

**EXPLAINING DEPRESSION: A DISCOURSE ANALYSIS OF FAMILY PHYSICIANS'  
AND NEUROSCIENTISTS' ACCOUNTS OF EXPLANATORY MODELS AND THE  
CHEMICAL IMBALANCE HYPOTHESIS OF DEPRESSION**

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## Abstract

The etiological explanations for depression, along with the received views of the way the brain and body function, have shifted from an excess of black bile to impaired neuroplasticity and neuroimmune functions. A common biological explanation for depression is the chemical imbalance hypothesis, which posits that depression is caused by a deficiency of monoamines, particularly serotonin, in the depressed person's brain. Many scholars have argued that the chemical imbalance hypothesis is unable to adequately explain depression and antidepressant treatment. However, while the etiological understanding of depression is complex and incomplete, the chemical imbalance hypothesis remains pervasive and persuasive among laypersons and clinicians.

I begin this dissertation with an introduction to biological psychiatry and neuroscience. The dissertation includes a brief history of Western/English approaches to the diagnosis and etiology of depression, a chapter on my ontological, epistemological, and methodological assumptions, two manuscript-style research studies, and concludes with a general discussion. In the two studies, I demonstrate how a sample of family physicians and neuroscientists accounted for using the chemical imbalance hypothesis of depression and other explanations of depression, the persuasive rhetorical features in their arguments, and the functions achieved by these accounts.

In study 1, I analyzed an interview data set with 11 family physicians. Using a discursive analytic approach, I argue that these physicians are utilizing the chemical imbalance hypothesis as a persuasive rhetorical device to motivate patients toward treatment, to attempt to minimize self-blame and stigma, to instill hope and confidence in the treatment, and to contribute generally to scientific knowledge among patients. In the discussion I provide a critique of the general assumptions upon which their arguments rely. For study 2, I interviewed 10 neuroscientists who conduct depression research. Using a discursive analytic approach, I present how a sample of neuroscientists working on a biological understanding of depression argue for and/or against the chemical imbalance hypothesis of depression. I argue that they maintain support for the chemical imbalance hypothesis through the construction of depression as a brain-based disorder and the brain as functioning through chemical transmissions, and that they argue against the chemical imbalance hypothesis by defining this hypothesis as a specific deficiency of serotonin and drawing attention to the failings and shortcomings of the hypothesis. I argue that their rhetorical construction of a distinction between a general chemical imbalance and a specific serotonin deficiency allows for the maintenance and support of the fundamental assumption that depression is a brain-based disorder, while simultaneously denying that depression is exclusively a problem with the serotonin system. I discuss alternative explanations of depression proposed by the scientists and show how they construct the serotonin hypothesis as a persuasive rhetorical device resistant to replacement.

The results of studies 1 and 2 suggest that the chemical imbalance hypothesis of depression, while limited in its specific form to explain the cause of depression, has value and merit in scientific and lay discourses. In the general discussion, I summarize the arguments for and against the chemical imbalance hypothesis and suggest ways that the general chemical imbalance explanation can be augmented with additional ideas from contemporary neuroscience. I discuss the discipline of translational neuroscience, which aims to bridge the gap between science and practice, and provide commentary using extracts from the interviews. I conclude with a reflexive examination of my position.

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## **Chapter One: Introduction**

Depression is a common mental illness with an unknown and debated etiology. Explanations often range from biological, to social, to psychological, or to a combination of these foci. A common biological explanation is the chemical imbalance hypothesis, which posits that depression is caused by a deficiency of monoamines, such as serotonin and norepinephrine, in the depressed person's brain. In the mid-1960s, scientists hypothesized that medications thought to alleviate depression functioned by increasing the amount of serotonin and/or norepinephrine in the brain (e.g., Schildkraut, 1965; Coppen, 1967). The pharmaceutical industry promoted antidepressants on the grounds of this hypothesis (Lacasse & Leo, 2005); however, scholars have argued that the chemical imbalance hypothesis is unable to adequately explain depression and have criticized direct-to-consumer advertising for promoting it as a causal explanation (e.g., Healy, 1997; Kirsch, 2010; Leo & Lacasse, 2008). The chemical imbalance hypothesis has been called "the potentially dominant cultural story of depression" (p. 411, France, Lysaker, & Robinson, 2007) and laypersons generally report that depression is caused by a chemical imbalance in the brain (Pescosolido et al., 2010). However, the etiology of depression (or perhaps the etiologies of depressions) is largely unknown, with many different causes at many different levels purported to explain the condition (e.g., Kendler, 2012).

### **1.1 Outline**

This dissertation is built around two manuscript-style research papers on the topic of the chemical imbalance hypothesis (Chapters 4 and 5). In this introductory chapter, I introduce the disciplines of neuroscience and psychiatry. In Chapter 2, I provide an overview of the historical and current ideas on the biological causes of depression, including the chemical imbalance hypothesis, as well as a brief overview of prominent psychological and social models of depression. In Chapter 3, I present my ontological, epistemological, and methodological assumptions that pertain to the two research studies that follow. In the two studies, I present my analyses of discourses on depression etiology, focusing on the chemical imbalance hypothesis, from interviews with family physicians and neuroscientists. Finally, in Chapter 6, I summarize and discuss the arguments for and against the chemical imbalance hypothesis of depression and suggest ways that the chemical imbalance explanation can be augmented with additional ideas from contemporary neuroscience. I discuss the discipline of translational neuroscience, which aims to bridge the gap between science and practice, and provide commentary using extracts from the interviews. I conclude the final chapter of the dissertation with a reflexive examination of my position as a researcher and a trainee clinician in psychology.

