

2020

Breaking Away: The Role of Homeostatic Drive in Perpetuating Depression

Jonathan Tory Toole

Follow this and additional works at: https://nsuworks.nova.edu/cps_stuetd



Part of the Psychology Commons

Share Feedback About This Item

This Dissertation is brought to you by the College of Psychology at NSUWorks. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of NSUWorks. For more information, please contact nsuworks@nova.edu.

**BREAKING AWAY: THE ROLE OF HOMEOSTATIC DRIVE
IN PERPETUATING DEPRESSION**

by

Jonathan Tory Toole

A Dissertation Presented to the College of Psychology
of Nova Southeastern University
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

NOVA SOUTHEASTERN UNIVERSITY

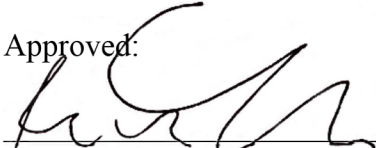
2020

DISSERTATION APPROVAL SHEET

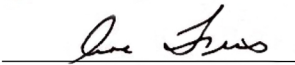
This Dissertation was submitted by Jonathan Tory Toole under the direction of the Chairperson of the Dissertation Committee listed below. It was submitted to the School of Psychology and approved in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Clinical Psychology at Nova Southeastern University.

8/21/2019
Date of Defense

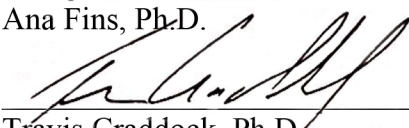
Approved:



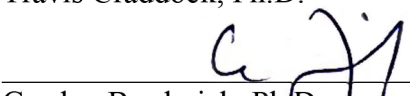
Barry Nierenberg, Ph.D., Chairperson



Ana Fins, Ph.D.

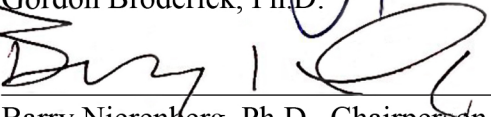


Travis Craddock, Ph.D.



Gordon Broderick, Ph.D.

6/12/2020
Date of Final Approval



Barry Nierenberg, Ph.D., Chairperson

Statement of Original Work

I declare the following:

I have read the Code of Student Conduct and Academic Responsibility as described in the *Student Handbook* of Nova Southeastern University. This dissertation represents my original work, except where I have acknowledged the ideas, words, or material of other authors.

Where another author's ideas have been presented in this dissertation, I have acknowledged the author's ideas by citing them in the required style.

Where another author's words have been presented in this dissertation, I have acknowledged the author's words by using appropriate quotation devices and citations in the required style.

I have obtained permission from the author or publisher—in accordance with the required guidelines—to include any copyrighted material (e.g., tables, figures, survey instruments, large portions of text) in this dissertation manuscript.

Jonathan Tory Toole
Name

June 12, 2020
Date

ACKNOWLEDGMENTS

This research was conducted in collaboration with the High Performance Computing group at the University of Miami Center for Computational Science (CCS) (<http://ccs.miami.edu>) using the Pegasus2 platform. This research was also enabled by the use of computing resources provided by WestGrid and Compute/Calcul Canada. Funding for this work was provided by the US Department of Defense Congressionally Directed Medical Research Program (CDMRP) awards (<http://cdmrp.army.mil/>) GW093042 (Broderick - PI), GW140142 (Broderick - PI), GW080152 (Klimas - PI), as well as GW120045 (Morris - PI). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ABSTRACT

BREAKING AWAY: THE ROLE OF HOMEOSTATIC DRIVE IN PERPETUATING DEPRESSION

by

Jonathan Tory Toole

Nova Southeastern University

2020

The brain can be considered a complicated system of feedback mechanisms that maintain physiological homeostasis. Through psychological activity, neurochemicals act as homeostatic regulators. This study proposes that these components are part of a regulatory system that is capable of supporting multiple homeostatic regimes that, in turn, give rise to self-sustaining psychological behaviors. This project hypothesizes that such alternate regulatory programs may play a role in perpetuating psychological dysfunction. Interactions within and between components of the neurotransmitter network are represented as a set of discrete logic circuits. Neurotransmitter levels are linked to psychological constructs such as depression based on current literature. These networks were analyzed to find any stable regulatory regimes possible given the established connections. Analysis indicated that this model network supported two distinct and stable homeostatic regimes. The first corresponds to typical health, while the second presents with depression accompanied by increased and decreased levels of various neurochemicals. Treatment simulations were then run to mimic the effects of receiving an SSRI both in and out of the presence of stress, and to compare recidivism rates of returning to a normal regime to real-world statistics. This analysis suggests a new way to conceptualize depression as a naturally occurring stable regulatory regime within a complex neurotransmitter-psychobehavioral network system capable of supporting multiple stable states. Furthermore, it was found that efforts to shift the body's stable regime from depression to health using SSRIs is impeded by stress, suggesting that some form of stress management would complement the effects of SSRI treatment.

Keywords: computational modeling homeostatic depression

TABLE OF CONTENTS

CHAPTER I: STATEMENT OF PROBLEM	1
CHAPTER II: REVIEW OF THE LITERATURE	3
CHAPTER III: MATERIAL AND METHODS.....	13
A PSYCHOBIOLOGY REGULATORY MODEL.....	13
DISCRETE TERNARY LOGICAL ANALYSIS	19
MONTE CARLO SIMULATION OF STATE EVOLUTION	20
SIMULATING INTERVENTION COURSES	21
GENETIC ALGORITHM FOR OPTIMIZING TREATMENT COURSE	22
SENSITIVITY ANALYSIS	24
PATHWAY ANALYSIS.....	25
CHAPTER IV: RESULTS.....	26
MULTIPLE STABLE BEHAVIORS.....	26
SIMULATING CONVENTIONAL TREATMENT WITH SSRI.....	26
SIMULATING COMBINATION THERAPY WITH GABA INHIBITION	28
BEHAVIORAL INTERVENTION AND STRESS MANAGEMENT	30
SENSITIVITY ANALYSIS AND PREDISPOSING FACTORS OF ONSET	30
PATHWAY ANALYSIS.....	33
CHAPTER V: DISCUSSION.....	35
REFERENCES	44

TABLE LIST

Table	Page
1. Remission rates of simulated SSRI treatment under various conditions	31

FIGURE LIST

Figure	Page
1. Coarse Logic Model of Behavior and Neurotransmission in the Brain and Corresponding Behavioral Constructs	18
2. Multiple Naturally Occurring Stable States	27
3. Simulated Intervention Time Steps.....	29
4. Sensitivity Analysis of the Key Factors in Developing Depression	32
5. Path Strip Chart of Fastest Route to Illness State	34

Chapter I: Statement of Problem

In 2012, an estimated 16 million adults in the U.S. had at least one major depressive episode (Substance Abuse and Mental Health Services Administration, 2013). This is indicative of several conclusions, such as over the course of a year, 6.9 percent of adults in the U.S. experience a period of two weeks or longer during which there is either depressed mood or loss of interest or pleasure, and at least four other symptoms that reflect a change in functioning, such as problems with sleep, eating, energy, concentration, and self-image (American Psychiatric Association, 2013). This also means that each year, one of every fourteen adults is at an increased risk of suicide, the tenth leading cause of death in the U.S. Apart from the obvious personal ramifications of suffering from depression, this disease can have a serious impact on loved ones, caregivers, and the economy. In 2010, the annual costs associated with major depressive disorder were \$210.5 billion. This amount of money is not only staggering, it is also rising, compared to the \$173.3 billion annual costs associated with the disease in 2005 (Greenberg et al., 2015). These costs come in many forms, from antidepressant medications like SSRIs and psychotherapy treatment hours, to workplace costs like increases in annual sick days and higher rates of short-term disability. Depressed workers are significantly less productive at work and more likely to be absent. If the cost of depression is so high, what is being done to alleviate this crippling issue? There are several common forms of treatment available for people suffering from depression (Antonuccio, Danton, & DeNelsky, 1995). One of the most common forms is psychotropic medication. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are just two types of drugs commonly

prescribed to reduce depressive symptoms. More recently, inhibition of GABA transport has been investigated in animal models of depression (Salat et al., 2015). Cognitive behavioral therapy and interpersonal therapy are among the various types of psychotherapies used to treat depression (Cuijpers et al, 2008). Where medications act directly on the brain chemistry to alleviate symptoms, psychotherapy acts on mental constructs like thought patterns, interpersonal relationships, and coping skills to reduce depression. Regardless of the form of treatment, depression has an unusually high recurrence rate. Half of all patients who recover from a first episode of depression have one or more additional episodes in their lifetime, and nearly 80% of people with a history of two episodes will have at least another recurrence. Individuals with a history of depression will have five to nine separate episodes in their lifetime (Borcusa & Iacono, 2007). The numbers alone reveal the serious gravity of this situation. The reason why, even treated, depression has a significant recurrence rate, is as shrouded in mystery as a key aspect to the disease – the etiology. Despite decades of intensive research, the etiology of depression remains elusive. What is clear is that there are biological, genetic, environmental, and interpersonal aspects to the cause of major depression. Until it is better understood where depression comes from, and what exactly is happening on a systematic level, it will be impossible to directly target illness mechanisms.

Chapter II: Review of the Literature

One of the most primary concerns in understanding and treating depression is to first understand what is meant by “depression.” Asking any two people suffering from depression to describe in detail the components of their suffering will likely result in very different answers. Indeed, the one of the most defining features of psychological constructs is their inherent subjectivity. No two people can directly share the same subjective experience, and therein lies one of the most fundamental issues when understanding a mental state like depression. Not only in subjective experience, but also in clinical presentation, depression can mean different things to different people. The current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) contains eight distinct disorders under the “Depressive Disorders” category (American Psychiatric Association, 2013). Additionally, many other disorders within the DSM-5 contain potential specifiers of depressed mood in addition to the disorder. The specifically depressive disorders, however, are eight functionally unique presentations of depression. The common feature of these disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual’s capacity to function. What differs among them are issues of duration, timing, or presumed etiology. The most common and central depressive disorder, Major Depressive Disorder (MDD), is at the core of this category. Beyond the variances that exist within this category (duration, timing, etiology, etc.), MDD primarily consists of that which can be found in the other depressive disorders, namely, a major depressive episode. This central component of the depressive disorders is typically what is being referred to by the term “depression” in a clinical context. Through the several iterations

of the DSM, professionals within the mental health field have narrowed down the specific criteria necessary to adequately describe a major depressive episode. Currently, the criteria are as follows:

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).
 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
 4. Insomnia or hypersomnia nearly every day.
 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
 6. Fatigue or loss of energy nearly every day.
 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

What is of particular note when discussing the definition of “depression,” is that even within this well defined clinical explanation, only five of the nine criteria are required, with one of those five being at least one of the first two criteria. This echoes the earlier idea of depression being a fundamentally subjective and difficult to quantify phenomenon. While a pinpoint singular definition of depression has remained elusive, the cluster of potential clinical symptoms has been mostly sufficient for professionals within the various health fields to label, discuss, and develop treatments for depressed patients and clients. However, the lack of a clear and distinct mechanistic understanding of exactly what is happening in the body and mind of someone suffering from depression leads inevitably to the lack of clear and distinct methods of efficient treatment. If, while on a walk through the woods, someone is bitten by a venomous spider, they can be quickly taken to the nearest hospital or clinic and given specific anti-venom to counteract the spider’s damage. This is possible because of the knowledge of the mechanisms behind the spider’s venom and the correlating anti-venom. On the other hand, if someone

is afflicted with depression, prescribing an anti-depressant does not always effectively treat his or her symptoms. Nor do all anti-depressant medications equally treat all patients. This is due to an overwhelmingly unfortunate lack of understanding of the mechanisms that underlie this illness. The outward symptoms and expressions of depression can be observed, described, and in some cases quantified. Despite debate between mental health professionals of these symptoms and expressions, they tend to do a more or less sufficient job at describing depression. What they do not do, however, is point to a specific etiology, a system of mechanisms, or a clearly defined, individualized treatment protocol.

