monoamine theory of depression was "accidentally" discovered. The mood enhancing effects of the hydrazine antidepressants were initially mistaken for simple stimulatory

effects on the nervous system. Through some sharp clinical observation, some researchers proposed that these side effects could be considered primary effects in a different population of patients. However, the early clinical trials with hydrazines reported only modest "antidepressant" effects in patients with response rates varying between 18 to 70% (cited above). These findings were a major underpinning of the monoamine theory, however, they are not without their criticisms. In evaluating these studies, we should consider the criteria the researchers were using for their diagnosis of depression. The major diagnostic tool during the time these studies took place was the DSM-I, published in 1951 and prior to its publishing, there were a number of different references offering differing diagnostic criteria for depression. In the DSM-I, affective disorders such as depression were grouped under the larger category of "*Psychoneurotic Reactions*," with the cause of such disorders attributed to two factors: 1) "psychogenic" factors such as those proposed under the Freudian theories of unresolved unconscious conflicts, and 2) some undefinable and intangible structural change (i.e. unknown biological alterations). The DSM-I does not actually list any direct symptoms of depression, or *Depressive Reactions*, but instead gives a general description of overall depressive behavior attributing it to recent losses in the patient's life and/or some sense of guilt being experienced by the patient. The limited description of depressive symptoms given in the first edition of the DSM brings into question the validity of diagnoses made in early patients, and thus early clinical trials. It also brings into question the validity of how "antidepressant" effects were measured in patients in these early trials. For example, the clinical study performed by Smith in 1953 proposed that improvements or increases in self-opinion, curiosity of hospital activities, and personal hygiene as evidence for iproniazid's antidepressant effects. While changes in these behaviors were

certainly an improvement for patients, are they truly representative of a positive change in mood?

Another issue with these findings lies in the research methodology employed in these early clinical studies. None of them report using any kind of control group for comparison, nor report any blind procedures but instead measure improvement via researcher observations. Lack of control in these studies suggest the possibility of a placebo effect in patients not blinded to experimental design and the possibility of researcher bias in the interpretation of behavioral changes/improvement in non-blinded observers, both of which are a huge concern in antidepressant trials. In an analysis of clinical trials with monoaminergic antidepressants in the years between 1985 and 1997, Khan and Brown found that investigator and rater bias influenced the magnitude of symptom reduction in these studies, reporting the following on the difference between monoaminergic antidepressants and placebo:

"*Specifically, it became evident that the magnitude of symptom reduction was about 40% with antidepressants and about 30% with placebo."* (Khan and Brown, 2015).

Additionally, the authors found that evaluators of depression symptoms graded a higher magnitude of effect for antidepressants in non-blind trials compared to antidepressant effects in blinded trials. While the analysis by Khan and Brown did not directly analyze the early clinical trials with hydrazines, the lack of proper controls in those early trials suggest their results may have also been influenced by observer/researcher biases and/or the placebo effect. These factors cast doubt on one of the pillars that served as the basis of the monoamine theory.

The other pillar in the development of the monoamine theory of MDD was the depressionogenic effects of reserpine. As detailed above, reserpine's mechanism results in a

depressed mood state by reducing synaptic monoamine levels. However, the early studies demonstrating reserpine's effect on mood were also flawed. The trials conducted by Freis in 1952 and Harris in 1957 included patients suffering from chronic illnesses and/or hypertension. Depression rates among the chronically ill are very high (approximately 50% according to Bant, 1978). Depression thought to be caused by reserpine in chronically ill patients could be misattributed to the drug instead of being attributed no normal rates of depression within that specific population. Furthermore, the depression rates for hypertension patients that were taking reserpine was reported at approximately 10% (Baumeister et al., 2003). If you recall from the introduction in this paper, a 2003 study by Kessler et al. found that approximately 6.6% of the general population suffered from a depressive episode within the prior 12 months leading up to the study. Comparison of these statistics imply only a marginal increase in depression rates among hypertension patients taking reserpine. Combined, these issues suggest that reserpine may not actually be depressionogenic.

Finally, current antidepressants developed based on the monoamine theory have some serious limitations. These drugs, as a whole, possess numerous undesirable side effects including dizziness, constipation, hypertension and other cardiac issues, and sexual dysfunctions. While it has been demonstrated that monoaminergic antidepressants are capable of elevating synaptic monoamine levels within hours after administration, four to six weeks of daily drug administration is needed to produce adequate MDD symptom relief (Paul & Skolnick, 2003; Trivedi, Rush, Wisniewski, 2006). Moreover, not all MDD patients show depressive symptom alleviation following monoaminergic antidepressant use. It is reported that between 40 to 60% of MDD patients fail to see depressive symptom relief following adequate regimens of typical

antidepressants (Paul, Skolnick, 2003; Trivedi, Rush, Wisniewski, 2006) resulting in roughly half of all MDD patients undergoing treatment with typical antidepressants being diagnosed with TRD.