### **1.2 Neuroscience, Psychiatry, and the Study of Depression**

Neuroscience is a relatively new scientific discipline and there is much interest and excitement in brain research. Neuroscience has been described as a hybrid discipline with origins in molecular biology, chemistry, genetics, and anatomy and physiology (Abi-Rached & Rose, 2010; Abi-Rached, Rose, & Mogoutov, 2010). Explanations implicating the brain are widespread in Western society, from descriptions of how babies learn to how people age. Former United States President George H. W. Bush delivered a proclamation that the 1990s would be the "decade of the brain" (p. 1, Bush, 1990). His proclamation proposed that individuals suffering from disorders of the brain such as Alzheimer's disease, Parkinson's disease, Huntington's disease, spinal cord injuries, stroke, autism, schizophrenia, depressive disorder, speech and language disorders, and epileptic seizures, "are justifiably hopeful, for a



new era of discovery is dawning in brain research” (p.1, Bush, 1990). Neuroscience research since has proliferated and it continues to be a pervasive enterprise in science and medicine with great optimism for clinical breakthroughs.

Psychiatry, the medical discipline concerned with the diagnosis, treatment, and management of conditions labelled as mental illnesses, is presently coupled with the rise in neuroscience. For over two millennia, depression, or melancholia, was thought to be caused by an excess of black bile, and in the beginning of the 19<sup>th</sup> century, poor blood circulation in the brain and sluggish nerve fluid were proposed as causative (Jackson, 2008). However, near the turn of the 20<sup>th</sup> century, psychiatrists, without comprehensive knowledge of the function of the nervous system, turned away from the biological bases of mental disorders in favour of psychoanalytic conceptualizations, which proffered such disorders as being the result of repressed unconscious drives (Shorter, 1997). Shorter (1997), a medical historian, described the period in psychiatry up to the mid-1960s as the psychoanalytic ‘hiatus,’ and argued that the decades of psychoanalytic thinking were a mere and misguided interruption to the “smashing success” (p. vii) of biological psychiatry; he opined that psychiatry is most fruitful when on the “high road of science” (p. 295). While there are certainly dissenting views within psychiatry, and some psychoanalytic concepts and treatments remain, biological psychiatry appears to be the dominant paradigm for the diagnosis, treatment, and management of mental illnesses in Canada and the United States.

Psychiatry presently appears to be aligned with neuroscience research as the scientific foundation for mental health research, and prominent and influential psychiatrists have argued that it is the “future of psychiatry” (p. 1, Reynolds, Lewis, Detre, Schatzberg, & Kupfer, 2009). In the forward to the sixth edition of Goodwin and Guze's *Psychiatric Diagnosis* (North & Yutzky, 2010), Charles Zorumski, a professor of psychiatry, wrote, “Where do we go from here? Again, psychiatry seems to be at a crossroad. Most importantly the field has to decide whether or not it is really a branch of neuroscience” (p. xxviii). Zorumski conceptualized the current “crossroad” as a problem of diagnostic validity in psychiatry. He argued that the proliferation of diagnostic categories in each iteration of the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders* has occurred without the research required to validate each diagnosis. While he does not go on to directly answer his question of where to go from here, he espoused the merits of neuroscience and posited, “Eventually, the scientific hope is that we will revise our diagnostic system based on neuroscience and genetics” (p. xxviii). It seems that influential individuals and associations in psychiatry have chosen the path of neuroscience.

Psychiatry, with no biological markers or definitive diagnostic tests for conditions with largely unknown etiologies, is an anomaly among the medical disciplines. Psychiatric diagnoses, such as those contained in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, are clusters of mostly subjective symptoms (American Psychiatric Association, 2013). Reynolds et al. (2009), however, have argued that the division between psychiatry and neurology, which is primarily based on whether a condition’s etiology is known or unknown, is becoming an “artificial... boundary” (p. 2). They argued that psychiatry and neurology should be united as the discipline of clinical neuroscience because researchers are learning more about the mechanisms underlying psychiatric conditions. Michael Fitzgerald, a professor of psychiatry, also argued for the reintegration of neurology and psychiatry (Fitzgerald, 2015). However, diversity and variability abound among psychiatrists, and psychiatrist Ronald Pies (2005), for example, argued

that combining neurology and psychiatry will not be a straightforward task and will require the creation of a new common language.

With regard to depression, current hypotheses in clinical neuroscience propose that its causes and correlations are manifold, and involve the endocrine system, the immune system, and neuroplastic mechanisms. These and other etiological hypotheses are presented in detail in Chapter 2. While the exact causes of depression are still unknown and no reliable biological markers currently exist, we seemingly know more about depression and the nervous system than ever before due to the proliferation of neuroscience research in the past few decades. Despite the accumulating knowledge regarding depression, the chemical imbalance hypothesis, which posits that depression is caused by a deficiency of neurotransmitters, remains the most publicly popular explanation of the cause of depression, and is the focus of the chapters in this dissertation.

My interest in this topic originated in the apparent disconnect between scientific research in depression and clinical and lay understandings of the causes of depression, most notably the hypothesis that depression is caused by a deficiency of serotonin. Knowledge translation in clinical science is generally conceptualized as going from *bench to bedside*, i.e., applying findings, techniques, and treatments from scientific laboratories to clinical populations. Potentially, the knowledge that scientists are building about depression is not being translated effectively to clinical and lay society. This lack of knowledge translation seems evident in the way the chemical imbalance hypothesis of depression persists, at least among laypersons, despite the existence of scientific observations that do not support the hypothesis. How primary clinicians explain the etiology of depression is not well known. Additionally, while scientists are accumulating a great deal of knowledge about the brain and depression, the etiology of depression largely remains a mystery. I was interested in the following questions in particular: How do family physicians, who are responsible for the vast majority of the diagnosis and treatment of depression in Canada, describe and account for their etiological explanations of depression and what discursive resources do they draw on when presenting how they explain depression to their patients? How do scientists who are working toward a biological understanding of depression account for the use of the chemical imbalance hypothesis of depression, and structure arguments for or against it? It is these questions that form the basis of my empirical investigations in this dissertation.