The complexity of depression doesn't stop with the nebulous nature of its symptoms and characteristics. Depression rarely occurs in a vacuum. More often than not, someone suffering from clinical depression is also suffering from one or more of a myriad of other, clinically different diseases or disorders (Kang, et al., 2015; Hasin, et al., 2018). A study done of patients with a lifetime history of MDD found that 57.9% had a history of a substance use disorder, 37.3% had a previous anxiety disorder, and 31.9% had a history of a personality disorder. Additionally, they found that 74.6% of MDD cases included the anxious/distressed specifier (Hasin, et al., 2018). A 1-year prevalence study in the United States found that patients with chronic medical diseases were nearly three times more likely to get depressed than their healthy counterparts (Egede, 2007). Another study of patients from 60 countries found that 9.3% to 18% of subjects with a single physical disorder also suffered from depression, compared to 3.2% of subjects without a single physical disorder, and 23% of patients with two or more physical conditions reported having depression (Moussavi, et al., 2007). Other studies conducted

on these comorbidities have found a significant level of depression in 20.4% of breast cancer patients, 20.7% of stroke patients, and 20.7% of patients with acute coronary syndrome (Kang, et al., 2015). Additionally, 33.8% of patients with chronic pain meet criteria for severe depression, with 60.8% meeting criteria for probable depression, based on specific measures (Rayner, et al., 2016). The comorbidity with chronic pain is particularly sinister, as the pain tends to exacerbate the patient's depression, which, in turn, exacerbates the pain perception, creating a vicious cycle. A possible key player in all of these comorbidities could be the link between depression and the immune system. Recent studies suggest that proinflammatory cytokines may contribute to some of the major symptoms of depression (Dowlati, et al., 2010). This connection between depression and a compromised immune system creates a new clinical picture, one that considers multiple levels of mechanistic action within the patient and may help account for many of the other comorbidities already mentioned. Some of these comorbidities seem obvious. It is fairly intuitive that someone suffering from chronic pain or going through the challenges of a cancer diagnosis would take a subsequent, and sometimes significant, hit to their mood functioning. However, whether the connection is obvious or more surprising, the implication is that depression and its mechanisms of action are part of a much deeper and more complex clinical symptom constellation that may require a new way of thinking to adequately understand, and ultimately treat, depression.

The concept of modeling depression has a long history. In Ancient Greece, Hippocrates theorized that diseases, including "melancholia," or what we now might call depression, could be explained by Imbalances in four basic bodily fluids, or humors (Coar, 1982). A few thousand years and many evolutions of the medical field later,

depression began to be modeled and explained in the context of psychology. In 1917 Sigmund Freud first developed a psychoanalytic view of depression, or melancholia, stating that it can result from an objective loss, such as the loss of a valued relationship, leading to subjective loss, the mechanism of which is the depressed individual's identification with the object of affection through an unconscious, narcissistic process, which he called the libidinal cathexis of the ego. As the field of psychology developed further, new theorists began attempting to understand depression from new points of view. In the 1950s, cognitive psychologists began theorizing explanations and models for depression. Albert Ellis hypothesized that depression stemmed from irrational "shoulds" and "musts" which would lead to inappropriate self-blame, self-pity, and other-pity (Ellis, 1962). In 1972 Martin Seligman developed the idea that learned helplessness underlies depression. In his theory, repeated exposure to aversive stimuli would reinforce a sense of regular helplessness in the individual, which would consequently result in depressed mood. In the 1960s and 70s, Aaron Beck developed one of the first true interactional models of depression (Beck, 1967). In his "cognitive triad," depression resulted from negative thinking patterns about oneself, one's future, and the world. These negative schemas were bidirectional, and influenced one another creating vicious cycles and rudimentary feedback loops. Utilizing Beck's theories, cognitive-behavioral therapy has become one of the most successful and widespread forms of treatment for depression in a variety of populations (Brown, et al., 2016; Balleio, et al., 2018; Twomey, et al., 2017; Unwin, et al., 2016). The success and efficacy of CBT speaks to the utility of a depression model that incorporates interacting components such as Beck's.

While many psychological models of depression focus on intangible constructs as

key players (e.g., cognitions, trauma, beliefs, etc.), medical models of the illness have often focused on more concrete ways of conceptualization. These models tend to rely on physical components such as chemical imbalances in the brain (Valenstein, 1998), degenerative conditions (Wragg & Jeste, 1989), toxicological syndromes (Onishchenko, et al., 2008), injuries (Jorge, et al., 2004), or deficiency states (Poeldinger, Calanchini, & Schwarz, 1991) to adequately explain the etiology of depression. Mirroring its conceptualizations, the medical models of depression offer treatments that often target physiological constructs. As opposed to psychological treatments, they rely on the use of medications, or antidepressants. The idea that depression is the result of a chemical imbalance in the brain took root in the 1950s. New clinical trials testing anti-tuberculosis drugs began to show a significant effect on the mood of patients. Specifically, these drugs were improving the mood of patients who were also diagnosed with depression (López-Muñoz & Alamo, 2009). The world of psychopharmacology grew rapidly after this discovery, with various types of drugs being developed over the following years to treat mood disorders, including depression. Mono-amine-oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were among the first types of widely available antidepressants. As mentioned, the nature of depression is complex, however, and it quickly became apparent that not all drugs are created equal. Efficacy rates varied among classes of drugs and types of depression, and side effects from these drugs could often be severe. However, the scientific value of these drugs cannot be understated. They provided highly relevant data on the action mechanisms of pharmacological agents at the synaptic transmission level. This level of understanding opened the door for new, more specific drugs, such as selective serotonin reuptake inhibitors (SSRIs). Understanding the crucial

role that serotonin plays in depression, SSRIs have become one of the gold standards for pharmacological treatment of depression. It acts by blocking the reabsorption of serotonin into the presynaptic cell, increasing the extracellular level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. The use of this medical model of depression has allowed researchers to better understand at least part of the mechanisms of depression. However, the efficacy rates of all antidepressants, including SSRIs are highly debated, but conservative estimates putting the remission rate of SSRIs around 50-60% (Linde, et al., 2015). This suggests that current physiological models are far from complete. A major hurdle in these biological models of depression is matching the complexity of the disease. Serotonin and other neurotransmitters may be key players, but until these models can account for all active contributing aspects during a depressive episode, treating the disease will continue to stop with covering of symptoms. An apt analogy may be that the success rate of a baseball team may be improved by training the pitcher, a key player, but unless you understand and train all players on the field, that success rate of the team will continue to be severely limited.

The current study takes an unconventional approach to a better understanding of major depression. In an ongoing effort to create a comprehensive modeling network to better understand various complex chronic illnesses, an interactional biobehavioral model of imbalances was built using existing literature and drawing connections between various neurochemicals and behavioral constructs. The model started as a biobehavioral point of entry into existing models of complex illnesses such as Chronic Fatigue Syndrome and Gulf War Illness. In an effort to better understand the psychological components and potential drivers behind these illnesses, common behavioral constructs

(depression, anxiety, fatigue, hyperarousal, etc.) as well as common neurotransmitters often implicated in the activation or reduction of these behavioral constructs (serotonin, dopamine, norepinephrine, etc.) were chosen to build the first iteration of our interactional biobehavioral model of imbalances. A literature review was then conducted, searching for any and all established connections between any two nodes of the model (e.g., any clinically established effect that serotonin has on GABA, and vice versa). By creating a system of feedback and feed-forward mechanisms and applying to it a ternary logic set of interaction rules, complex homeostatic regimes can be found. These regimes may give a new level of systematic insight into the underlying physiology of various illnesses.

The problem addressed by this study is the lack of a comprehensive and detailed understanding of the physiological mechanisms underlying mental illness. Feedback mechanisms throughout the brain play a significant role in maintaining physiological homeostasis. Specifically, brain chemicals and neurotransmitters contribute important oversight of psychological activity and homeostatic regulation. This paper proposes that these components form an overarching regulatory system that is capable of supporting multiple homeostatic regimes, including maladaptive illness states. Moreover, these regimes give rise to psychological behaviors that emerge as a result of the extensive feedback mechanisms involved in neurotransmitter signaling. Indeed, many psychological issues such as depression, anxiety, personality disorders, and post-traumatic stress reactions display a certain element of chronicity, almost as if the person suffering is “stuck” in a vicious cycle of distress. Here, this paper models the interaction of neurotransmitter function to explore the role of naturally occurring brain activity in

homeostatic regulation. Initial analysis of the model found homeostatic regimes that could possibly help garner a more complete understanding of the perpetuation of depression and anxiety. In addition, this work simulates an SSRI treatment by altering the level of serotonin in the model, comparing the evolution of the model from depression to health to known SSRI treatment success rates. Simulations such as these add to the validity of the model to accurately represent a naturally occurring physiological state. Though coarse, these models may nonetheless support the design of robust new treatments. As a further exploration and to cast SSRI treatment in a broader context, the introduction of GABA inhibition both alone and in combination with SSRI treatment was simulated. In all cases the model found a significant contribution of behavioral stress management to improving the predicted rate of remission beyond that achieved by pharmacologic intervention alone.

Chapter III: Material and Methods

A Psychobiology Regulatory Model

An important obstacle in building models across regulatory systems remains the scarcity of detailed human in vivo kinetic data as its collection can present significant health risks to subjects. The model proposed here circumvented this using a discreet logic representation based solely on literature of physiological and biochemical connectivity to provide a qualitative description of system behavior. The model addressed only a handful of neurochemicals that were chosen based on their prevalence in the literature and their perceived importance in various aspects of psychological functioning. While this limited set by no means fully accommodates the vast complexity of the neurological signaling system underlying psychological function and behavior, the corresponding coarse-grained circuit model supports a first approximation of physiologically relevant and experimentally verifiable response dynamics. The components of the model were chosen based on a specific set of criteria, the first of which was the limitations of the modeling technology employed. The methodology of analyzing these functional kinetic networks require significant computing power based on the number of nodes in the network, as well as the total number of incoming connections to each node. Based on these constraints, a target of 15-20 nodes was chosen. The final count of 16 nodes included 9 physiological neurochemicals, 6 psychological constructs, and stress. The psychological constructs were chosen based on two criteria: the goal of analyzing depression and anxiety as part of a functional feedback network, and readily available laboratory data to facilitate further future study of the network and its analyses. These criteria led to the inclusion of depression, anxiety, attention, hyperarousal, working memory, and physical

fatigue as the psychological construct nodes. Once these nodes were decided on, a brief literature review was conducted to determine what neurochemicals were primarily involved in the functioning of each psychological construct. This led to the inclusion of cortisol, dopamine, serotonin, glutamate, GABA, neuropeptide y, acetylcholine, epinephrine, and norepinephrine. Finally, a general node for stress was included to analyze how the system might evolve under the influence of a stress response, essentially mimicking in a very coarse-grained way, the real life conditions under which a neurobehavioral network would find itself. Once the list of neurotransmitters was decided upon, a literature review was conducted to discern how each chemical influenced the others. Priority was given to data observed in humans. Where there was limited or no data directly observed in humans, non-human animal studies were accepted. Furthermore, while many of the connections between these neurochemicals can be very complex, and differ based on brain region, genetic changes, and other confounding variables, for the purpose of this model, a general regulatory dynamic was chosen between any two nodes based on the overall, average way that the nodes caused each other to behave, as reported in literature. In the following section, each of these signaling connections are described with references to the supporting literature.

Cortisol is a steroid hormone released in response to stress, and therefore is a key element in any psychological homeostatic regime, as stress plays a significant role in psychology and the induction of maladaptive psychological states like depression. Based on the literature review, it was determined that cortisol is necessary for the activity of the synthesizing enzyme responsible for epinephrine (Wurtman, et al., 1972). Furthermore, cortisol can increase levels of dopamine and glutamate in the brain. Specifically,

glucocorticoids contribute to an increase in dopaminergic activity (Piazza, et al., 1996). They also increase glutamatergic transmission in the prefrontal cortex through modifying postsynaptic NMDA and AMPA receptors (Yuen, et al., 2009). Increased cortisol also inhibits serotonin levels by increasing serotonin uptake (Tafet, et al., 2001).