The moderate response rate and lag time of therapeutic effects from drugs targeting monoaminergic systems suggests that increased synaptic monoaminergic levels are not sufficient for depressive symptom relief and brings into question the validity of the monoamine theory of depression. If these drugs elevate synaptic monoamine levels within hours, why does it take weeks before depressive symptom relief appears? And if the Monoamine Theory of depression is a valid explanatory model, why do only half of people who take current antidepressants show symptom relief/remission? These treatment shortcomings suggest that the true therapeutic mechanism of current antidepressants may be some other downstream process or processes that are eventually achieved as a result of the increases in monoamine activity produced by antidepressants, and not their direct and immediate influence on monoaminergic neurotransmitter levels. In a review of the mechanisms of antidepressants and their effects, while commenting on the mechanism of tricyclic antidepressants, Andrade and Rao explained it in these terms:

"A fundamental problem with the synaptic explanations described above is that, while they are immediate, the antidepressant response is delayed. For example, the TCA's inhibit the reuptake of monoamines as soon as they are absorbed into the body and transported across the blood-brain-barrier, i.e. within hours of administration. However, the antidepressant response takes weeks or longer to develop and complete and, hence, for response and remission to occur. Therefore to say that the TCA's act by increasing the presence of neurotransmitters in the synapse is about as complete as saying that cars run because of an increased presence of fuel in

the tank. Clearly, just as mechanisms downstream to the presence of fuel in the tank enable a car to move, so too must there be something downstream to increase the synaptic availability of monoamines to fully explain antidepressant mechanisms." (Andrade and Kumar Rao, 2010).

2.2: Secondary Effects of Monoaminergic Antidepressants

Numerous preclinical studies report that many of the conventional monoaminergic antidepressants have a number of secondary biological effects. For example, typical antidepressants increase neurotrophic growth factors, such as brain-derived neurotropic factor (BDNF) (reviewed in Altar, 1999). These growth factors are responsible for neuronal survival, synaptogenesis, and neurogenesis. Chronic administration of representative compounds from monoaminergic antidepressant classes have been shown to increase the required genetic precursor, messenger ribonucleic acid (mRNA), which codes for BDNF production (Nibuya, Morinobu, Duman, 1995; Fujimaki et al., 2000 de Foubert, et al., 2004; Reagan, et al., 2007). Additionally, in the study cited above by Reagan and colleagues, the researchers measured increases in BDNF protein levels themselves in several major brain regions implicated in the pathology of MDD following chronic administration of monoaminergic antidepressants. Interestingly, de Foubert and colleagues reported that chronic administration (21 days) but not acute administration of the SSRI fluoxetine (Prozac) was required to produce an increase in BDNF mRNA levels, a time course similar to the requirements for the antidepressant effects of fluoxetine and other monoaminergic-based drugs seen in MDD sufferers (4 – 6 weeks). Furthermore, pre-clinical trials utilizing rodent models of depression have shown that direct administration of BDNF can alleviate depression-like behavior in these models within minutes following administration (Siuciak, et al., 1997).

In addition to conventional antidepressants effect on BDNF, monoaminergic antidepressants have also been shown to modulate the expression of specific glutamate receptors.

Two studies by Barbon and colleagues examine the effects of conventional antidepressants on glutamatergic 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propionic acid (AMPA) receptor expression. In 2006, Barbon and colleagues found that after 14 days of treatment with either the SSRI fluoxetine or the SNRI reboxetine, rat hippocampal and prefrontal cortex (PFC) samples showed increases in AMPA receptor mRNA (Barbon et al., 2006). In a 2011 follow-up time course study, Barbon and colleagues examined the effect of chronic administration of classic antidepressants on the number of expressed AMPA receptors. However, in this study rodent hippocampal and PFC samples were collected at multiple time points over a two week period from animals treated with either fluoxetine or reboxetine and were analyzed for AMPA receptor mRNA. The researchers found non-significant increases in AMPA receptor mRNA was achieved after one week of treatment and significant, and maximal, AMPA receptor mRNA upregulation was achieved after 14 days of treatment (Barbon et al., 2011). This finding is incredibly important as the time-course for depressive symptom relief under chronic (daily) administration of typical antidepressants is four to six weeks. The studies by Barbon et al., demonstrate that chronic administration of typical antidepressants increases the number of receptors of a completely different neurotransmitter system, the glutamate system, and implicate the glutamate system as a possible mediator of their antidepressant effects.

2.3: The Role of Glutamate in MDD

Glutamate is the major excitatory neurotransmitter in the nervous system and it plays a major role in learning and memory, neurogenesis, synaptogenesis, and neuronal survival (Matteson, 2008). Glutamatergic neurons are located throughout the brain with high concentrations found in the cerebral cortex, amygdala, hippocampus, and cerebellum, among others, which project to numerous subcortical structures such as the striatum, thalamus, some limbic system structures, and areas in the brainstem. There are two distinct classes of glutamate receptors, ionotropic and metabotropic, and each class has multiple receptor subtypes. The ionotropic family consists of kainate, *N*-methyl *D*-aspartate (NMDA), and 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid (AMPA) receptors. There are 8 metabotropic glutamate receptors (mGluRs; labeled 1 through 8) that are sub-divided into 3 individual families based on functionality and location.