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## **Chapter Two: The Diagnosis and Etiology of Depression in Canada and the United States of America**

Depression is notoriously difficult to define. People use the term to refer to a variety of conditions, from a disabling chronic disease to a temporary state of mind. For nearly two and a half millennia, depression, or melancholia, has been understood as encompassing a wide range of “dejected states” (p. 443, Jackson, 2008), including a distinct clinical pathology, a non-pathological mood state, a symptom of another disease, and a temperament or personality type. Some (e.g., Wilson, 2009) have argued for conceiving of depression as melancholic realism and a creative, innovative, and insightful force in life. Currently, in Canada and the United States, the term ‘depression’ is often used to refer to a clinical syndrome known as Major Depressive Disorder in the nomenclature of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

### **2.1 The Diagnosis of Depression**

In the latest version of the DSM (DSM-5; American Psychiatric Association, 2013), a diagnosis of Major Depressive Disorder requires the presence of at least five symptoms occurring during a two-week period, with at least one of the symptoms being either depressed mood or loss of interest or pleasure, and the remainder being either significant weight loss/gain, insomnia/hypersomnia, psychomotor agitation/retardation, fatigue, or feelings of worthlessness or excessive/inappropriate guilt. Consistent with almost all diagnoses in the DSM-5, the symptoms must be accompanied by distress or impairments in important areas of functioning and must not be attributable to an effect caused by a substance or another medical condition. The diagnosis of Major Depressive Disorder in North America has remained largely unchanged since the major shift that occurred with the publication of the DSM-III (American Psychiatric Association, 1980), when psychoanalytic concepts like neurosis were eschewed and attempts were made to improve the reliability and validity of psychiatric diagnoses.

Prior to the introduction of the DSM-III, Major Depressive Disorder was diagnosed as Depressive Reaction (DSM-I; American Psychiatric Association, 1952) or Depressive Neurosis (DSM-II; American Psychiatric Association, 1968). In the DSM-II, a Depressive Neurosis was defined simply as “an excessive reaction of depression due to an internal conflict or to an identifiable event such as the loss of a love object or cherished possession.” (p. 40). The DSM-II also contained a diagnosis of Neurasthenic Neurosis, which is a condition characterized by weakness, fatigue, and exhaustion, accompanied by chronicity and moderate depression, which might be classified as Major Depressive Disorder or Persistent Depressive Disorder (Dysthymia) in DSM-5.

#### **2.1.1 DSM-5 controversy.**

There was much controversy at the release of the DSM-5. Psychiatrist Allen Frances, who chaired the task-force for the DSM-IV, was one of the most vocal critics of the DSM-5. He argued that the DSM-5 expanded diagnostic categories too far, and would medicalize normality and result in unnecessary and potentially harmful treatment (Frances, 2013). With Major Depressive Disorder, for example, the DSM-5 no longer contains a bereavement exclusion; in DSM-IV-TR (American Psychiatric Association, 2000), a depressive episode that occurred within two months of losing a loved one was considered the result of bereavement and not a psychiatric disorder. The change to Major Depressive Disorder is one example of how Allan

Frances and others expected the DSM-5 to further pathologize normal human suffering (Pickersgill, 2014).

Thomas Insel, Director of the US National Institutes of Mental Health (NIMH) at the time, criticized the DSM-5 for being unscientific (Insel, 2013). Insel argued that the DSM, rather than being based on objective laboratory measures as is the case in other medical disciplines, is based on “consensus about clusters of clinical symptoms” (para. 2) that have questionable validity. He argued that DSM diagnoses have limited the scientific search for biomarkers of mental disorders because a potential biomarker of an underlying disease may be discarded when it does not align with a DSM symptom cluster. Insel championed the Research Domain Criteria (RDoC) as a new and improved approach to studying mental disorders, and he stated that the NIMH would only fund research that cuts across or reduces diagnostic clusters to core elements as found in the RDoC. For example, rather than studying a group of individuals with Major Depressive Disorder, researchers would study all patients seeking treatment for a mood disorder, or examine a particular symptom, such as anhedonia, that is shared by more than one diagnosis. While he described the RDoC as a framework for guiding research and not a clinical tool, he also described it as “a first step towards ‘precision medicine’” (para. 6). Precision medicine, sometimes referred to as personalized medicine, refers to the ideal of tailoring treatment based on the underlying causes of a specific disease process within the individual; it is currently utilized in oncology and the treatment of cancers. Thus, while the RDoC is not about to replace the DSM in clinical practice, it aims to “transform clinical practice by bringing a new generation of research to inform how we diagnose and treat mental disorders” (para. 6).

The ultimate goal of the RDoC is to improve diagnostic validity in biological psychiatry by understanding the etiological mechanisms at play across various levels of analysis. The DSM is devoid of etiological statements. It does report on incidence, prevalence, and features statistically associated with a diagnosis, but does not make any claim as to the underlying pathology. The etiology of depression is largely unknown, but researchers are following several ideas regarding the underlying pathology of depression.

## **2.2 Biologically-Based Etiologies of Depression**

Recent developments in the science of depression have led to a more detailed and sophisticated understanding of the potential biological mechanisms underlying depression. The scientific community has moved the discourse from depression being caused by an excess of black bile to being caused by a complex interaction of environmental and constitutional factors, genetic vulnerabilities, neuroplasticity, neurotransmitter functioning, endocrine functioning, and immune functioning. The idea that depression is caused by a simple deficiency of serotonin and norepinephrine at the synapse, which has dominated both public and medical discourses for decades, and spurred the invention of the SSRIs and related antidepressants, has been abandoned in favour of more sophisticated explanations and explorations of the biological effects of stress and antidepressant medications.

In the sections below, I present the major historical and contemporary biologically-based etiological explanations for depression, followed by a brief overview of prominent psychological models of depression and social risk factors. I focus primarily upon the biologically-based etiologies of depression in this chapter because this is where the chemical imbalance hypothesis is situated. I briefly present psychosocial explanations to orient the reader to concepts discussed

later in the dissertation. With regard to the chemical imbalance hypothesis, I rely upon the writings of controversial scholars to construct my argument, including David Healy and Irving Kirsch. David Healy is a psychiatrist and psychopharmacologist who has written extensive critiques of antidepressants and the pharmaceutical industry. In his book, *The Antidepressant Era*, Healy (1997) argues that pharmaceutical companies have promoted and expanded the concept of depression as a disease in order to sell antidepressants. He is also well-known for his argument that antidepressant use is associated with an increased risk of suicide. Healy cited his controversial views on depression and antidepressants as leading to a job offer being rescinded (Dyer, 2000; Spurgeon, 2002)<sup>1</sup>. Similarly, Kirsch (2010), a research psychologist, constructs a particular version of depression in his polemic against antidepressant efficacy. In his book he states, “Depression may not even be an illness at all. Often, it can be a normal reaction to abnormal situations” (p. 238). I acknowledge that there are a variety of positions on depression; my intention in the following sections is to present the major ideas about the biological causes of depression as defined by contemporary biological psychiatry.