Various additional connections between the different nodes of the model were also found through the literature review. Elevated levels of epinephrine, for example, are shown to increase anxiety (Janssen, et al., 1998). Dopamine, applied iontophoretically, consistently attenuates the inhibitory actions of GABA (Bergstrom & Walters, 1984). Similarly, dopamine acts antagonistically with serotonin (Daw, et al., 2002), neuropeptide y (Gillard, et al., 1993), and norepinephrine (El Mansari, et al., 2010). Dopamine also has an inverse relationship with acetylcholine (Calabresi, et al., 2006). According to current literature, neuropeptide y (NPY) can block the phase shift of glutamate, reducing its cortical levels (Biello, et al., 1997). Increases in NPY can also inhibit levels of acetylcholine and norepinephrine (Serfozo, et al., 1986), and serotonin (Dryden, et al., 1993). According to Herman et al. (2003), norepinephrine pathways modulate synthesis of GABA in central limbic stress circuits. Elevated levels of norepinephrine also promote neuropeptide y (Wahlestedt, et al., 1990). Behaviorally, this neurotransmitter can increase anxiety (Bremner, et al., 1996), hyperarousal (Southwick, et al., 1999), attention (Bymaster, et al., 2002), and working memory (Zhang, et al., 2004), and decrease depression (Delgado & Moreno, 1999).

GABA, or *gamma*-Aminobutyric acid, is a primary inhibitory neurotransmitter. Therefore by increasing its levels, dopamine (Casey, et al., 1980), norepinephrine (Moises & Woodward, 1980), and serotonin are all inhibited (Bankson & Yamamoto,

2004). Elevated GABA can also lead to decreased levels of attention (Edden, et al., 2012). As opposed to GABA, glutamate is a primary excitatory neurotransmitter in the brain. It acts by increasing levels of norepinephrine (Russell & Wiggins, 2000), cortisol (Mathew, et al., 2001), and GABA (Carlsson, et al., 2001), and also increasing working memory (Aultman & Moghaddam, 2001) and depression (Paul & Skolnick, 2003). It can, however, inhibit attention (Carrey, et al., 2007).

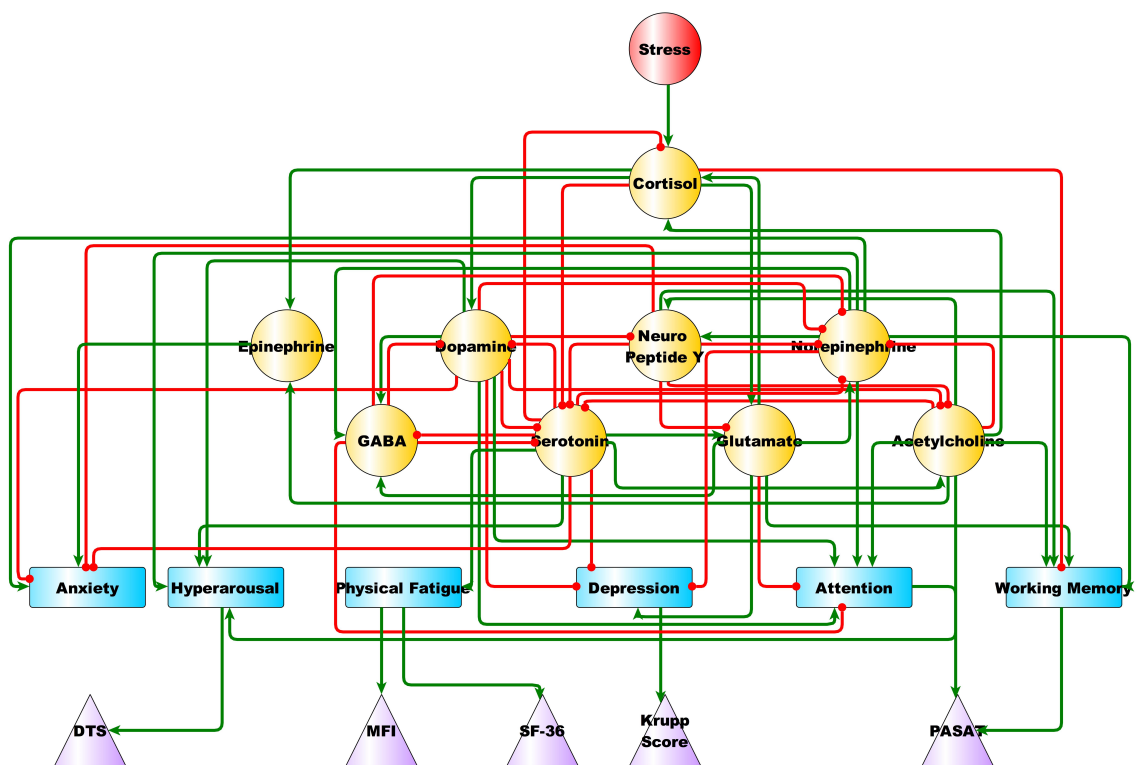
Serotonin is one of the primary neurotransmitters involved in depression (van Praag, et al., 1987). It is often the target of pharmaceutical interventions for depression. Because of the key role serotonin plays in this disorder, its place in the model is of particular importance. Based on current literature, elevated serotonin can lead to a number of different things. Certain serotonin receptors can facilitate glutamate release (Aghajanian & Marek, 1999). Serotonin also depolarizes certain cell types to increase acetylcholine release (MacDermot, et al., 1979). Serotonin has also been found to have a reciprocal relationship with norepinephrine (Guiard, et al., 2008), dopamine (Korsgaard, et al., 1985), cortisol (O'hara, et al., 2007), and GABA (Bankson & Yamamoto, 2004). Psychologically, elevated serotonin can increase hyperarousal (Connor & Davidson, 1998), but inhibit both anxiety (Charney, et al., 1987) and depression (Owens & Nemeroff, 1994). One study also found that keeping serotonin levels high for too long can lead to serotonin syndrome, with one symptom being physical fatigue (Roelands & Meeusen, 2010).

Acetylcholine is a neurotransmitter that acts on both the peripheral nervous system (PNS) and the central nervous system (CNS). For discussion within this model, its effects within the CNS are of primary focus. Acetylcholine can increase levels of

epinephrine (Keely & Lincoln, 1978), neuropeptide y (Dixon, et al., 2000), and cortisol (Walker, et al., 1990), while decreasing levels of norepinephrine (Kalsner & Quillan, 1988) and serotonin (Leboulenger, et al., 1988). Behaviorally, increased acetylcholine activity can increase hyperarousal (Czermak, et al., 2008), attention (Botly & Rosa, 2008), and working memory (Daniel & Dohanich, 2001).

It is of note that these aforementioned connections represent a “normal model” of functioning. There are likely to be deviations from this model at the individual level, but these deviations should be apparent by comparing an individual with this “averaged model” from the literature. The constructed model is represented in Figure 1.

Figure 1



Coarse Logic Model of Behavior and Neurotransmission in the Brain and Corresponding Behavioral Constructs. A simple causal regulatory network model linking 15 soluble mediators in the brain and associated behavioral constructs.

Discrete Ternary Logical Analysis

The discrete ternary logical network analysis used in the present work is an extension of a methodology proposed by Mendoza and Xenarios (2006) and Thomas (1991), and has been reported previously in the construction and analysis of similar models focused on the HPA axis and components of immune functioning (Craddock et al., 2014; Fritsch et al., 2013). This project encodes documented feedback mechanisms within the neuro-psychological system using only the direction (source and target) and type (activator or inhibitor) of interaction. As data describing the magnitude of changes remains limited, all cell types and behavioral constructs are considered to be equally responsive to the actions of the neurotransmitters for which they express receptors. Accordingly, neurochemical synthesis is also considered to be equivalent regardless of source. Using this formalism, the number and type of stable resting states supported by the regulatory circuitry as well as the specific qualitative neuro-psychological signatures at each of these stable points could be determined without requiring detailed kinetic information. That is, the proposed model determines where the system would eventually come to rest even though it may not be known how quickly this equilibrium will be reached. In this model, signaling molecules and cell types are represented as individual variables each capable of adopting 3 discrete states: -1 (down-regulated), 0 (nominal), and 1 (up-regulated). At any point in time t , the state of a system with N variables can be represented by the vector $\vec{x}(t)$, such that:

$$\vec{x}(t) = (x_1(t), x_2(t), \dots, x_N(t)) \quad (1)$$

where $x_i(t)$ is the state of the i^{th} variable of the N variable system at time t . The image vector $\vec{x}(t+1)$ describes the preferred state towards which the system evolves in the next

time increment. The state value of the image vector for the i^{th} variable is determined from its current state and a set of balanced ternary logic statements based on the current value of variable and the mode of action (i.e. activate or inhibit) of the neighboring input variables. These logic statements are expressed as follows (Eq. 2):

$$x_i(t+1) = \begin{cases} (x_{i1}^A(t) \vee x_{i2}^A(t) \vee \dots \vee x_{iX}^A(t)) \nabla (x_{i1}^I(t) \vee x_{i2}^I(t) \vee \dots \vee x_{iY}^I(t)) \\ (x_{i1}^A(t) \vee x_{i2}^A(t) \vee \dots \vee x_{iX}^A(t)) \\ \neg (x_{i1}^I(t) \vee x_{i2}^I(t) \vee \dots \vee x_{iY}^I(t)) \end{cases} \quad (2)$$

where the ∇ , \vee , and \neg symbols are ternary HIGH/LOW PASS, OR and NOT operators,

x_{ij}^A is the state of the i^{th} variable's j^{th} activator, x_{ik}^I is the state of the i^{th} variable's k^{th} inhibitor. The ternary operators given in Equation (2) are described in further detail in Craddock et al. (2014) and Fritsch et al. (2013). The first entry in Equation (2) is used when the variable possesses X activators and Y inhibitors, the middle when the variable has only X activators and last when the activator has only Y inhibitors.

The number of nodes determines the total number of allowable states available to a model, such that a model of N nodes possesses 3^N states. Steady states are defined as those state nodes from which there is no allowable escape or which possesses an out degree of 0. Since the current regulatory network model (Figure 1) contains 15 soluble mediators and behavioral constructs, the number of possible system states is $3^{15} = 14,348,907$. Though quite large this remains a computationally tractable problem and an exhaustive search of all possible state nodes was conducted to determine which of the latter constituted a steady homeostatic state as in Fritsch et al., (2013).

Monte Carlo Simulation of State Evolution

The evolution of state transitions supported by the model was simulated by

applying a Monte Carlo algorithm. From any initial starting state, allowable state transitions are determined based on Equation (2). Applying the latter to each variable in the model for the m^{th} state of the system, $\bar{x}^m(t)$, defines the image vector $\bar{x}^m(t+1)$ for the m^{th} state. With $\bar{x}^m(t+1)$ defined, the system is updated asynchronously (allowing only one variable to change at a time) following the generalized logical analysis of Thomas (1991). According to this method the i^{th} variable of the m^{th} state vector $x_i^m(t)$ is moved one step towards its preferred image $x_i^m(t+1)$ (e.g. If $x_i^m(t) = -1$ and $x_i^m(t+1) = 1$, then $x_i^m(t+1)$ is set to 0). Thus, for each current state of the system there are potentially several subsequent states towards which it may asynchronously evolve. From the allowable transitions a target state is chosen at random using a uniform equal distribution and used to generate the next set of allowable target states. Executing the simulation multiple times gives a distribution of paths that is used to determine the behavior of the system from any given start state.