There is a growing body of evidence implicating that the glutamatergic system plays a role in the neurobiology of MDD. Several studies have reported increased glutamate levels in blood and cerebrospinal fluid (CSF) of patients suffering from MDD (Kim, 1982; Altamura et al., 1993; Mauri, 1998; Mitani et al., 2006). Mitani and colleagues also reported a positive correlation between plasma glutamate levels and the severity of symptoms in patients with MDD (Mitani et al., 2006). Furthermore, increased levels of glutamate have been reported in the frontal cortex of postmortem brain samples from MDD patients (Hashimoto, Sawa, Iyo, 2007b), and an in vivo study using magnetic resonance spectroscopy (MRS) revealed elevated levels of glutamate in the occipital cortex of MDD patients (Sancora et al., 2004a). However, numerous

studies using MRS have reported contrasting findings of decreased levels of glutamate and its precursor glutamine in the anterior cingulate cortex, prefrontal cortex, and hippocampus of MDD patients (Auer et al., 2000; Ajilore et al., 2007; Hasler et al., 2007; Block et al., 2009). Postmortem studies of brain samples from MDD patients show decreased levels of glutamate NMDA receptor subtypes, AMPA receptor subtypes, and one metabotropic glutamate receptor (mGluR5) in various brain regions such as the superior temporal cortex, perirhinal cortex, hippocampus, and prefrontal cortex (Nudmam-Thanoi, 2004; Beneyto et al., 2007; Law, Deakin, 2001; Feyissa et al., 2009). When combined, these findings suggest that alterations in glutamate levels play a role in the pathophysiology of MDD.

2.4: Glutamate and Neurogenic Processes

In 1966, Terje Lomo discovered that repeated high frequency stimulation of glutamatergic neurons via microelectrodes in the hippocampal perforant path lead to prolonged excitation of cells in the dentate gyrus (Lomo, 1966). Follow-up experiments demonstrated that stimulation of the perforant path led to a state of increased excitability of cells in the dentate gyrus lasting for up to 10 hours post stimulation (Bliss and Lomo, 1973). This long lasting excitability was termed long-term potentiation, or LTP. Further investigations demonstrated that LTP consists of two stages: an early and a late stage, and that NMDA receptor activation is required for the development of both types of LTP (Collingridge et al., 1983; Harris et al., 1984). Early LTP encompasses local changes occurring within a pre-existing synapse while late LTP involves the stimulation of intracellular pathways that promote the growth of new synapses (synaptogenesis) and completely new neurons (neurogenesis). Electrical stimulation of neurons in the perforant path causes them to release glutamate into their synaptic connections with cells in the dentate gyrus. Synaptic glutamate acts upon both AMPA and NMDA receptors on the post-synaptic cell and co-activation of these receptors results in an excitatory post-synaptic potential (EPSP) which triggers the production and expression of even more AMPA receptors. In 1999, Shi and colleagues demonstrated that this increase in the number of AMPA receptors expressed into the synaptic space strengthens the synaptic connection between the pre-synaptic and post-synaptic cells. More importantly, Shi and colleagues demonstrated that NMDA receptor activation is a pre-requirement for increased AMPA receptor activation in that administration of the NMDA receptor antagonist (D,L)-2-amino-5-phosphono valeric acid (AP-5) prior to

neuronal stimulation prevented the increased expression of AMPA receptors (Shi et al., 1999). This strengthening of the local synapse through AMPA receptor up-regulation via NMDA receptor activation is the mechanistic process of early LTP. While early LTP is confined to the local production of new AMPA receptors, late LTP involves activation of internal protein pathways which stimulate the synthesis of new proteins called growth factors, such as BDNF. Once released into the synapse, these growth factors trigger the production of new dendritic spines on post-synaptic cells and new axon terminals on pre-synaptic cells (Nägerl et al., 2007). Frey and colleagues demonstrated that administration of drugs that prevent the synthesis of these growth factors prevent the induction of late LTP (Frey et al., 1988).

In his Croonian Lecture, Santiago Ramon y Cajal suggested that memories may be formed by the strengthening of communication between already connected neurons (Cajal, 1894). If the processes of glutamatergic NMDA receptor activation and additional AMPA receptor expression seen in LTP are the underlying biological mechanisms of learning and memory, then it would follow that antagonism of one of these receptors should impair and/or prevent these processes. As NMDA receptor activation is the initial step in LTP, then it makes the most logical target to test this theory. In 1986, Morris and colleagues administered the NMDA antagonist AP-5 to rodents exposed to spatial memory task (the Morris Water Maze, Morris, 1984) and found that the pharmacological blockade of NMDA receptors impaired performance, as measured by increased time of performance, compared to control animals (Morris et al., 1986). Since the study published by Morris, there have been numerous subsequent studies demonstrating that NMDA receptor blockade impairs learning in a variety of memory tasks (Danysz et al., 1988; Butelman E., 1989). Furthermore, mice with increased NMDA

receptor expression via genetic manipulation have demonstrated increased capacity for learning and memory (Tang et al., 1999) highlighting this receptor's role in these processes.