### **2.2.1 Humoral explanations.**

The clinical features of depression, or melancholia, have been described similarly for over two millennia (Healy, 1997; Jackson 1986; Jackson, 2008). From the time of the Ancient Greeks up until the early 18<sup>th</sup> century, the humoral conception of illness was dominant. Melancholia, originally a Greek term but also transliterated in Latin, was used to describe a state of “prolonged fear and depression” (p. 444, Jackson, 2008). The Greek melancholia was derived from *melaina chole*, or black bile. In the humoral theory of illness, diseases are caused by imbalances of the four humors, i.e., blood, phlegm, yellow bile, and black bile. The four humors were also associated with personality features or temperaments. Melancholia was thought to be caused by an excess of black bile in the blood, which had an effect upon the brain. The spleen, which was thought responsible for filtering black bile that formed in the liver, was also seen as a central organ in the pathophysiology of depression since the time of Galen (Jackson, 2008). In the humoral system of medicine, remedies generally revolved around countering the inherent properties of the illness. Treatment of melancholia revolved around removing the excess of black bile. Bloodletting with leaches was a popular method, as was using black hellebore, a purgative herb (Healy, 1997). Melancholia, a dry and cold illness, was treated with hot baths and prolonged exposure to moisture.

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<sup>1</sup> In 2000, Healy accepted a professorship at the University of Toronto (UofT) that included the position of clinical director of the mood disorders unit at the Centre for Addiction and Mental Health (CAMH). After delivering a lecture critical of SSRIs, the UofT rescinded the offer and claimed that Healy’s views were extreme and incompatible with scientific evidence. Supporters of Healy noted that CAMH received significant funding from the pharmaceutical industry, which might have played a role in the job being rescinded and Healy subsequently filed a defamation lawsuit for \$9m CAD (Dyer, 2000). Healy settled his dispute and, according to a report in the *British Medical Journal*, Healy, CAMH, and the UofT provided a joint statement that “Dr Healy accepts assurances that pharmaceutical companies played no role in either CAMH’s decision to rescind his clinical appointment or the University of Toronto’s decision to rescind his academic appointment” (p. 1177, Spurgeon, 2002).

The humoral system was a general framework to explain and treat illnesses, including depression. The treatments, which today appear misguided, were congruent with the etiological conceptualization. In the humoral system, the brain was implicated in depression but was not seen as a central location of pathology. In etiological explanations that follow the humoral system, the brain becomes a central figure.

### **2.2.2 Mechanical explanations.**

By the 18<sup>th</sup> century, mechanical and hydrodynamic explanations, popular in other realms of science, became prominent explanations for melancholia (Jackson, 1983; 2008). Jackson (2008), a psychiatrist and medical historian, summarized the mechanical explanations during this time as being first vasocentric then neurocentric. Vasocentric explanations of melancholia blamed sluggish blood or reduced circulation; neurocentric explanations blamed sluggish nerve fluid or depleted energy levels in the brain. Jackson (2008) concluded that the mechanical explanations had little effect on the overall conceptualization and treatment of melancholia; treatments such as bloodletting and purging continued to be prescribed.

In the beginning of the 19<sup>th</sup> century, a reconciliation of vasocentric and neurocentric explanations was prominent, with a focus on the blood circulation within the brain, and hereditary factors were posited to play a large role (Jackson, 1986; 2008). The neurocentric explanations rose in prominence over the century, with the cause of mental illnesses attributed to the effect cerebral blood flow had upon nerve cells in the brain. Decreased blood flow to the brain resulted in a decay of brain cells and caused melancholia. Mental disorders, including melancholia, were increasingly viewed as brain diseases rather than diseases of the soul. Prior to the beginning of the 19<sup>th</sup> century, a person afflicted with a mental disorder was deemed “wholly insane, in the sense of someone who had lost complete possession of all his or her faculties” (Healy, 1997, p. 28), and this conception was due to a particular understanding of mind and body: the soul as an indivisible entity. During this period, scientific discoveries changed the conception of the mind, and, in effect, contributed to a different understanding of mental disorders. For example, in 1823, learning of the reflex arc demonstrated that things could happen in the body automatically, without control of the soul (Healy, 1997). The dysfunctional brain was now seen as the principal cause of mental illnesses.

In the 18<sup>th</sup> and 19<sup>th</sup> centuries, brain-based understandings of depression began to take shape, first through the influence of reduced blood circulation to the brain and then to dysfunctions in nerve cells. The developing scientific understanding of the nervous system was influential but treatments for depression remained the same as those congruent with the humoral system. In the 20<sup>th</sup> century, the advent of drugs that became known as the antidepressants made an impact upon the etiological explanation of depression.

### **2.2.3 Influence of antidepressants.**

The “serendipitous discovery” (Ban, 2006, p. 341) of the drugs that became known as the antipsychotics and antidepressants had a massive influence on psychiatry. To understand the subsequent biological explanations, it is important to briefly review the invention of the antidepressants. In 1957, scientists Roland Kuhn and Nate Kline independently discovered the first tricyclic antidepressant (TCA, imipramine) and the first monoamine oxidase inhibitor (MAOI, iproniazid), but, as Healy (1997) reported, the discovery of antidepressants owed much to the 1952 discovery of the first antipsychotic (chlorpromazine).



The discovery of chlorpromazine began with antihistamine research in the 1930s and 40s (Healy, 1997). Researchers noted that antihistamines seemed to change behaviour, and some suggested that they might have a sedative effect. Scientists began research with animals to test the behavioural effects of different antihistamine-like molecules. There were sedative-like effects found for chlorpromazine. Rats that had been trained to climb a rope to get food would no longer do so. However, the behavioural effects were different from sedatives; the rats would display a complete lack of interest in seeking the food, while their motor abilities were seemingly unimpaired. The application to mental disorders did not happen immediately. The pharmaceutical company Smith, Kline & French focused on possible anesthetic uses, perceived to be more financially rewarding. Despite the pharmaceutical company's reluctance to pursue development as a psychiatric drug, chlorpromazine was about to make an impact in the psychiatric world. Reports of the marked effects in clinical settings were growing; clinicians in asylums reported that patients treated with chlorpromazine emerged from hallucinations and delusions that had previously persisted for years. Word travels fast, and chlorpromazine use was soon widespread in asylums.