Simulating Intervention Courses

To identify a robust sequence of interventions capable of moving the neuro-psychological system from a pathological mode of regulation to that of normal health, solutions combining a specific choice of treatment targets (e.g., serotonin uptake inhibition and/or GABA inhibition) as well as the sequence, spacing and type of external perturbation were allowed to evolve through the system. For each of these candidate treatment courses, simulations were conducted to evaluate the occurrence of normal homeostasis. Specifically, each clinical intervention of serotonin and/or GABA modulation was represented as a treatment vector with N variables. Interventions applied

to the system state at some point in time t , were represented by the vector $\vec{T}(t)$, such that:

$$\vec{T}(t) = (T_1(t), T_2(t), \dots, T_N(t)) \quad (4)$$

where T_i is a ternary value describing the effect of the clinical treatment on the i^{th} element of the system: -1 (suppressing), 0 (untreated), and 1 (elevating). At those time points where an intervention is being applied, the image vector $\vec{x}(t+1)$ describing the preferred state towards which the system should evolve is now defined as follows in contrast to the unperturbed logic described in Eq. 2:

$$\vec{x}(t+1) = \vec{x}(t) + \vec{T}(t) \quad (5)$$

Due to the ternary nature of this system no value can extend beyond the range of -1 to 1, hence values beyond this range were rounded accordingly (i.e. if $x_i(t) = 1$ and $T_i(t) = 1$, then $x_i(t+1) = x_i(t) + T_i(t) = 2$ is rounded to 1). At times t when there is no treatment applied (i.e. all $T_i = 0$), state transition continues according to the logic in Eq. 2.

Genetic Algorithm for Optimizing Treatment Course

Using this model-based strategy, repeated simulations were performed, each with a new externally applied intervention as prescribed by a global search algorithm in order to identify the optimal selection and spacing of interventions involving serotonin uptake inhibition, GABA suppression, or a combination of both leading to stable remission. A Genetic Algorithm (GA) based search (Whitley et al., 2003) was used to optimize this treatment course, as its form naturally accommodates the discrete definition of each system state.

A treatment course vector \vec{C} with M interventions is therefore defined as,

$$\vec{C} = (\vec{T}(t_1), \vec{T}(t_2), \dots, \vec{T}(t_M)) \quad (6)$$

where $\vec{T}(t_i)$ is the intervention treatment vector at the i^{th} intervention time point. Due to the asynchronous nature of the model each treatment vector \vec{T} only contains a single target intervention T_i that affects the i^{th} element variable in the system at any given time step.

The GA starts by generating a population of 1000 candidate treatment courses each composed of a specific number of randomly selected interventions consisting of serotonin re-uptake inhibition, GABA inhibition or both, applied at random points along the time course. The response of the system to each treatment course in this initial generation of candidates is then simulated for 1000 time steps. Over the course of these time steps the state of the system evolves according to Eq. 2, except at those times when interventions are applied. At these intervention events the state transition follows Eq. 5. These 1000 iterations provide a distribution of paths that are then ranked according to a fitness function based on the number of times a treatment successfully reached the healthy stable state (% HHM). After all treatments in the generation have been ranked, the top 10% are retained without change for the next generation. Thus, treatments generated by the GA that have a higher probability of leading to the HHM are re-executed and re-evaluated over many generations. The remainder of the next generation of candidate solutions is created by choosing random pairs from the total set of treatment courses (including the top 10th percentile) and combining (cross-over recombination) them. Combination, \otimes , of two treatment courses \vec{C}_1 , and \vec{C}_2 is performed at a single

random splice point s to create a new treatment course \bar{C}_1' for the next generation, such that,

$$\begin{aligned} \bar{C}_1 \otimes \bar{C}_2 &\Rightarrow \bar{C}_1' \\ (\bar{T}_1(t_1), \dots, \bar{T}_1(t_s) | \bar{T}_1(t_{s+1}), \dots, \bar{T}_1(t_M)) \otimes (\bar{T}_2(t_1), \dots, \bar{T}_2(t_s) | \bar{T}_2(t_{s+1}), \dots, \bar{T}_2(t_M)) \\ &\Rightarrow (\bar{T}_1(t_1), \dots, \bar{T}_1(t_s) | \bar{T}_2(t_{s+1}), \dots, \bar{T}_2(t_M)) \end{aligned} \quad (7)$$

The response to the new treatment courses, including members of the previous top 10th percentile, are then simulated once again and ranked as a new generation. This process is continued iteratively for 1000 generations. The final treatment course with the highest % HHM was taken as the best treatment solution for a given run. The overall best treatment course was chosen from 100 repeated GA runs. Optimal pharmacological interventions identified in this way were repeated, this time with the addition of stress, simulated as an increase in cortisol. This stress was added to the treatment vector randomly across the time course, such that the stressful events occurred at a prescribed frequency (e.g. 30% or one out of every three time points).

Sensitivity Analysis

To develop an understanding of a possible predisposition to falling into the depressed steady state based on the logic and wiring of the model, a sensitivity analysis was conducted. Starting at health, each neurotransmitter, one at a time, was either held high or low, and the system was allowed to respond naturally following a stressful event serving as a trigger. This was repeated 1000 times for both abnormal levels of each neurotransmitter to determine a percentage of times that the system degenerated into the depressed attractor, thus demonstrating which neurotransmitters, if any, had the greatest weight in predisposition to the onset of depression in the wake of a triggering event.

Pathway Analysis

Once it was established that increased levels of glutamate provided the backdrop for the quickest descent into the depressed steady state, the network was run while holding glutamate high to find the step-by-step path of the shortest route to illness. While there may be many possible routes to illness, this theoretical route would be the shortest, based on the sensitivity analysis.

Chapter IV: Results

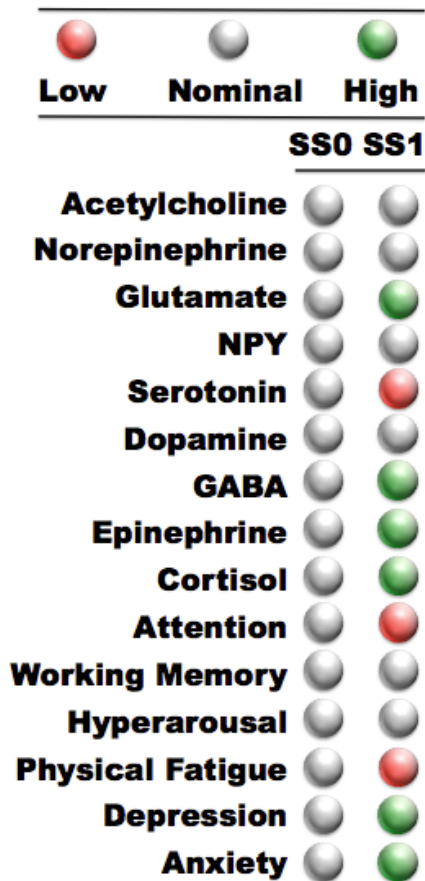
Multiple Stable Behaviors

As described above, steady homeostatic states are defined as those states to which the system naturally evolves at rest. These were determined here by enumerating all possible states that may be occupied by the model shown in Figure 1. This exhaustive search pointed to two steady homeostatic states (SS) where neurotransmitter and psycho behavioral constructs converged to the levels described in Figure 2. The reference steady state (SS0) described typical health with all markers being expressed at their nominal levels or zero. In addition to typical healthy regulation (SS0) we found that the model can also accommodate a shift towards an exacerbated depressive state with increased anxiety accompanied by reduced physical fatigue, impaired attention, and chronically low levels of serotonin in the context of elevated cortisol, GABA, and epinephrine. This would suggest that persistent depressive mood might be perpetuated at least in part by normal regulatory circuitry.

Simulating Conventional Treatment with SSRI

A common pharmaceutical treatment for depression focuses on the neurotransmitter, serotonin. Specifically, selective serotonin reuptake inhibitors (SSRIs) increase the amount of serotonin in the brain by blocking its reuptake into presynaptic neurons. This increase in serotonin affects mood, and can decrease depression, consistent with the wiring of this model. While reported efficacy rates of SSRIs vary greatly, current statistics put the efficacy rate of SSRIs in clinic at around 50-60% (Linde, et al., 2015). As a partial validation of this simple neurotransmission model, SSRI treatment was

Figure 2



Multiple Naturally Occurring Stable States. This basic model of neurotransmission supports an alternate homeostatic state where physiologic regulation now ensures a sustained depressive state with increased anxiety accompanied by reduced physical fatigue, impaired attention, and chronically low levels of serotonin in the context of elevated cortisol, GABA, and epinephrine.

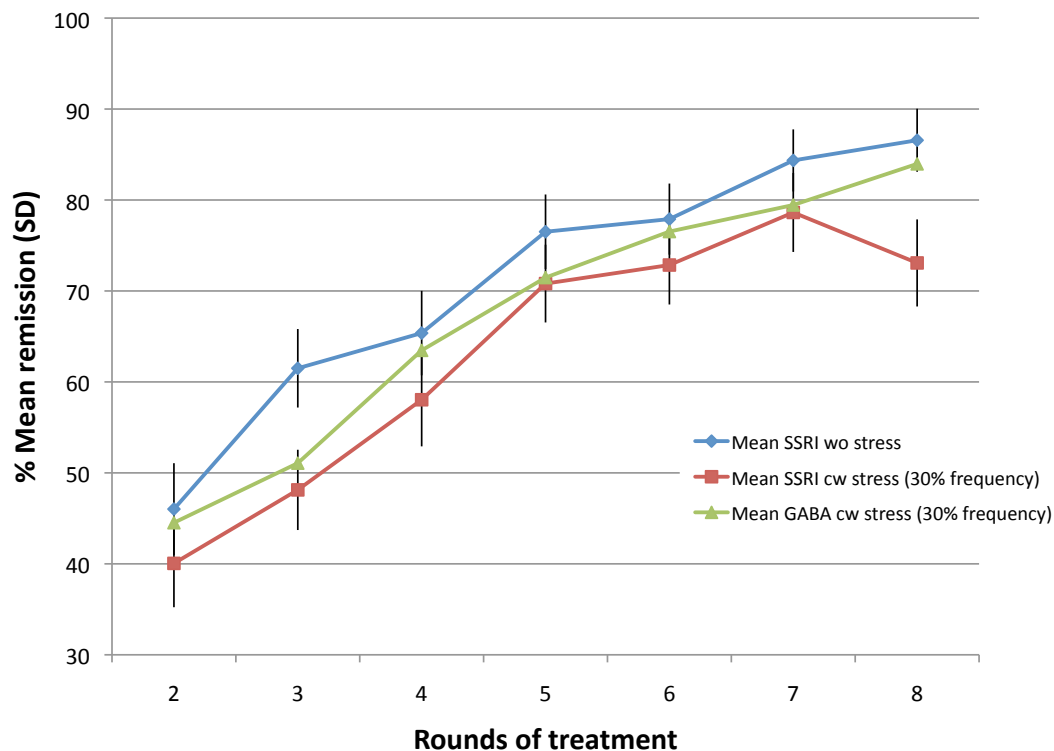
simulated computationally. First a numerical optimization was applied to identify the frequency of treatment with exogenous serotonin that delivered the highest predicted rate of lasting remission. Because the state of model neurotransmission network evolves in a probabilistic manner, a second step of simulation involved the artificial introduction of available serotonin according to this optimal frequency in 100 repeated treatment rounds, each in 100 simulated subjects. This was performed based on a schedule of predicted optimal treatment frequencies that encompassed between 2 and 8 treatment cycles.

To include the effects of stress on neurotransmission patterns in the model, and since real world subjects must deal with environmental stressors, random stressful events were superimposed at a frequency of occurrence of 30%. Under these simulated real-world conditions, the rate of predicted treatment responses potentially leading to lasting remission increased with repeated treatment, eventually reaching a saturation level of roughly 75% after 8 simulated cycles of SSRI treatment (Figure 3).

Simulating Combination Therapy with GABA Inhibition

Treatment with GABA inhibitors is also often used as a second line of therapy. Again, the numerical optimization was repeated, this time allowing for the optimal scheduling of both SSRI intervention as well as SSRI alone or in combination. The optimal treatment course of combination therapy repeated from 2 up to 8 cycles were again simulated 100 times each in a 100 virtual subjects. Overall, it was determined that these optimal treatment courses only included GABA inhibition very sparingly and that the primary driver was SSRI treatment. Nonetheless, the inclusion of GABA blockade improved the predicted remission rates slightly under simulated real-world conditions of 30% stressful events; however, this improvement did not reach statistical significance.