2.5: Research into Glutamate, Neurogenesis, and Depression

Early animal models of depression centered on producing a depressive phenotype utilizing rodents. That is, producing a behavioral pattern analogous to depressive symptoms seen in humans. Paradigms such as the forced-swim test (FST) (Porsolt, 1977), the tail-suspension test (TST) (Steru et al., 1985), and inescapable shock paradigm (Seligman & Beagley, 1975) became the standard pre-clinical depression models used to evaluate novel antidepressants. The common manipulation in these models involves exposing the animal to an inescapable stressor resulting in a reduction in behavioral activity, which is referred to as a state of learned helplessness or behavioral despair. In these preclinical rodent models, compounds that are able to reduce immobility (i.e. attenuate behavioral despair) are deemed to have antidepressant effects.

As early depression models attempted to create a state of learned helplessness and given the role of glutamatergic NMDA receptors in learning, it would follow that antagonism of this receptor may prevent the onset of learned helplessness. Following this hypothesis, Trullas and Skolnick evaluated two NMDA receptor antagonists, AP-7 (2-amino-7-phosphonoheptanoic acid) and MK-801 (Dizocilpine) in the FST. Both compounds were found to attenuate the depressive phenotypes (i.e. reduce immobility) in this model equal to the effects of the tricyclic antidepressant imipramine (Trullas and Skolnick, 1990). Since this initial investigation there have been numerous studies replicating these results and evaluating the efficacy of other NMDA antagonists in preclinical rodent models of depression. Two subsequent studies investigating MK-801 demonstrated antidepressant effects in in a chronic mild stress (CMS) paradigm (Papp

and Moryl, 1994) and again in the FST (Maj et al., 1992). However, MK-801's antidepressant effects have not been evaluated in clinical trials due to its numerous undesirable side effects such as cognitive disruptions, psychotic-spectrum disorders, and the induction of brain lesions, referred to as Olney's lesions. Another NMDA antagonist, memantine, has also demonstrated antidepressant effects in rodent models of depression (Reus et al., 2010, Quan et al., 2011). However, other research has produced opposing findings with memantine in that it failed to produce antidepressant effects in the rodent FST and the newer novelty-suppressed feeding paradigm (Gideons et al., 2014). In line with these latter findings, clinical trials with memantine failed to demonstrate any antidepressant effects in both unipolar (Zarate et al., 2006b) and bipolar depressive patients (Anand et al., 2012).

More recent research has identified another NMDA antagonist, ketamine, as a potential novel and fast acting antidepressant. Ketamine is a synthetic compound, high doses of which have long been known to produce dissociative effects and anesthesia. As such, ketamine has been used as a general pre-surgery anesthetic (Domino, E., Chodoff, P., Corssen, G., 1965, Corssen, G., Miyasaka, M., Domino E., 1968). Pre-clinical animal models of depression have demonstrated ketamine's antidepressant effects (Sufka et al, 2009; Chaturvedi, Chandra, Bapna, 1999; Yilmaz et al., 2002). In addition to its success in animal models, ketamine has also demonstrated antidepressant effects in clinical trials with MDD sufferers (Berman et al., 2000). Furthermore, in a 2006 study in TRD patients, a single sub-anesthetic dose of ketamine demonstrated antidepressant effects as early as 2 hours after administration. The same study found that after 24 hours, 71% of the patients reported depressive symptom improvement, and these antidepressant effects of this one time administration were sustained for more than a week

(Zarate, 2006a). This finding of ketamine's antidepressant effects in TRD sufferers specifically has been replicated in another, more recent, clinical trial (Price et al., 2009). However, despite these promising findings, ketamine is structurally similar to phencyclidine (PCP) and produces a similar dissociative state, hallucinations, and euphoria, and possess abuse/addictive potential (Siegel, 1978), making it an unlikely candidate for long-term use in the clinical treatment of depressive disorders. Additionally, given the NMDA receptor's role in learning and memory, an investigation into the cognitive effects of ketamine administration in TRD patients found that after an intravenous infusion of 0.5 mg/kg dose of ketamine, patients showed cognitive impairments as measured by scores on a battery of cognitive tests including intelligence quotient (IQ) tests and the MATRICS Consensus Cognitive Battery test (Murrough et al., 2013). Yet, the preclinical and clinical findings with ketamine are promising and prompted research on other glutamatergic targets.