The discovery of reserpine was also an important event that especially contributed to the monoamine hypothesis of depression (Healy, 1997). Reserpine was extracted from a root plant popular in India for the treatment of hypertension, snakebites, and insanity. The drug had tranquilizing effects in animals: their eyelids drooped, they were sedated, and sometimes spasmodic. As reported by Healy (1997), a clinical study with 710 psychiatric patients compared reserpine with a placebo. The effects were noticeable even by hospital staff; for example, the maintenance workers reported they found fewer windows to repair in the wards where patients were receiving reserpine treatment. Clinical reports also suggested that reserpine caused a depressed state, and occasionally made people suicidal.

Like chlorpromazine, the discovery of imipramine also stemmed from research with antihistamines (Healy, 1997). Chlorpromazine and imipramine share a similar chemical structure, and the psychiatric effects of chlorpromazine prompted Roland Kuhn to revisit imipramine, an antihistamine compound he recalled having had interesting properties. Imipramine was trialed on schizophrenic patients with no effect. However, patients suffering depressive symptoms appeared to show signs of remittance, with a restored interest in social interaction and activities. Kuhn noted that it sometimes took four weeks to see the effects, which was notably different from the psychosis-lifting effects of chlorpromazine, which were typically evident within an hour. Kuhn described the antidepressant effects of imipramine. While his reports contained no quantitative data, he described the "potent antidepressant action" (Kuhn, 1958, p. 464) he observed in patients, who were, sometimes within days, cured of their depression. The pharmaceutical company Geigy did not think there was much point pursuing the development of imipramine because, unlike schizophrenia, there were simply not enough depressed patients to make it worthwhile. Eventually, it was a Geigy board member, whose wife had successful remission of depression using imipramine, who convinced Geigy to market the drug (Healy, 1997).

Iproniazid as an antidepressant was discovered independently at virtually the same time as imipramine (Healy, 1997). In World War II, German rockets were powered by oxygen and ethanol, but by the end of the war, they were running low on these chemicals. The Germans produced hydrazine to use as rocket fuel, and there were massive stocks left over at the end of the war. Pharmaceutical companies benefited; hydrazine was a compound that could be altered

to produce a series of chemical derivatives, and some of these derivatives were tested as a treatment for tuberculosis. Iproniazid, one of the derivatives, was found to be an effective treatment, and was released as a tuberculostatic in 1952. Physicians became aware of the mood elevating properties when treating sick patients, and researchers subsequently examined the chemical properties (Loomer, Saunders, & Kline, 1957). Research demonstrated iproniazid to be useful for treating certain forms of depression. Like Geigy, the pharmaceutical company Roche was reluctant to market iproniazid, but since the pills were already being pressed and distributed as a tuberculostatic, they felt the risk was minimal (Healy, 1997).

It was the next antidepressant to come on the market, amitriptyline, that made a real impact (Healy, 1997). First trialed as a treatment for schizophrenia in 1958, clinicians noticed amitriptyline had similar effects to imipramine. In 1961, Merck released amitriptyline as an antidepressant. Merck, unlike Geigy and Roche, took a proactive marketing approach. Frank Ayd had recently published a book, *Recognizing the Depressed Patient*, which described depression as common and easily diagnosed in primary care. Merck bought 50,000 copies of the book to distribute to physicians as promotional material. Amitriptyline became the best-selling antidepressant at the time, and perhaps more significantly, it opened a new era in the treatment and the understanding of depression (Healy, 1997).

Moncrieff (2008), in an historical analysis of the rise of the antidepressant as a medical concept, argued that the discipline of psychiatry was transformed in the 1950s with the invention of the antidepressant drugs. During the 1950s and 1960s, the drugs we now know as antidepressants were increasingly viewed as drugs that counter or correct an underlying disease state, rather than as drugs that induce abnormal states that produce beneficial results in psychiatric symptoms, such as sedation or stimulation (Moncrieff & Cohen, 2006). Searching MEDLINE articles from 1957 to 1965, Moncrieff (2008) reported that the term 'antidepressant' went from being mentioned in a handful of articles in 1958, to over 100 in 1959, and 500 to 600 articles in 1963 to 1965. The concept of an antidepressant as a disease-specific drug grew in popularity despite a lack of understanding regarding the underlying pathology of depression and a lack of evidence that the drugs had disease-specific effects (Moncrieff, 2008).

The discovery that certain drugs seemed to have antidepressant properties marks an important shift in the etiology of depression. Previously, etiological understandings were proffered and treatments followed. In the 20<sup>th</sup> century, scientists, encouraged by the clinical effects these drugs, turned their attention to studying the mechanisms of action. It was from these empirical efforts that influential hypotheses, such as the monoamine imbalance hypothesis, were offered as explanations for depression.

#### **2.2.4 The monoamine hypothesis.**

Driven by a desire to explain the disease-specific actions of the antidepressants, the monoamine hypothesis of depression, also known as the chemical imbalance hypothesis, was proposed. In a seminal paper, Schildkraut (1965) argued that the antidepressants of the time, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), function by increasing the concentrations of monoamines, specifically the catecholamines, which are epinephrine, norepinephrine, and dopamine, in the synaptic cleft by either preventing enzymes from breaking them down or by preventing their reuptake into the releasing cell. Schildkraut also argued that reserpine, a drug thought to induce a depressed state, functions by reducing levels of norepinephrine available in the synaptic cleft. Schildkraut proposed norepinephrine as

the main catecholamine responsible for depressive states. Two years later, Coppen (1967) similarly argued that a lack of serotonin at important receptor sites in the brain was responsible for depression. Like Schildkraut, a core tenet of his argument was that reserpine depletes monoamines, and that if a person without a psychiatric illness takes reserpine, he or she will “suffer from a depression not distinguishable from severe endogenous depression” (Coppen, 1967, p. 1258).