Figure 3



Simulated Intervention Time Steps. Summary of simulated intervention time courses with the maximum predicted frequency of remission as a function of repeated intervention events simulated in (A) SSRI with behavioral stress management, and treatment in the presence of randomly occurring stressful events (30% frequency) without behavioral intervention using (B) SSRI only and (C) SSRI with GABA blockade.

Behavioral Intervention and Stress Management

Since pharmacological intervention is typically accompanied by behavioral therapy, the experiments described above were repeated, but this time under the assumption that the virtual subjects were receiving behavioral therapy that provided them with effective strategies for managing stressful events. Optimization of treatment schedules and their subsequent simulation was conducted in the absence of stress altogether. Results indicated that this simulated behavioral intervention increased the efficacy of SSRI treatment significantly. The predicted rate of remission rose almost uniformly by up to 10% of treatment attempts across the range of treatment cycles (Figure 3; Table 1), far more significantly than the use of combination drug therapy in the absence of counseling and lifestyle changes.

Sensitivity Analysis and Predisposing Factors of Onset

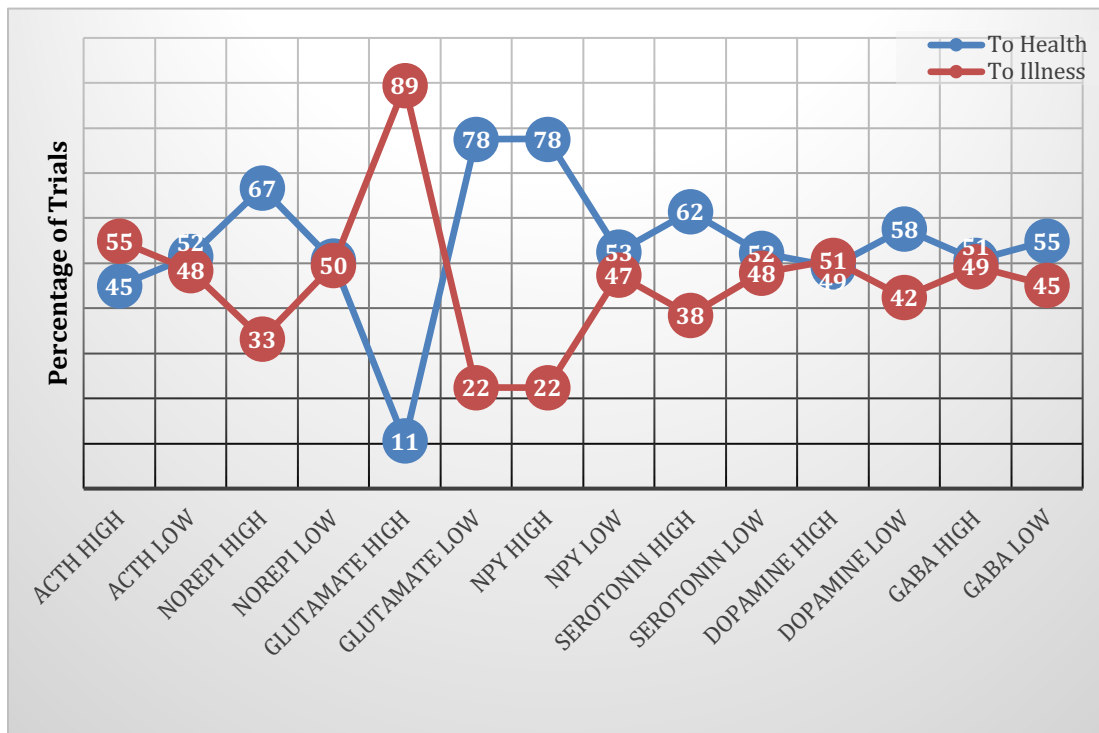
The results of the sensitivity analysis (Figure 4) showed that starting with health, individual deviations in almost all of the neurotransmitters provided no increased risk for falling into the depressed steady state beyond random chance. There were, however, three significant exceptions. Starting from health, increased levels of NPY served to prevent the system from falling into the depression attractor 776 times out of 1000. Low levels of NPY had no significant effect. Glutamate, however, had a significant effect at both high and low levels. Starting from health with high glutamate, the system fell into depression 894 times out of 1000. Low levels of glutamate prevented the system from falling into depression 775 times out of 1000.

Table. Remission rates of simulated SSRI treatment under various conditions

Number of Treatment Pulses		2	3	4	5	6	7	8
SSRI with stress management or no superimposed stress	Mean	46.02	61.50	65.37	76.51	77.90	84.35	86.57
	SD	5.04	4.31	4.64	4.10	3.91	3.41	3.46
SSRI treatment with 30% stressful events	Mean	40.05	48.13	58.04	70.81	72.85	78.63	73.08
	SD	4.82	4.41	5.12	4.27	4.34	4.34	4.79
Combined SSRI/GABA with 30% stressful events	Mean	44.52	51.07	63.47	71.47	76.53	79.45	83.97
	SD	5.11	4.78	4.92	4.00	4.73	3.83	3.34

Mean and standard deviation (SD) of remission rates obtained in simulations of multiple interventions using SSRI alone with an idealized behavioral stress management (BSM) therapy (0% stressful events), SSRI treatment without BSM in the presence of external stressors (30% frequency of stressful events) both alone and supplemented with a GABA inhibitor.

Figure 4

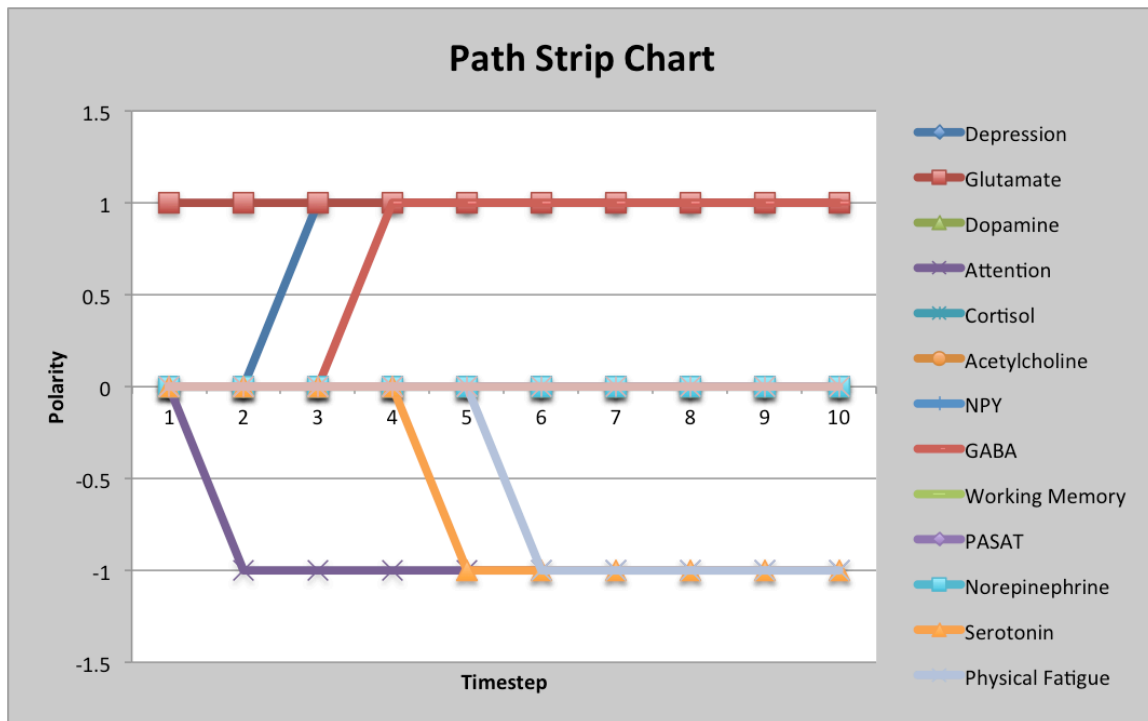


Sensitivity Analysis of the Key Factors in Developing Depression. Each node was artificially held high, and then low, one at a time. During each orientation, the system was allowed to naturally evolve under stress 1000 times. Of those 1000 iterations for each orientation, the number of times the system settled in the illness state versus the health state was recorded to determine which individual nodes provided the largest risk or protective factors.

Pathway Analysis

A pathway analysis was conducted to determine the fastest route that the system could take to the depressed steady state once introduced to an acute stressor if glutamate is held high. This would, in fact, be the fastest route because as the sensitivity analysis demonstrated, elevated glutamate provides the environment in which the illness state is most often reached when the system is put under stress. Figure 5 shows that the quickest route takes a total of six steps to reach depression. In the first step, glutamate and cortisol are held high. Attention then drops in step two, followed by an increase in depression in step three. GABA is then increased in step four, and serotonin is decreased in step five. Finally, due to the decrease in serotonin, physical fatigue decreases in step six. At this point the system is stuck in the depressed steady state.

Figure 5



Path Strip Chart of Fastest Route to Illness State. This analysis determines that, with glutamate held high, under the presence of an acute stressor, the system only takes six steps to reach the depressed steady state. This breakdown of the temporal progression of the shift from health provides insight into which pieces of the system are in motion at what times. Beginning with chronically high glutamate levels, the progression involves a decrease in attention, an increase in depression, an increase in GABA, a decrease in serotonin, and a decrease in serotonin-related physical fatigue.

Chapter V: Discussion

Selective serotonin reuptake inhibitors are often used in clinical practice to treat depression. The efficacy of this treatment option varies, but estimates of effectiveness are around 50-60%, compared to placebos that work about 40% of the time (Linde, et al., 2015). The reason why SSRIs do not work 100% of the time to alleviate depression remains elusive, but the complicated subjective nature of depression coupled with the equally complicated neurophysiological nature of depression likely makes treatment that targets a single neurotransmitter too reductive to be an end-all treatment. The intricate interworking of depression make this disease, like all mental disorders, difficult to pinpoint, and therefore difficult to effectively treat. The model proposed here suggests, in a concrete but coarse way, that depression can arise from a web of neuronal activity in which more than one piece of the puzzle is off. Serotonin is accurately one of those pieces. Modulating serotonin to mimic the introduction of an SSRI treatment, the analysis of this model was able to produce similar, but idealized results to SSRI treatment under artificial conditions. This suggests two things: the core processes of the model are likely correct, and additional granularity is required to further improve accuracy. Future iterations of the model will incorporate an even broader, but more comprehensive set of systems for developing the full picture of depression. The fact that this is indeed an iterative process leaves the door open for further exploration, which is necessary when trying to understand something as complex as mental illness.

Impaired immune system functioning is a common and significant side effect of depression (Reiche et al., 2004). A recent study by Yirmiya et al. (2015) proposes a new way of framing depression. They suggest that depression is a microglial disease,

intimately tied to the immune system within the brain. Furthermore, Louveau et al. (2015) recently discovered lymphatic vasculature in the central nervous system. This anatomical finding will likely have significant implications for the future of neuroimmunology. These newfound discoveries stress the importance of developing an understanding of psychoneuroimmunology in terms of one interconnected system, and not simply in terms of various separate, but peripherally connected, systems. Due to this information, the incorporation of the immune system at the molecular level will be the most logical next step in the evolution of this model. It is expected that the next iteration will provide a more detailed picture of depression and perhaps other mental illnesses and neuroimmune disorders. Given the comorbidity rates between depression, anxiety disorders such as Generalized Anxiety Disorder and Post-Traumatic Stress Disorder, personality disorders, neuroimmune disorders, and physical ailments such as cancer, stroke, and cardiovascular disease, it is also expected that future iterations of this model will shed some light on the underlying mechanisms connecting any and all of these various illnesses.