The two glutamatergic receptors NMDA and AMPA are co-localized on the post-synaptic dendritic spine and, as such, co-activate upon the release and binding of the neurotransmitter glutamate. Therefore, probing the nearby AMPA receptor for antidepressant effects was the first and most obvious glutamatergic candidate. A study in 2001 by Li and colleagues measured the antidepressant effects of the AMPA receptor potentiator LY392098 in the rodent FST and TST. Acting similarly to a true agonist, a receptor potentiator increases activity at receptor; however, a potentiator requires the presence and activation of the receptor by the parent neurotransmitter, in this case glutamate. When both the neurotransmitter and a receptor potentiator act at a receptor simultaneously, the potentiator increases the activity at the receptor by keeping the ion channel open longer, allowing for greater excitement of the post-

synaptic neuron. Li and colleagues found that LY392098 attenuated behavioral despair (i.e. possess antidepressant effects) in both models. Furthermore, pre-treatment with an AMPA receptor antagonist, LY300168, blocked the antidepressant effects of LY392098 (Li et al., 2001). In 2008, Maeng and colleagues investigated the relationship between NMDA and AMPA receptors and demonstrated that AMPA receptor activation is required for ketamine's antidepressant effect. In this study, the researchers first administered the AMPA receptor antagonist NBQX prior to the administration of ketamine to rodents prior to exposure to the FST and found that pre-treatment with NBQX prevented ketamine's antidepressant effects (Maeng et al., 2008). These findings suggest that activation of the glutamatergic AMPA receptor is the true mechanism that provides antidepressant effects.

Research from Li and colleagues proposes the exact pathway and methodology of how AMPA receptor activation leads to an antidepressant response. Since it is well accepted that AMPA receptor activation leads to the promotion of growth factors seen in LTP processes, the study examined one of the intracellular protein kinases responsible for the cytoskeletal reorganization and branching required in neurogenic processes, the mammalian target of rapamycin (mTOR). The researchers hypothesized that since ketamine exerts its antidepressant effects through AMPA receptor activation leading to LTP processes of synaptogenesis and neurogenesis, that a pharmacological inhibition or blockade of the mTOR protein might prevent ketamine's antidepressant effects. In a drug challenge study, Li and colleagues inhibited the mTOR pathway with the protein antagonist rapamycin prior to the administration of ketamine in animals tested in the FST. The pre-treatment with rapamycin prevented ketamine from demonstrating antidepressant effects in the model (Li et al., 2010). While inhibition of the

mTOR pathway via rapamycin does provide us with an understanding of how ketamine might indirectly provide its antidepressant effects, it does not answer the question of how ketamine, an NMDA receptor antagonist, would potentiate or activate the nearby AMPA receptor.

More recent research performed in collaboration from various institutes including the National Institute of Mental Health (NIMH) has provided a possible answer to this question. There are numerous metabolites produced from the enzymatic breakdown of ketamine, and prior research has demonstrated that only ketamine and its metabolite (R,S) norketamine produce anesthesia, although (R,S) norketamine is less potent. Other ketamine metabolites fail to produce any level of anesthesia, and as such, were thought to be biologically inactive. In an extensive 2016 study, Zanos and colleagues examined the mechanisms behind ketamine's antidepressant effects, and included all of ketamine's metabolites. First, they evaluated the antidepressant effects of the NMDA antagonist ketamine compared to the tricyclic antidepressant desimipramine at time points of 1-hour post drug administration and again at 24 hours post drug administration. The researchers found that both desimipramine and ketamine demonstrated antidepressant effects at the 1 hour mark, but only ketamine exhibited antidepressant effects at the 24 hour mark. These findings are consistent with other preclinical findings and with the clinical effects of ketamine's anti-depressant effects. Furthermore, the researchers demonstrated that the NMDA antagonist MK-801 produced antidepressant effects at the 1 hour mark, but failed to produce antidepressant effects at the 24 hour mark in the FST. These findings led the researchers to hypothesize that NMDA receptor antagonism may not be the mechanism behind ketamine's antidepressant effects. The researchers then evaluated the antidepressant effects of a number of ketamine's metabolites. Through evaluation in the FST, the researchers showed that

similar to ketamine, a single administration of one ketamine metabolite, (2*R*,6*R*)-hydronorketamine (HNK), induced persistent antidepressant effects lasting for at least 3 days of testing in the FST. However, unlike ketamine, HNK did not displace MK-801 at the NMDA receptor, suggesting that its mechanism of behavioral effects lies elsewhere. The researchers then showed that HNK facilitates AMPA receptor activity via an increase in frequency and amplitude of AMPA receptor excitatory potentials. Next the researchers sought to determine if AMPA receptor activation is required in HNK's antidepressant effects by performing a challenge study wherein animals were pretreated with the AMPA antagonist NBQX prior to either ketamine or HNK administration then evaluated in the FST. In line with research mentioned earlier, pretreatment with NBQX prevented ketamine's antidepressant effects. Furthermore, pre-treatment with NBQX also prevented HNK's antidepressant effects seen at both the 1 hour and 24 hour mark. As it has been implied that ketamine's antidepressant effects are mediated through both the activation of the mTOR protein and increased BDNF production, the researchers sought to determine if HNK also increases activity or levels of these separate proteins. Interestingly, the study showed that neither ketamine nor HNK produced increased activity in the mTOR protein in hippocampal and prefrontal cortex tissue samples. However, both ketamine and HNK increased hippocampal BDNF production. The researchers then demonstrated that both ketamine and HNK produce increases in AMPA receptor expression 24 hours after administration. Moreover, HNK's antidepressant effects remained long after the time point where HNK was undetectable in select brain tissue samples, suggesting its antidepressant effects are the result of long-lasting synaptic changes as seen in LTP (Zanos et al., 2016).