Schildkraut (1965) and Coppen (1967) both admitted that the evidence supporting the hypothesis that depression is caused by a deficiency of norepinephrine and/or serotonin at certain receptor sites in the brain was preliminary and incomplete. Schildkraut wrote, “Although the hypothesis may not be directly testable by currently available experimental methods, this formulation is nonetheless of considerable heuristic value” (Schildkraut, 1965, p. 509). Coppen wrote, “the weight of evidence, although it is by no means conclusive, suggests that biochemical changes are the most important in the aetiology of affective disorders” (Coppen, 1967, p. 1237), but concluded, “we must face the very real possibility that we are far from the primary disturbance in depression” (p. 1258). Thus, these scientists, while convincing in their argument in support of a monoamine/catecholamine hypothesis of depression, cautioned that the hypothesis might be incorrect.

The shortcomings of the monoamine hypothesis of depression have been well documented (e.g., Bentall, 2009; France, Lysaker, & Robinson, 2007; Healy, 1997; Kirsch, 2010; Leo & Lacasse, 2008; Valenstein, 1998; Whitaker, 2010). In a comprehensive review of depression and depression treatments appearing in *Nature Reviews Neuroscience*, Wong and Lucino (2001) wrote that there are “serious gaps and limitations in the monoamine hypothesis” (p. 347), and pointed to research indicating that there is increased norepinephrine output in depression and that antidepressant drugs affect neurotransmitters within hours but treatment of depression takes weeks. In addition, a search for the biological marker of depression, such as depleted monoamines or a defective serotonin or norepinephrine system, has been elusive. Healy (1997) presented additional problems with the hypothesis. He argued that reserpine, the compound that supposedly causes depression by depleting brain amines, was an effective treatment for depression. Isoniazid, a related compound to iproniazid, was also an antidepressant, but unlike iproniazid, isoniazid did not inhibit monoamine oxidase. For the TCAs, animal researchers demonstrated that monoamine levels decreased with chronic usage, and there was no correlation between the amount of reuptake blocked, or enzyme inhibited, with behavioural antidepressant effects (Healy, 1997).

Kirsch (2010), in his polemic against antidepressants, provided a comprehensive argument against the chemical imbalance hypothesis. He argued against the hypothesis, first by undermining the idea that reserpine induces a state of depression, which was presented by Coppen and Schildkraut as an essential piece of evidence for the hypothesis, and by challenging the idea that reserpine depletes monoamines. Kirsch reported that the evidence for reserpine causing a state of depression was based on observational clinical reports, and that when the clinical reports were later analyzed, only 6% of patients on reserpine had developed clinical depression. While this research was presented after Coppen and Schildkraut’s papers, Kirsch (2010) argued that a decade earlier, Davies and Shepherd reported that reserpine was effective as a treatment for depression (Shepherd, 1956). Further, Kirsch argued that Coppen and Schildkraut ignored a key piece of evidence regarding reserpine. Coppen (1967) and Schildkraut (1965) both cited the works of Julius Axelrod, Nobel Laureate, and colleagues, who

demonstrated that imipramine functioned to inhibit the uptake of norepinephrine and serotonin back into the releasing cell (Hertting, Axelrod, & Whitby, 1961). Kirsch wrote that Axelrod, in the same papers cited by Schildkraut and Coppen, had reported that reserpine, amphetamine, and chlorpromazine, in addition to imipramine, reduced the reuptake of serotonin and norepinephrine. Kirsch argued, “acknowledging that reserpine had the same effect as imipramine on the reuptake of neurotransmitters would have demolished one of the two empirical pillars of the theory, the supposed fact that reserpine decreased levels of norepinephrine and serotonin and thereby caused depression (p. 90, Kirsch, 2010). He argued that the scientists in question ignored key evidence contrary to their hypotheses.

Next, Kirsch argued that the chemical imbalance hypothesis is untenable because depleting monoamines such as serotonin does not induce depression. He argued that at least 90 studies have attempted to cause depression symptoms in healthy people by reducing levels of monoamine neurotransmitters in the brain, and that the conclusion is that experimentally decreasing monoamines has no effect on mood. If depression was indeed caused by a deficiency of monoamines, rapid depletion of serotonin and norepinephrine would result in non-depressed participants becoming depressed.

Kirsch (2010) then turned his attention to undermining the other pillar of the chemical imbalance argument: that antidepressants treat the specific disease process underlying depression. Kirsch argued that too many different types of antidepressants work equally well. For example, SSRIs (selective serotonin reuptake inhibitors) and NDRIs (norepinephrine dopamine reuptake inhibitors) are all estimated to work at approximately the same rate – 59% of patients respond to NDRIs and 60% to SSRIs (Kirsch, 2010). Kirsch argued that if each drug treated a specific underlying monoamine pathology, the benefits of these antidepressants would not account for 119% of patients who respond. He further argued that when people fail to respond to an initial antidepressant treatment, they can be switched to a SSRI or a NDRI with equivalent results. He then addressed a potential counter-argument: that some depressed people have a deficiency of serotonin, some norepinephrine, and some both. He argued that, if that were the case, antidepressants that selectively block the reuptake of serotonin and norepinephrine (SNRIs) would be the most effective antidepressant, but data suggest that the treatment response rate is equivalent to the other antidepressants. Kirsch utilized the efficacy equivalence data to support his claim that antidepressants function because they are “active placebos” (p. 96), i.e., antidepressants show benefit over placebo in severe cases of depression because the side-effects of the medication signal to the participant that they are taking the active drug and thereby increase their hope for improvement.

Finally, Kirsch proposed that the chemical imbalance hypothesis is untenable because a recent antidepressant, tianeptine, is a selective serotonin reuptake enhancer (SSRE). According to the hypothesis, tianeptine should induce depression. In clinical trials, tianeptine produced an antidepressant response in 63% of patients with depression. Kirsch referred to this as “the last nail in the coffin” (p. 96), and concluded that the chemical imbalance hypothesis is an historical relic that was born from a selective presentation of the data and from incorrectly attributing placebo effects to drug effects, and propagated because of its simple medical narrative. However, researchers have since noted that tianeptine may not act upon the serotonin system at all and suggest that its antidepressant properties are due to action upon the glutamate system (McEwen et al., 2010). Kirsch’s ‘last nail’ may have been based on an inaccurate understanding of tianeptine’s mechanism of action.