There have been studies modeling the efficacy of various treatments for depression, including SSRI use, different forms of psychotherapy, and combinations of drug treatment and psychotherapy. Soeteman et al. (2012) used a disease simulation model to address the issue of efficacy versus suicide rate of SSRI treatment, cognitive behavioral therapy (CBT), and a combination of the two. They found that in the short term, a combination treatment worked significantly greater than either form of therapy on its own, but when symptoms and suicidality persisted into the long term, CBT was marginally superior to both SSRIs and combination treatment. Another model

constructed by Gruwez et al. (2007) studied the kinetic-pharmacodynamics of the antidepressants clomipramine and lithium and how they would be best administered in a clinical trial. What these models have in common with the one presented here is the ability to see depression and how molecular changes (drug therapy) in combination with stress management (psychotherapy) provide the most efficacious treatment outcomes. There are, however, significant differences between the established models of depression and the one constructed for this study. The first of which is the scope. This model did not begin with a theory of depression with which to fit, but instead began as an interconnected networking of various neurotransmitters based on current literature. The search for possible homeostatic states within working brain chemistry produced a state of depression. By first constructing the model and then finding a depressed state, this model is better able to see more potential pieces of the network involved in depression than current models. These pieces may go unnoticed due to seemingly clinical irrelevance, but may, in fact, be key pieces when put into the larger context of the system. Exactly what parts these pieces play, and how they interact with stress helps to paint a more vivid picture of the underlying mechanisms of depression. For example, this model predicts that in this depressed steady state, both cortisol and epinephrine are elevated. These are two neurochemicals that aren't always implicated in typical treatments for depression, but according to the wiring of this model based on current literature, they may be somehow involved, and therefore potential targets for treatment. Additionally, none of the established models sufficiently capture the temporal nature of treatment. This model is able to optimize the number and spacing of treatment time steps in order to most efficiently push the system back to a healthy steady state. By utilizing this method of

computer programming and processing, the analyses presented are able to show quantitatively the optimal way to treat depression based on the model with SSRIs in the presence of stress. Lastly, this model shows the inherent regulatory dynamics of depression. Unlike other models and theories, this explains depression as a naturally occurring stable regulatory regime within a system that is capable of multi-stability. This shows both a new way to conceptualize depression and a new way to address treatment plans.

To complicate things further, but to add to the homeostatic regime hypothesis of the disease, depression is a chronic and recurring illness. Nearly half of all individuals who suffer from one episode of major depression will suffer from at least one more later in life, and nearly 80% of those who suffer from two episodes will suffer from at least a third (Burcusa & Iacono, 2007). These numbers are impressive and demand a more comprehensive understanding of depression and what can be done to alleviate it. Stress is often one of the triggers for depressive episodes. It is also one of the major causes of recurrence (Hammen, 2005). Therefore, in these simulations, 8-treatment serotonin-boosting and serotonin-and-GABA-combination modules were run, with stress and cortisol levels spiking 30% of the time to determine how, based on the model, the ability of the depressed steady state to move back toward health would be affected. As one might imagine, introducing stress during and after the SSRI treatments, prevented the system from returning to health more often than without stress. The success rate of the treatment dropped to around 75%, which is closer to real-world statistics. Stress is a normal part of everyday life, and the fact that the individual is already suffering from depression suggests that he or she is under more stress or less capable of successfully

handling the stress that they are under.

The role that stress plays in depression coupled with the findings from this model's treatment simulations suggest that some form of stress management would be beneficial to someone undergoing SSRI treatment for depression. This is consistent with the literature that shows different forms of psychotherapy, such as cognitive behavioral therapy, in conjunction with SSRIs, produce greater reductions in depression than either treatment alone (Chisholm, et al., 2004). Even without pharmacological intervention, psychotherapies have been shown to effectively reduce depressive symptoms. Furlong and Oei (2002) found that group CBT for depression was effective at reducing scores on the Beck Depression Inventory (BDI) by changing automatic thoughts and dysfunctional attitudes, thereby adding alternate cognitive pathways to reducing experienced stress. Farrer et al. (2011) found that an internet-based CBT program was also significantly effective at reducing depression symptoms. While these studies show that CBT can be effective at treating depression, March et al. (2004) found that a combination of CBT with the SSRI, fluoxetine, significantly reduced scores on the Children's Depression Rating Scale-Revised in 71.0% of subjects, compared to 60.6% of subjects on fluoxetine alone, 43.2% of subjects on CBT alone, and 34.8% on placebo. It would seem that learning the skills to handle stress is pivotal in maintaining alleviation and remission of depression while taking SSRIs. Using this study's current model and future iterations, and the homeostatic drive hypothesis for depression, even more comprehensive treatment methods may be uncovered.

The sensitivity analysis that was conducted also provided very interesting results, suggesting that high levels of glutamate could serve as a risk factor for developing

depression. This is supported in the literature, as glutamate-blocking compounds have been used to treat depression (Niciu, et al., 2014). Müller and Schwarz (2007) actually hypothesized that an integrated feedback system between a dysregulated HPA axis, an underproduction of serotonin, and an overproduction of glutamate might create a more comprehensive picture of depression. The analysis suggests that this line of thinking is not only on the right track, but the overproduction of glutamate could potentially lie at the source of the depression, providing a key insight into depression onset. This, in itself, could have far-reaching implications in terms of the connection between depression and healthy lifestyle habits, as the primary source of glutamate in the body comes from monosodium glutamate, a common compound found in various types of processed foods.

Additionally, the sensitivity analysis found that increased levels of NPY before a stressor served a protective role against the onset of depression. This is also supported by empirical literature, as Morgan et al. (2002) found that greater levels of NPY release during stress are associated with less psychological distress, suggesting that NPY confers anxiolytic activity. Similarly, Thorsell (2010) examined the therapeutic implications of NPY as a stress mediator. Neuropeptide Y affects the body outside of the brain and neurotransmission, however. It has been shown to have direct and significant effects on the HPA axis and the immune system. The release of NPY in the brain due to an acute stressor has been linked to the release of CRH and the activation of the HPA axis (Hirsch & Zukowska, 2012). The discovery of NPY's potential protective role from this model's depressed steady state suggests that it could be a reasonable target for treatment or prevention of depression.

Understanding the most likely course for the system to take towards depression is

also of vital importance. The pathway analysis shows not only that the shortest path involves six steps, but also exactly what happens in each step. This can have very important implications for treatment, because knowing the temporal progression of the steady state can provide insight into which molecular targets should be the focus of attention, as well as provide further understanding of how depression develops. It could also be used to improve current treatment methods by understanding at which relative time points various treatments would be most effective. It is important to note, however, that the six steps involved in this pathway analysis capture order, but not time steps. Further exploration is necessary to determine the length of time between each step.

The limitations of this study are exemplified in the coarse-grained development of such a complex system. Defining inclusion criteria when creating the network was an attempt to limit the amount of noise and erroneous information in the network. However, being curated by hand, the network is naturally prone to errors and missing data, despite the subsequent analyses supporting a correct construction. Furthermore, liberties were taken to determine the direction and polarity of connections. As mentioned, connections between any two neurochemicals can be very complex. They can differ based on brain region, amount of varying receptors, genetic changes, etc. For the purpose of this study, these connections were determined based on an overall, naturally occurring, average way that two entities would influence one another, as determined by the literature. As technology continues to improve, future studies along these lines will utilize text-mining software to determine connections between given entities by compiling data from a vast amount of literature to reduce human error, and allow for the inclusion of more information from more sources.

Future implications for this research also extend to individualizing treatment. By developing an individual illness profile for a patient, an optimized treatment protocol can be chosen. Using that same logic, by simulating known treatment protocols, like the SSRI simulation, models such as this can potentially discover which illness profiles respond to treatment, and which do not, as well as what makes the non-responders unique in their presentation. Furthermore, using an existing, validated network, a treatment protocol, or other psychological variable with known psychological outcomes or effects, can be connected into the model to determine the potential physiological underpinnings. For example, by hypothesizing a certain number of incoming and outgoing connections to cognitive behavioral therapy, and by constraining those connections to produce a network that is less likely to shift from a healthy stable state to a depressed or anxious steady state, or, vice versa, more likely to shift from depression or anxiety to health (simulating CBT's antidepressant and anxiolytic effects), a determination could be made on what physiological components are directly being influenced by CBT to produce those psychological effects. Toole, et al. (2018) did exactly this with psychological well-being, examining in a proof-of-concept experiment the physiological components of increasing well-being, given its protective role in psychological health.

Understanding the true scope of mental illness continues to elude clinicians and researchers. What is clear, however, is that mental illness is a very intricate, complicated form of disease, affecting or being affected by the interconnected neural network of the brain. The concept of the molecular homeostatic drive of the brain and body supporting multiple stable states opens the door to new possibilities in understanding the etiologies and treatments of various disorders and diseases. Depression is just one example of a

mental illness that needs to be better understood in terms of its intricacies in order to illuminate more comprehensive treatment approaches. This project's model makes a first step towards understanding depression, and all mental illness, as one of many prospective self-stabilizing states in which the naturally occurring chemistry of the brain can become stuck. The discrete logic analysis shows that, in fact, based on current literature-established neurochemical wiring, the brain is capable of supporting a regime of depression. Furthermore, increasing serotonin within this network – mimicking an SSRI treatment – can return this dysfunctional steady state back to health. When under random instances of stress, however, this return to health is significantly impeded, suggesting that for optimal treatment of a depressed neurochemical steady state, some form of behavioral intervention involving stress management is necessary. These concepts are reflected in clinical cases and real-world depression statistics. By understanding and expounding upon this theoretical approach to the underlying mechanisms of depression, and indeed all mental illness, it may be possible to soon have a broader, more complete knowledge of the diseases and disorders that pervade our society.

References

- Aghajanian, G. K., & Marek, G. J. (1999). Serotonin–glutamate interactions: a new target for antipsychotic drugs. *Neuropsychopharmacology*, 21, S122-S133. doi: 10.1007/s00213-012-2921-8
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: Author.
- Antonuccio, D. O., Danton, W. G., and DeNelsky, G. Y. (1995). Psychotherapy versus medication for depression: Challenging the conventional wisdom with data. *Professional Psychology: Research and Practice*, 26(6): 574-585. <http://dx.doi.org/10.1037/0735-7028.26.6.574>
- Aultman, J. M., & Moghaddam, B. (2001). Distinct contributions of glutamate and dopamine receptors to temporal aspects of rodent working memory using a clinically relevant task. *Psychopharmacology*, 153(3), 353-364. doi: 10.1007/s002130000590
- Ballesio, A., Aquino, M. R. J. V., Feige, B., Johann, A. F., Kyle, S. D., Spiegelhalder, K., ... & Baglioni, C. (2018). The effectiveness of behavioural and cognitive behavioural therapies for insomnia on depressive and fatigue symptoms: a systematic review and network meta-analysis. *Sleep Medicine Reviews*, 37, 114-129. doi: 10.1016/j.smr.2017.01.006
- Bankson, M. G., & Yamamoto, B. K. (2004). Serotonin–GABA interactions modulate MDMA-induced mesolimbic dopamine release. *Journal of neurochemistry*, 91(4), 852-859. doi: 10.1111/j.1471-4159.2004.02763.x
- Beck, A. T. (1967). *Depression: Clinical, experimental, and theoretical aspects*.

University of Pennsylvania Press.