2.6 Converging Lines of Evidence

A quick summary of the numerous lines of research discussed so far is necessary. Firstly, separate research has demonstrated that traditional monoaminergic antidepressants induce the production of the growth factor BDNF and that chronic administration of these compounds also increases the expression of glutamatergic AMPA receptors and do so in a time-course that resembles their antidepressant effects. Secondly, direct administration of BDNF has demonstrated antidepressant effects in pre-clinical models of depression. Thirdly, numerous clinical studies have detected glutamatergic alterations in MDD patients implying a role for glutamate in the etiopathology of MDD. Finally, pharmacological potentiation of the glutamatergic AMPA receptor has demonstrated antidepressant effects in pre-clinical models of depression and pharmacological antagonism of the glutamatergic NMDA receptor via ketamine has demonstrated antidepressant effects in both pre-clinical models and in a number of clinical trials for both MDD, TRD, and bi-polar patients. Furthermore, pre-clinical studies have demonstrated that AMPA receptor activation is required for ketamine's antidepressant effects.

Combining these lines of research, a conclusion can be drawn that explains exactly how monoaminergic antidepressants and ketamine produce their therapeutic effects. Chronic administration of traditional antidepressants that target the monoaminergic system result in increased expression of more AMPA receptors far downstream in the glutamatergic system, and by doing so, allow for greater glutamate-AMPA receptor activity which stimulates the underlying processes seen in LTP, such as production of and release of growth factors, namely

BDNF. A number of studies have indicated that decreased levels of BDNF are associated with MDD and that BDNF levels increase following antidepressant pharmacotherapy. (Duman and Monteggia, 2006; Martinowich et al., 2007). Synaptic BDNF acts on both pre- and post-synaptic tyrosine receptor kinase B (Trk-B) receptors and stimulate the mTOR protein pathway responsible for cytoskeletal growth of new dendritic branches and axon terminals (synaptogenesis), eventually leading to the growth of new neurons (neurogenesis). The resulting increase in neuronal plasticity offsets the losses caused by stress-induced release of hormones. However, more evidence is needed before concluding that these neuroplastic changes are the underlying mechanisms behind the antidepressant effects seen across multiple pharmacotherapies.

As mentioned in the earlier sections of this paper, prior to the discovery of the hydrazines, outside of psychotherapy, the primary treatment method for depression was electro-convulsive shock therapy. While its biological effects were not understood at the time, advances in science have allowed for closer examinations. Numerous studies have examined the relationship and effect of ECT and biological alterations, specifically, changes to BDNF production. In a systematic review and meta-analysis of both pre-clinical and clinical studies investigating the effect of ECT on BDNF, Polyakova and colleagues found that animal and human studies report similar findings in regard to effects of ECT on BDNF; that is, that ECT increases brain BDNF in both preclinical and clinical studies. Moreover, multiple treatments with ECT, compared to a single ECT treatment, were associated with larger increases in BDNF in both animals and humans. These findings suggest that a dose-response relationship exists

between the schedule of ECT and BDNF increases (Polyakova M., et al., 2015) and that neuroplastic process are responsible for the antidepressant effects of ECT.

Though ECT may be an effective treatment option, it is generally a method of last resort in depressed patients who have failed to respond to both pharmacotherapies and psychotherapies. There are a variety of psychotherapies that have been employed to treat MDD including (but not limited to) interpersonal therapy (IPT) and cognitive-behavioral therapy (CBT). Recent studies have investigated the effects of such psychotherapies on the activity, volumetric size, and rate of metabolism in key brain structures associated with MDD. Neuroimaging of MDD patients reveals a decrease in activity and metabolism of cells within the dorsolateral prefrontal cortex (DLPFC), which is correlated with depressive symptom severity (Brody et al., 2001). The DLPFC is involved in executive functions such as working memory, cognitive flexibility, planning, reasoning, and behavioral inhibition. On a note of interest, the main neurotransmitters involved in DLPFC functioning are glutamate, dopamine, norepinephrine, and acetylcholine, with very little serotonin activity. This may explain why some MDD patients fail to show symptom relief with typical antidepressants designed to increase serotonin activity. A review by Frewen and colleagues in 2008 found within therapy responders that both IPT and CBT restored normal functioning of the DLPFC as measured by both rates of activity and metabolism (Frewen et al., 2008). Frewen and colleagues also reported that the increased activity in DLPFC remained long after the conclusion of therapy, findings resembling the effects of electrical stimulation and the discovery of LTP process in the hippocampus by Bliss and Lomo mentioned earlier. Furthermore, cognitive therapy has been demonstrated to increase the volume of grey matter in the DLPFC (Seminowicz et al., 2013). Similarly, a study by Straub and colleagues found

increases in hippocampal activity in MDD patients following CBT (Straub et al., 2015), and a 2013 study by Moustafa reported increases in volumetric size of the hippocampus following 12 weeks of CBT (Moustafa, 2013). Together, these findings suggest that the various forms of psychotherapy increase activity and volume of key brain structures involved in MDD, although BDNF levels have not been directly measured, the increases in these measures implies the role neuroplastic processes play in the benefits of psychotherapy.