Kirsch's argument against the efficacy of antidepressants is controversial and faces considerable challenge from other scholars. In addition, researchers continue to publish analyses claiming that antidepressants are more effective than placebo (Cipriani et al., 2018). However, Kirsch and others' claims against the chemical imbalance hypothesis are, for the most part, accepted as uncontroversial by scientists who study the biological bases of depression. Despite the widespread endorsement of the chemical imbalance hypothesis of depression among the public, the scientific community no longer describes depression as caused by a chemical imbalance of monoamines in the synaptic cleft. It is this disjunction that is the focus of this dissertation.

### **2.2.5 The amine-receptor hypothesis.**

In the 1970s, some difficulties with the monoamine hypothesis led scientists to propose that antidepressants function at the receptor level (Healy, 1997). It was claimed that all antidepressants, including novel drugs whose action was not explained by the monoamine hypothesis, down-regulated beta-adrenergic receptors (e.g., Extein, Tallman, Smith, & Goodwin, 1979; Siever & Davis, 1985). This action took approximately two weeks, which could account for the delayed onset of antidepressant effects. Healy (1997) reported that the receptor research was limited, mostly by an inability to clearly distinguish proper receptors (those that elicit change) from proteins that drugs bind to but are not receptors, and a difficulty detecting small amounts of receptors and neurotransmitters in specific areas when they are present all over the brain. Wong and Lucino (2001) summarized that theories which proposed long-term changes in receptor sensitivity have been unsuccessful.

### **2.2.6 Genetics and heritability hypotheses.**

Genetic factors have long been purported to play an important role in depression. Rees (1960) wrote, "Depressive illnesses are the resultant of the interaction of genetic and constitutional factors on one hand with environmental and other exogenous influences on the other" (p. 114). Based on data from twin studies, the heritability of depression is estimated to account for approximately 30 to 42 percent of the lifetime risk for developing depression (Kendler, Gatz, Gardner, & Pedersen, 2006). Unlike disorders that display classic Mendelian inheritance, such as Huntington's disease, depression is a genetically complex disorder, similar to heart disease and diabetes. Although depression has been long assumed to be caused by the interaction of environmental stressors and genetic vulnerability (e.g., Lewis, 1934), there has been no confirmed or replicated genetic association.

The most extensively studied gene potentially related to depression is 5-HTTLPR, which is responsible for promoting the coding of the serotonin transporter protein. Serotonin transporter is responsible for the reuptake of serotonin at synapses. The 5-HTTLPR gene has several variants, but it is generally categorized into long or short allele variants, with the long/long genotype associated with greater transcriptional efficiency of serotonin transporter when compared to the short/long or short/short genotype (Caspi et al., 2003). Caspi et al. (2003) proposed that depression is caused by an interaction of stressful life events and a genetic vulnerability, specifically two short alleles or one short allele at the promoter region of 5-HTTLPR. They argued that individuals who have two short alleles display more self-reported and informant-reported depressive symptoms, higher probability of suicidal ideation, and higher probability of meeting criteria for a major depressive episode than those with two long alleles, but that the effect was evident only when accompanied by multiple stressful life events.

A great deal of research attention has been dedicated to studying 5-HTTLPR and the effect of stressful life events. While some researchers (e.g., Kendler, Kuhn, Vittum, Prescott, & Riley, 2005) replicated the Caspi et al. (2003) study, others have not. Risch et al. (2009) conducted a meta-analysis of published data on the association between 5-HTTLPR genotype and frequency of stressful life events. The authors reported that, while stressful life events were associated with depression, the 5-HTTLPR genotype was not associated with depression, even at higher levels of stressful life events. Many replications and meta-analyses followed, with inconsistent results. In an attempt to settle the conflicting results, Culverhouse et al. (2017), working as a large consortium of scientists who had previously published on the topic, reanalyzed a large corpus of published and unpublished data. They reported that there was no evidence for an interaction between stressful life events and 5-HTTLPR genotype. They concluded, “This lack of evidence for a strong, robust effect should be taken into account before planning future research on this topic” (p. 7).

While there appears to be a consistent effect of genetic heritability associated with depression, there has yet to be clear evidence of the genes responsible for depression. Wong and Licinio (2001) had predicted that the advancements in genetic studies would “yield results in the next few years” (p. 349). Despite these new techniques and the mapping of the genome, the specific genetic vulnerabilities remain elusive.

### **2.2.7 The neuroendocrine hypotheses.**

Stress is considered a risk factor for developing a number of distinct mental illnesses, including depression. The hypothalamic-pituitary-adrenal (HPA) axis is implicated in the body’s response to stress, which involves a cascade of hormones released from the hypothalamus to the pituitary gland, and from the pituitary gland to the adrenal cortex, where the hormones cortisol and corticosterone are released. The HPA axis is central to the body’s sympathetic, or fight-flight response. Sustained elevated activity of the HPA axis can lead to hypercortisolaemia, which is associated with disturbances in anxiety regulation and monoaminergic systems, cognitive impairments, and volume reductions in limbic brain structures, similar to those observed in depressed individuals (de Kloet, Joels, & Holsboer, 2005).

Among the correlational data for stress as a risk factor in the etiology of depression is the impaired suppression of cortisol following an injection of dexamethasone, a synthetic form of cortisol. The dexamethasone suppression test typically involves an injection of dexamethasone followed by a measurement of cortisol levels 12 to 24 hours later; persons with depression tend to have higher cortisol levels following the test than persons without depression, which is thought to indicate a hyperactive HPA axis (Stetler & Miller, 2011). Once thought to be a potential diagnostic biomarker for depression, the dexamethasone suppression test lacked the specificity to differentiate depression from comorbid conditions such as Alzheimer’s disease, alcohol withdrawal, obsessive compulsive disorder, and schizophrenia (Nierenberg & Feinstein, 1988). However, the effect of the dexamethasone suppression test suggests the presence of HPA axis disturbances in persons with depression when compared to non-depressed individuals (de Kloet, Joels, & Holsboer, 2005). After a comprehensive meta-analysis of studies assessing depression and stress hormones, Stetler and Miller (2011) concluded that HPA hyperactivity in depression varies across patient groups and depression subtypes, with the greatest effect observed in older patients with more severe symptoms.