- Bergstrom, D. A., & Walters, J. R. (1984). Dopamine attenuates the effects of GABA on single unit activity in the globus pallidus. *Brain research*, 310(1), 23-33. doi: 10.1016/0006-8993(84)90006-4
- Biello, S. M., Golombek, D. A., & Harrington, M. E. (1997). Neuropeptide Y and glutamate block each other's phase shifts in the suprachiasmatic nucleus in vitro. *Neuroscience*, 77(4), 1049-1057. doi: 10.1016/s0306-4522(96)00547-7
- Botly, L. C., & De Rosa, E. (2008). A cross-species investigation of acetylcholine, attention, and feature binding. *Psychological science*, 19(11), 1185-1193. doi: 10.1111/j.1467-9280.2008.02221.x
- Bremner, J. D., Krystal, J. H., Southwick, S. M., & Charney, D. S. (1996). Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. *Synapse*, 23(1), 39-51. doi: 10.1002/(SICI)1098-2396(199605)23:1<39::AID-SYN5>3.0.CO;2-I
- Brown, G. K., Karlin, B. E., Trockel, M., Gordienko, M., Yesavage, J., & Taylor, C. B. (2016). Effectiveness of cognitive behavioral therapy for veterans with depression and suicidal ideation. *Archives of suicide research*, 20(4), 677-682. doi: 10.1080/13811118.2016.1162238
- Burcusa, S. L. and Iacono, W. G. (2007). Risk for Recurrence in Depression. *Clinical Psychology Review*, 27(8): 959-985. doi: 10.1016/j.cpr.2007.02.005
- Bymaster, F. P., Katner, J. S., Nelson, D. L., Hemrick-Luecke, S. K., Threlkeld, P. G., Heiligenstein, J. H., ... & Perry, K. W. (2002). Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity

disorder. *Neuropsychopharmacology*, 27(5), 699-711. doi: 10.1016/S0893-133X(02)00346-9

Calabresi, P., Picconi, B., Parnetti, L., & Di Filippo, M. (2006). A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance. *The Lancet Neurology*, 5(11), 974-983. doi: 10.1016/S1474-4422(06)70600-7

Carlsson, A., Waters, N., Holm-Waters, S., Tedroff, J., Nilsson, M., & Carlsson, M. L. (2001). Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annual review of pharmacology and toxicology*, 41(1), 237-260. doi: 10.1146/annurev.pharmtox.41.1.237

Carrey, N. J., MacMaster, F. P., Gaudet, L., & Schmidt, M. H. (2007). Striatal creatine and glutamate/glutamine in attention-deficit/hyperactivity disorder. *Journal of child and adolescent psychopharmacology*, 17(1), 11-17. doi: 10.1089/cap.2006.0008

Casey, D. E., Gerlach, J., & Christensson, E. (1980). Behavioral aspects of GABA-dopamine interrelationships in the monkey. *Brain Research Bulletin*, 5, 269-273. [https://doi.org/10.1016/0361-9230\(80\)90044-1](https://doi.org/10.1016/0361-9230(80)90044-1)

Charney, D. S., Woods, S. W., Goodman, W. K., & Heninger, G. R. (1987). Serotonin function in anxiety. *Psychopharmacology*, 92(1), 14-24. <https://doi.org/10.1007/BF00215473>

Chisholm, D., Sanderson, K., Ayuso-Mateos, J. L., & Saxena, S. (2004). Reducing the global burden of depression: population-level analysis of intervention cost-effectiveness in 14 world regions. *The British Journal of Psychiatry*, 184(5), 393-

403. doi: 10.1192/bjp.184.5.393

Coar, T. (1982). *The aphorisms of Hippocrates: with a translation into latin, and english.*

Classics of Medicine Library.

Connor, K. M., & Davidson, J. R. (1998). The role of serotonin in posttraumatic stress disorder: neurobiology and pharmacotherapy. *CNS Spectrums*, 3(S2), 42-51.

<https://doi.org/10.1017/S1092852900007318>

Craddock, T. J., Fritsch, P., Rice Jr, M. A., del Rosario, R. M., Miller, D. B., Fletcher, M.

A., ... & Broderick, G. (2014). A role for homeostatic drive in the perpetuation of complex chronic illness: Gulf War Illness and chronic fatigue syndrome. *PloS one*, 9(1). <https://doi.org/10.1371/journal.pone.0084839>

Cuijpers, P., van Straten, A., Andersson, G., & van Oppen, P. (2008). Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *Journal of consulting and clinical psychology*, 76(6), 909. doi: 10.1037/a0013075

Czermak, C., Staley, J. K., Kasserman, S., Bois, F., Young, T., Henry, S., ... &

Neumeister, A. (2008). β_2 Nicotinic acetylcholine receptor availability in post-traumatic stress disorder. *International Journal of Neuropsychopharmacology*,

11(3), 419-424. doi: 10.1017/S1461145707008152

Daniel, J. M., & Dohanich, G. P. (2001). Acetylcholine mediates the estrogen-induced

increase in NMDA receptor binding in CA1 of the hippocampus and the

associated improvement in working memory. *The Journal of Neuroscience*,

21(17), 6949-6956. <https://doi.org/10.1523/JNEUROSCI.21-17-06949.2001>

Daw, N. D., Kakade, S., & Dayan, P. (2002). Opponent interactions between serotonin

and dopamine. *Neural Networks*, 15(4), 603-616. <https://doi.org/10.1016/S0893->

6080(02)00052-7

- Delgado, P. L., & Moreno, F. A. (1999). Role of norepinephrine in depression. *The Journal of clinical psychiatry*, 61, 5-12.
- Dixon, J. S., Jen, P. Y., & Gosling, J. A. (2000). The distribution of vesicular acetylcholine transporter in the human male genitourinary organs and its co-localization with neuropeptide Y and nitric oxide synthase. *Neurourology and urodynamics*, 19(2), 185-194. [https://doi.org/10.1002/\(SICI\)1520-6777\(2000\)19:2<185::AID-NAU9>3.0.CO;2-2](https://doi.org/10.1002/(SICI)1520-6777(2000)19:2<185::AID-NAU9>3.0.CO;2-2)
- Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological psychiatry*, 67(5), 446-457. doi: 10.1016/j.biopsych.2009.09.033
- Dryden, S., McCarthy, H. D., Malabu, U. H., Ware, M., & Williams, G. (1993). Increased neuropeptide Y concentrations in specific hypothalamic nuclei of the rat following treatment with methysergide: evidence that NPY may mediate serotonin's effects on food intake. *Peptides*, 14(4), 791-796. [https://doi.org/10.1016/0196-9781\(93\)90115-W](https://doi.org/10.1016/0196-9781(93)90115-W)
- Edden, R. A., Crocetti, D., Zhu, H., Gilbert, D. L., & Mostofsky, S. H. (2012). Reduced GABA concentration in attention-deficit/hyperactivity disorder. *Archives of general psychiatry*, 69(7), 750-753. doi: 10.1001/archgenpsychiatry.2011.2280
- Egede, L. E. (2007). Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *General hospital psychiatry*, 29(5), 409-416. doi: 10.1016/j.genhosppsych.2007.06.002

- El Mansari, M., Guiard, B. P., Chernoloz, O., Ghanbari, R., Katz, N., & Blier, P. (2010). Relevance of norepinephrine–dopamine interactions in the treatment of major depressive disorder. *CNS neuroscience & therapeutics*, 16(3), e1-e17. doi: 10.1111/j.1755-5949.2010.00146.x
- Ellis, Albert (1962). *Reason and emotion in psychotherapy* (Rev. and update. ed.). Secaucus, NJ: Carol Publishing Group.
- Farrer, L., Christensen, H., Griffiths, K. M., & Mackinnon, A. (2011). Internet-based CBT for depression with and without telephone tracking in a national helpline: randomised controlled trial. *PloS one*, 6(11), e28099. <https://doi.org/10.1371/journal.pone.0028099>
- Freud, S. (1957). Mourning and melancholia. In *The Standard Edition of the Complete Psychological Works of Sigmund Freud, Volume XIV (1914-1916): On the History of the Psycho-Analytic Movement, Papers on Metapsychology and Other Works* (pp. 237-258).
- Fritsch, P., Craddock, T. J., del Rosario, R. M., Rice, M. A., Smylie, A., Folcik, V. A., ... & Broderick, G. (2013). Succumbing to the laws of attraction: Exploring the sometimes pathogenic versatility of discrete immune logic. *Systems Biomedicine*, 1(3), 179-194. <https://doi.org/10.4161/sysb.28948>
- Furlong, M., & Oei, T. P. (2002). Changes to automatic thoughts and dysfunctional attitudes in group CBT for depression. *Behavioural and Cognitive Psychotherapy*, 30(03), 351-360. <https://doi.org/10.1017/S1352465802003107>
- Gillard, E. R., Dang, D. Q., & Stanley, B. G. (1993). Evidence that neuropeptide Y and dopamine in the perifornical hypothalamus interact antagonistically in the control

of food intake. *Brain research*, 628(1), 128-136. doi: 10.1016/0006-8993(93)90947-1

Greenberg, P. E., Fournier, A., Sisitsky, T., Pike, C. T., and Kessler, R. C. (2015). The Economic Burden of Adults With Major Depressive Disorder in the United States (2005 and 2010). *The Journal of Clinical Psychiatry*, 76(2). doi: 10.4088/JCP.14m09298

Gruwez, B., Poirier, M. F., Dauphin, A., Olié, J. P., & Tod, M. (2007). A kinetic-pharmacodynamic model for clinical trial simulation of antidepressant action: Application to clomipramine–lithium interaction. *Contemporary clinical trials*, 28(3), 276-287. doi: 10.1016/j.cct.2006.09.001

Guiard, B. P., El Mansari, M., Merali, Z., & Blier, P. (2008). Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions. *International Journal of Neuropsychopharmacology*, 11(5), 625-639. doi: 10.1017/S1461145707008383

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, 1, 293-319. doi: 10.1146/annurev.clinpsy.1.102803.143938

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA psychiatry*, 75(4), 336-346. doi: 10.1001/jamapsychiatry.2017.4602

Herman, J. P., Renda, A., & Bodie, B. (2003). Norepinephrine–gamma-aminobutyric acid (GABA) interaction in limbic stress circuits: effects of reboxetine on GABAergic

- neurons. *Biological psychiatry*, 53(2), 166-174. [https://doi.org/10.1016/S0006-3223\(02\)01449-X](https://doi.org/10.1016/S0006-3223(02)01449-X)
- Hirsch, D., & Zukowska, Z. (2012). NPY and stress 30 years later: the peripheral view. *Cellular and molecular neurobiology*, 32(5), 645-659. doi: 10.1007/s10571-011-9793-z
- Janssen, S. A., Arntz, A., & Bouts, S. (1998). Anxiety and pain: epinephrine-induced hyperalgesia and attentional influences. *Pain*, 76(3), 309-316.
[http://dx.doi.org/10.1016/S0304-3959\(98\)00060-8](http://dx.doi.org/10.1016/S0304-3959(98)00060-8)
- Jorge, R. E., Robinson, R. G., Moser, D., Tateno, A., Crespo-Facorro, B., & Arndt, S. (2004). Major depression following traumatic brain injury. *Archives of general psychiatry*, 61(1), 42-50. doi: 10.1001/archpsyc.61.1.42
- Kalsner, S., & Quillan, M. (1988). Presynaptic interactions between acetylcholine and adrenergic antagonists on norepinephrine release. *Journal of Pharmacology and Experimental Therapeutics*, 244(3), 879-891.
- Kang, H. J., Kim, S. Y., Bae, K. Y., Kim, S. W., Shin, I. S., Yoon, J. S., & Kim, J. M. (2015). Comorbidity of depression with physical disorders: research and clinical implications. *Chonnam medical journal*, 51(1), 8-18. doi: 10.4068/cmj.2015.51.1.8
- Keely, S. L., Lincoln, T. M., & Corbin, J. D. (1978). Interaction of acetylcholine and epinephrine on heart cyclic AMP-dependent protein kinase. *American Journal of Physiology-Heart and Circulatory Physiology*, 234(4), H432-H438. doi: 10.1152/ajpheart.1978.234.4.H432
- Korsgaard, S., Gerlach, J., & Christensson, E. (1985). Behavioral aspects of serotonin-