Individuals suffering from MDD have provided anecdotal evidence suggesting that physical exercise can alleviate depressive symptoms. And indeed, in a meta-analysis of numerous scientific studies investigating such a relationship, Craft and Perna reported that response rates in antidepressant-naïve MDD patients who engaged in moderate to high physical exercise is slightly higher (approximately 70%-80%) on overage than patients taking antidepressant pharmacotherapies alone (Craft and Perna, 2004). Subsequent studies have demonstrated that exercise leads to an increase in BDNF production, particularly in the hippocampus (Cotman et al., 2007), and this increase promotes improvement in cognitive functioning and MDD symptoms (Marais et al., 2009; Russo-Neustadt et al., 2000). Again, these findings in the effects of exercise suggest that neuroplastic changes underlie the benefits of exercise in treating depression.

3.0: CONCLUSION: THE STRESS-NEUROGENIC THEORY OF DEPRESSION

The purpose of this paper was to examine the discovery of the monoamine theory of depression, evaluate its validity, and compare alternative treatment modalities in hopes of identifying common biological effects. While the monoamine theory remains the dominant explanatory model of MDD, the issues with its discovery and the shortcomings of monoaminergic antidepressants listed above bring into question its validity. The measureable downstream effects of conventional antidepressants on increased BDNF and up-regulation of AMPA receptors suggest the true mechanism of monoaminergic antidepressants may not be the direct elevation of synaptic monoamine levels. In short, I suggest that the Monoamine Theory of MDD is incomplete.

There is mounting evidence for an alternative explanatory model for the etiopathology of MDD, the Stress-Neurogenic Theory. This theory posits that unpredictable stress induces the production of stress hormones that lead to neuronal death in key brain structures, such as the hippocampus and amygdala, and this cell loss is responsible for the onset of MDD symptomology. Psychological stress activates the release of a stress hormone from the hypothalamus called corticotrophin-releasing hormone (CRH), which stimulates the pituitary gland to release corticotrophin that then stimulates the adrenal gland to release cortisol. Evidence of CRH's role in the pathology of MDD can be found in elevated levels of CRH in the

cerebrospinal fluid of MDD patients (Nemeroff, Widerlov, Bissette, 1984) as well as post-mortem studies that have found increased numbers of CRH releasing neurons in the limbic system structures in MDD patients (Raadsheer, Hoogendijk, Stam, 1994). Excessive levels of cortisol can cause decreased neurogenesis, neurotoxicity, and neuronal cell death. It is believed that repeated exposure to psychosocial stressors leads to over stimulation of the HPA-axis resulting in increased levels of glucocorticoids. This increase in stress hormones is responsible for the decrease in brain structure volume seen in the post-mortem studies of MDD patients. Furthermore, the Stress-Neurogenic theory suggests that MDD can be treated by stimulating synaptogenesis and neurogenesis in these structures, thus offsetting the neuronal loss due to repeated over-exposure to stress hormones.

Evidence in support of this theory can be seen in all of the various treatment forms that have efficacy in treating MDD. Typical monoaminergic antidepressants, ketamine and other glutamatergic agents, ECT, various forms of psychotherapy, and even exercise have all demonstrated the ability to increase either neurotrophic growth factors, such as BDNF, or structural volume in key brain regions affected by excess stress hormones. By identifying this commonality among the various treatment modalities, it is this author's hope that by targeting the brain's natural neurogenic pathways, newer and faster acting antidepressants can be identified for use in treating this debilitating disorder.

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VITAE

Stephen Walter White, PhD

ADDRESS:

Department of Psychology
University of Mississippi
University, MS 38677
email: swwhite1@olemiss.edu
Phone: 662-801-7974 (cell)

EDUCATION:

B.A., University of Mississippi, University, MS, 2007, Psychology
M.S., University of Mississippi, University, MS, 2014, Psychology
Ph.D., University of Mississippi, University, MS, 2018 Psychology/Behavioral Neuroscience

PROFESSIONAL AFFILIATIONS:

Society for Neuroscience

RESEARCH INTERESTS:

Development, validation and utilization of animal model simulations (stress, anxiety & depression; pain & analgesia)
Development of animal models with greater translational relevance
Drug efficacy screening (anxiolytics, antidepressants, analgesics)
Dysbiosis: behavioral effect and drug efficacy

COURSES OFFERED:

Psychology 201: General Psychology (11 sections)
Psychology 319: Brain and Behavior (3 sections)
Psychology 322: Drugs and Behavior (5 sections)

Future Courses of Interest:

- Statistics & Research Methods
- Neuroscience and Public Policy
- Neuroscience Lab Course

COMPETITIONS & PRESENTATIONS:

Three Minute Thesis (3MT) Competition: fall 2016 & fall 2017

AWARDS:

2014 Graduate Research Achievement Award, Psychology Dept., University of Mississippi.

2017 3MT: 1st place doctoral category

PATENTS:

Master's Thesis: *Identification of a stress vulnerable, treatment-resistant, ketamine-sensitive genetic line in the chick anxiety-depression model.* This work added unique contribution to the overall body of work performed by Dr. Kenneth J. Sufka on the development and validation of the chick anxiety-depression model. Based on thesis findings, the University of Mississippi filed for, and was awarded, a patent on this animal model. US # 8999293 B2

COMMITTEES:

2015-Current: University of Mississippi Conference on Psychological Science, Psychology Department, University of Mississippi.