- dopamine interaction in the monkey. *European journal of pharmacology*, 118(3), 245-252. doi: 10.1016/0014-2999(85)90135-9
- Leboulenger, F., Benyamina, M., Delarue, C., Netchitailo, P., Saint-Pierre, S., & Vaudry, H. (1988). Neuronal and paracrine regulation of adrenal steroidogenesis: interactions between acetylcholine, serotonin and vasoactive intestinal peptide (VIP) on corticosteroid production by frog interrenal tissue. *Brain research*, 453(1), 103-109. doi: 10.1016/0006-8993(88)90147-3
- Linde, K., Kriston, L., Rücker, G., Jamil, S., Schumann, I., Meissner, K., ... & Schneider, A. (2015). Efficacy and acceptability of pharmacological treatments for depressive disorders in primary care: systematic review and network meta-analysis. *The Annals of Family Medicine*, 13(1), 69-79. doi: 10.1370/afm.1687
- López-Muñoz, F., & Alamo, C. (2009). Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. *Current pharmaceutical design*, 15(14), 1563-1586. doi: 10.2174/138161209788168001
- Louveau, A., Smirnov, I., Keyes, T. J., Eccles, J. D., Rouhani, S. J., Peske, J. D., ... & Kipnis, J. (2015). Structural and functional features of central nervous system lymphatic vessels. *Nature*, 523(7560), 337-341. doi: 10.1038/nature14432
- MacDermot, J., Higashida, H., Wilson, S. P., Matsuzawa, H., Minna, J., & Nirenberg, M. (1979). Adenylate cyclase and acetylcholine release regulated by separate serotonin receptors of somatic cell hybrids. *Proceedings of the National Academy of Sciences*, 76(3), 1135-1139. doi: 10.1073/pnas.76.3.1135
- March, J., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., ... & Severe, J. (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents

- with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA: the journal of the American Medical Association*, 292(7), 807-820. doi: 10.1001/jama.292.7.807
- Mathew, S. J., Coplan, J. D., Smith, E. L., Schoepp, D. D., Rosenblum, L. A., & Gorman, J. M. (2001). Glutamate—Hypothalamic-Pituitary-Adrenal Axis Interactions: Implications for Mood and Anxiety Disorders. *CNS spectrums*, 6(07), 555-564. <https://doi.org/10.1017/S1092852900002091>
- Mendoza, L., & Xenarios, I. (2006). A method for the generation of standardized qualitative dynamical systems of regulatory networks. *Theoretical Biology and Medical Modelling*, 3, 13. doi: 10.1186/1742-4682-3-13
- Moises, H. C., & Woodward, D. J. (1980). Potentiation of GABA inhibitory action in cerebellum by locus coeruleus stimulation. *Brain research*, 182(2), 327-344. doi: 10.1016/0006-8993(80)91192-0
- Morgan, C. A., Rasmusson, A. M., Wang, S., Hoyt, G., Hauger, R. L., & Hazlett, G. (2002). Neuropeptide-Y, cortisol, and subjective distress in humans exposed to acute stress: replication and extension of previous report. *Biological psychiatry*, 52(2), 136-142. [https://doi.org/10.1016/S0006-3223\(02\)01319-7](https://doi.org/10.1016/S0006-3223(02)01319-7)
- Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., & Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet*, 370(9590), 851-858. doi: 10.1016/S0140-6736(07)61415-9
- Müller, N., & Schwarz, M. J. (2007). The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Molecular Psychiatry*, 12,

988-1000. doi: 10.1038/sj.mp.4002006

- Niciu, M. J., Henter, I. D., Luckenbaugh, D. A., Zarate Jr, C. A., & Charney, D. S. (2014). Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. *Annual review of pharmacology and toxicology*, 54, 119-139. doi: 10.1146/annurev-pharmtox-011613-135950
- O'hara, R., Schröder, C. M., Mahadevan, R., Schatzberg, A. F., Lindley, S., Fox, S., ... & Hallmayer, J. F. (2007). Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol. *Molecular psychiatry*, 12(6), 544-555. doi: 10.1038/sj.mp.4001978
- Onishchenko, N., Karpova, N., Sabri, F., Castrén, E., & Ceccatelli, S. (2008). Long-lasting depression-like behavior and epigenetic changes of BDNF gene expression induced by perinatal exposure to methylmercury. *Journal of neurochemistry*, 106(3), 1378-1387. doi: 10.1111/j.1471-4159.2008.05484.x
- Owens, M. J., & Nemeroff, C. B. (1994). Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clinical chemistry*, 40(2), 288-295.
- Paul, I.A, Skolnick P. (2003). Glutamate and depression. *Annals of the New York Academy of Sciences*, 1003(1), 250-272. <https://doi.org/10.1196/annals.1300.016>
- Piazza, P. V., Rougé-Pont, F., Deroche, V., Maccari, S., Simon, H., & Le Moal, M. (1996). Glucocorticoids have state-dependent stimulant effects on the mesencephalic dopaminergic transmission. *Proceedings of the national Academy of Sciences*, 93(16), 8716-8720. doi: 10.1073/pnas.93.16.8716
- Pöldinger, W., Calanchini, B., & Schwarz, W. (1991). A functional-dimensional

approach to depression: serotonin deficiency as a target syndrome in a comparison of 5-hydroxytryptophan and fluvoxamine. *Psychopathology*, 24(2), 53-81. doi: 10.1159/000284698

Rayner, L., Hotopf, M., Petkova, H., Matcham, F., Simpson, A., & McCracken, L. M. (2016). Depression in patients with chronic pain attending a specialised pain treatment centre: prevalence and impact on health care costs. *Pain*, 157(7), 1472. doi: 10.1097/j.pain.0000000000000542

Reiche, E. M. V., Nunes, S. O. V., & Morimoto, H. K. (2004). Stress, depression, the immune system, and cancer. *The lancet oncology*, 5(10), 617-625. doi: 10.1016/S1470-2045(04)01597-9

Roelands, B., & Meeusen, R. (2010). Alterations in central fatigue by pharmacological manipulations of neurotransmitters in normal and high ambient temperature. *Sports Medicine*, 40(3), 229-246. doi: 10.2165/11533670-000000000-00000

Russell, V. A., & Wiggins, T. M. (2000). Increased glutamate-stimulated norepinephrine release from prefrontal cortex slices of spontaneously hypertensive rats. *Metabolic Brain Disease*, 15(4), 297-304. <https://doi.org/10.1023/A:1011175225512>

Sałat, K., Podkowa, A., Kowalczyk, P., Kulig, K., Dziubina, A., Filipek, B., & Librowski, T. (2015). Anticonvulsant active inhibitor of GABA transporter subtype 1, tiagabine, with activity in mouse models of anxiety, pain and depression. *Pharmacological Reports*, 67(3), 465-472. doi: 10.1016/j.pharep.2014.11.003

- Seligman, M. E. (1972). Learned helplessness. *Annual review of medicine*, 23(1), 407-412. <https://doi.org/10.1146/annurev.me.23.020172.002203>
- Serfozo, P., Bartfai, T., & Vizi, E. S. (1986). Presynaptic effects of neuropeptide Y on [3 H] noradrenaline and [3 H] acetylcholine release. *Regulatory peptides*, 16(2), 117-123. [https://doi.org/10.1016/0167-0115\(86\)90055-8](https://doi.org/10.1016/0167-0115(86)90055-8)
- Soeteman, D. I., Miller, M., & Kim, J. J. (2012). Modeling the risks and benefits of depression treatment for children and young adults. *Value in health*, 15(5), 724-729. <https://doi.org/10.1016/j.jval.2012.03.1390>
- Southwick, S. M., Bremner, J. D., Rasmusson, A., Morgan, C. A., Arnsten, A., & Charney, D. S. (1999). Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biological psychiatry*, 46(9), 1192-1204. [https://doi.org/10.1016/S0006-3223\(99\)00219-X](https://doi.org/10.1016/S0006-3223(99)00219-X)
- Substance Abuse and Mental Health Services Administration (2013). *Results from the 2012 National Survey on Drug Use and Health: Mental Health Findings*, NSDUH Series H-47, HHS Publication No. (SMA) 13-4805. Rockville, MD: Substance Abuse and Mental Health Services Administration.
- Tafet, G. E., Toister-Achituv, M., & Shinitzky, M. (2001). Enhancement of serotonin uptake by cortisol: a possible link between stress and depression. *Cognitive, Affective, & Behavioral Neuroscience*, 1(1), 96-104. <https://doi.org/10.3758/CABN.1.1.96>
- Thomas, R. (1991). Regulatory networks seen as asynchronous automata: a logical description. *Journal of theoretical biology*, 153(1), 1-23. [https://doi.org/10.1016/S0022-5193\(05\)80350-9](https://doi.org/10.1016/S0022-5193(05)80350-9)

- Thorsell, A. (2010). Brain neuropeptide Y and corticotropin-releasing hormone in mediating stress and anxiety. *Experimental Biology and Medicine*, 235(10), 1163-1167. doi: 10.1258/ebm.2010.009331
- Toole, J. T., Rice, M. A., Cargill, J., Craddock, T. J., Nierenberg, B., Klimas, N. G., ... & Broderick, G. (2018). Increasing Resilience to Traumatic Stress: Understanding the Protective Role of Well-Being. In *Psychoneuroimmunology* (pp. 87-100). Humana Press, New York, NY.
- Twomey, C., O'Reilly, G., & Meyer, B. (2017). Effectiveness of an individually-tailored computerised CBT programme (Deprexis) for depression: a meta-analysis. *Psychiatry research*, 256, 371-377. doi: 10.1016/j.psychres.2017.06.081
- Unwin, G., Tsimopoulou, I., Kroese, B. S., & Azmi, S. (2016). Effectiveness of cognitive behavioural therapy (CBT) programmes for anxiety or depression in adults with intellectual disabilities: A review of the literature. *Research in Developmental Disabilities*, 51, 60-75. doi: 10.1016/j.ridd.2015.12.010
- Valenstein, E. S. (1998). *Blaming the brain: The truth about drugs and mental health*. New York: The Free Press.
- van Praag, H. M., Kahn, R. S., Asnis, G. M., Wetzler, S., Brown, S. L., Bleich, A., & Korn, M. L. (1987). Denosologization of biological psychiatry or the specificity of 5-HT disturbances in psychiatric disorders. *Journal of affective disorders*, 13(1), 1-8. [http://dx.doi.org/10.1016/0165-0327\(87\)90067-X](http://dx.doi.org/10.1016/0165-0327(87)90067-X)
- Wahlestedt, C. L. A. E. S., Hakanson, R. O. L. F., Vaz, C. A., & Zukowska-Grojec, Z. O. F. I. A. (1990). Norepinephrine and neuropeptide Y: vasoconstrictor cooperation in vivo and in vitro. *American Journal of Physiology-Regulatory, Integrative and*

Comparative Physiology, 258(3), R736-R742. doi:

10.1152/ajpregu.1990.258.3.R736

- Walker, S. W., Strachan, M. W. J., Lightly, E. R. T., Williams, B. C., & Bird, I. M. (1990). Acetylcholine stimulates cortisol secretion through the M3 muscarinic receptor linked to a polyphosphoinositide-specific phospholipase C in bovine adrenal fasciculata/reticularis cells. *Molecular and cellular endocrinology*, 72(3), 227-238. doi: 10.1016/0303-7207(90)90147-z
- Whitley, D., Garrett, D., & Watson, J. P. (2003). Quad search and hybrid genetic algorithms. In *Genetic and Evolutionary Computation—GECCO 2003* (pp. 1469-1480). Springer Berlin Heidelberg. https://doi.org/10.1007/3-540-45110-2_19
- Wragg, R. E., & Jeste, D. V. (1989). Overview of depression and psychosis in Alzheimer's disease. *The American journal of psychiatry*, 146(5), 577. doi: 10.1176/ajp.146.5.577
- Wurtman, RJ; Pohorecky LA; Baliga BS. (1972). Adrenocortical control of the biosynthesis of epinephrine and proteins in the adrenal medulla. *Pharmacological Reviews*, 24 (2), 411–426.
- Yirmiya, R., Rimmerman, N., & Reshef, R. (2015). Depression as a Microglial Disease. *Trends in neurosciences*, 38(10), 637-658. doi: 10.1016/j.tins.2015.08.001
- Yuen, E. Y., Liu, W., Karatsoreos, I. N., Feng, J., McEwen, B. S., & Yan, Z. (2009). Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *Proceedings of the National Academy of Sciences*, 106(33), 14075-14079. doi: 10.1073/pnas.0906791106

Zhang, K., Grady, C. J., Tsapakis, E. M., Andersen, S. L., Tarazi, F. I., & Baldessarini, R.

J. (2004). Regulation of Working Memory by Dopamine D₄ Receptor in

Rats. *Neuropsychopharmacology*, 29(9), 1648. doi: 10.1038/sj.npp.1300491