FUNDING:

Summer 2016 & summer 2017: Summer Research Stipend, Graduate School, University of Mississippi

PUBLICATIONS:

McCurdy C, Abdelazeem A, Khan S, White S, Sufka K, (2015). Design, synthesis and biological evaluation of bivalent benzoxazolone and benzothiazolone ligands as potential anti-inflammatory/analgesic agents. Bioorganic and Medicinal Chemistry, 23, 3248-3259.

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BOOK CHAPTERS:

White SW, Sufka KJ (2012) Chick anxiety-depression screening model. In A. Szallasi (Ed.), Methods in Pharmacology and Toxicology: TRP Channels in Drug Discovery, Vol. II. Springer/Humana Press, pp. 203-210

White SW, Sufka KJ (2016). Development and validation of pre-clinical models of treatment-resistant depression**.** Models of Treatment Resistant Depression. Nova Science Publishers

CONFERENCE PAPERS AND ABSTRACTS:

Stephen W. White, Kenneth J. Sufka, John M. Rimoldi, Rama S. Gadapelli (November, 2016). Antidepressant Effects of the AMPA Receptor Potentiator LY392098 in a Model of Treatment-Resistant Depression. Society for Neuroscience, San Diego, CA.

Anchor, Sydney M., Jourdan, Mary K., White, Stephen W., and Sufka, Kenneth J., (April, 2016). Effects on Environmental Enrichment on Genetic Vulnerability to Anxiety and Depression, Neuroscience Research Day, Oxford, MS.

Stephen W. White, Kenneth J. Sufka (April 2014). Identification of a Stress-Vulnerable, Treatment-Resistant, Ketamine Sensitive Genetic Line in the Chick Anxiety-Depression Model. Graduate Student Council Graduate Research Forum. University of Mississippi, University, MS. (2013) Society for Neuroscience, San Diego, CA.

Stephen W. White, Kenneth J. Sufka (November 2014). Differences in antidepressant drug sensitivity in inbred strains in the chick anxiety-depression model. Society for Neuroscience, Washington, D.C.

Loria MJ, White SW, Robbins SA, Salmeto, AL, Hymel KA, Manda P, Murthy SN, Sufka KJ (June 2013). BDNF response in vulnerable and resilient lines in the chick anxiety-depression model. 20th Annual International "Stress and Behavior" Neuroscience and Biopsychiatry Conference, New Orleans, LA.

Salmeto AL, Hymel KA, Loria MJ, White SW, Sufka KJ (June 2013). Strain Vulnerability and Resiliency in the chick anxiety-depression model. 20th Annual International "Stress and Behavior" Neuroscience and Biopsychiatry Conference, New Orleans, LA.

Hymel KA, Salmeto, AL, White SW, Loria MJ, Sufka KJ (November 2012). The sky is falling: Strain vulnerability and resiliency in the chick anxiety-depression model. Neuroscience and Behavior Research Day, University of Mississippi Medical Center, Jackson, MS. (October 2012) Society for Neuroscience, New Orleans, LA.

Loria MJ, White SW, Robbins SA, Salmeto, AL, Hymel KA, Manda P, Murthy SN, Sufka KJ (November 2012). Strains, brains and neurotrophic gains: BDNF response in vulnerable and resilient lines in the chick anxiety-depression model. Neuroscience and Behavior Research Day, University of Mississippi Medical Center, Jackson, MS. (October 2012) Society for Neuroscience, New Orleans, LA.

CURRENT PROJECTS:

Stephen W. White, Rama S. Gadapelli, John M. Rimoldi, Kenneth J. Sufka (manuscript in preparation). Antidepressant effects of the AMPA receptor potentiator LY392098 in a model of treatment-resistant depression.

Mary K. Jourdan, Sydney Anchor, Stephen W. White, Purnendu Kumar Sharma, S. Narashima Murthy, Kenneth J. Sufka. (manuscript under review) Biochemical and Behavioral Effects of Environmental Enrichment on strain-dependent vulnerability to anxiety and depression in the chick separation stress paradigm.

FUTURE PROJECTS:

- Evaluation of metabotropic glutamate receptors for anxiolytic and antidepressant properties in the chick anxiety-depression model

- Mapping ketamine's antidepressant effects: the role of 2-amino-3-(5-methyl-3-oxo-1, 2-oxazol-4-yl) propionic acid-Brain Derived-Neurotrophic Factor-mammalian Target of Rapamycin

- Investigating the relationship between antibiotic induced dysbiosis, behavioral changes, neurotrophic factors, and drug efficacy