Stress as a risk factor for depression is present in most models of depression, and acute and chronic stress is widely used as a precipitant of depression-like behaviour in animal models of depression (e.g., forced-swim test; tail-suspension test; social-defeat stress; chronic restraint stress). Acute stress models such as the forced-swim test were developed to test the efficacy of antidepressants and aid the search for new antidepressants (e.g., Porsolt, Le Pichon, & Jalfre, 1977). However, in acute stress models, antidepressant administration was observed to rapidly reverse the effect of the stress (i.e., immobility or ‘behavioural despair’), whereas in human patients antidepressants are known to take several weeks for effects to be observed. Later, chronic stress models, such as chronic social defeat stress (e.g., Tsankova et al., 2006) and chronic unpredictable stress (e.g., Monteiro et al., 2015), were preferred due to observations that these chronic stress models produced depression-like behaviours (i.e., lack of interest in novel or sweet foods; social avoidance) that were not rapidly ameliorated by antidepressant administration, but rather required chronic antidepressant administration. Current pre-clinical animal models of depression utilize chronically administered stressors to precipitate depression-like behaviours, and are a foundation for experimental studies of depression, and signal the primacy of stress as a precipitator of depression.

In summary, stress has been shown to affect the neuroendocrine system, which involves the hypothalamus and pituitary gland in the brain and the adrenal cortex in the adrenal glands, and is a risk factor for developing depression. The data are correlational in humans but preclinical researchers use stress as a causative precipitant of depression-like behaviour in animal models. However, research examining the primacy of the body’s response to cortisol as a biomarker for depression has not produced firm, replicable results.

### **2.2.8 The neuroplasticity hypotheses.**

Neuroplasticity is an umbrella term that describes the brain’s ability to adapt and change, functionally and structurally, to environmental stimuli and experiences throughout the lifespan (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Synaptic plasticity and neurogenesis are two forms of neuroplasticity. Synaptic plasticity refers to the strengthening and weakening of neural connections in the brain based on the activity of neurons, and is most apparent during neural development. Neurogenesis refers to the creation of neurons and is also most apparent during early development. Synaptic plasticity and neurogenesis, once thought to be principally the domain of early development, are also present in adulthood, and are often implicated in the pathophysiology of depression

Neuroscientists have stated that “the cause of depression is far from being a simple deficiency of central monoamines” (Krishnan & Nestler, 2008, p. 895), but monoamines such as serotonin may still play an important role. Krishnan and Nestler (2008) summarized that an increase in monoamines after administration of an antidepressant eventually influences neuroplasticity, which may account for the therapeutic delay of antidepressants. Kraus, Castrén, Kasper, and Lanzenberger (2017) argued that the interaction of serotonin and its receptors with proteins supporting synaptic plasticity and neurogenesis might contribute to the cause of depression.

Castrén (2005) presented the network hypothesis of depression and he proposed that increased monoamines in turn have an impact on the plasticity of the brain. The network hypothesis attempts to bring in brain development for a more encompassing understanding of depression. Serotonin and other monoamines contribute significantly to brain development, and

in critical periods, long-term structural adaptations create relatively stable information networks. The monoamine hypothesis does not incorporate the effects of development, while the network hypothesis places them in the domain of activity-dependent modification. The adult brain, while not as structurally plastic as the developing brain, continues to change in an activity-dependent fashion susceptible to environmental influences. Antidepressants are hypothesized to function by improving the activity-dependent state of the brain by increasing synaptic plasticity and neurogenesis.

While Castrén (2005) admitted that supporting evidence is “limited and mostly indirect” (p. 242), he argued that the best evidence to support the network hypothesis is the discovery that antidepressants increase hippocampal neurogenesis in rodents. Castrén purported that the newborn neurons correlate with the behavioural effects seen with antidepressants, and the delayed onset of antidepressant effects is due to the time it takes new neurons to be integrated and functioning in a network. The increased proliferation of neurons is accompanied by increased apoptosis (the death of cells that occurs as part of normal development), so rather than creating additional neurons to the network, Castrén hypothesized that antidepressants enhance the efficiency of information networks through activity-dependent plasticity, increasing the connectivity of neurons while selectively trimming defective neurons.

Castrén (2005) posited that brain derived neurotrophic factor (BDNF), which plays a role in the maintenance of neurons and the survival of new neurons, was a possible mechanism for altering activity-dependent neural plasticity. Krishnan and Nestler (2008) summarized the support for the BDNF hypothesis of depression, noting that scientists have measured reduced postmortem hippocampal BDNF in people who were depressed, reduced BDNF expression following chronic stress in animal models of depression, and increased BDNF expression following antidepressant treatment in animal models of depression. However, Krishnan and Nestler (2008) reported that the research on BDNF and depression is complex and sometimes contradictory, and they concluded that “BDNF-mediated signaling is involved in neuroplastic responses to stress and antidepressants, but these effects are both region-specific and antidepressant specific and function in the background of other potent genetic and environmental modifiers” (p. 897). Much like the monoamine hypothesis, the BDNF hypothesis does not provide an overall explanation for the underlying cause of depression, but does demonstrate the complexity of the disorder.

Over the past two decades, the drug ketamine, an anesthetic drug known to inhibit *N*-methyl-D-aspartate (NMDA) glutamate receptors, has gained attention for its rapid antidepressant effects in patients with treatment-resistant depression (e.g., Berman et al., 2000; Zarate et al., 2006), and scientists have posited that the antidepressant effect is due to increased synaptic plasticity (Krystal, Sanacora, & Duman, 2013; Zanos & Gould, 2018). Li et al. (2010) argued that, in an animal model, ketamine administration rapidly increases synaptic plasticity through enhancing the number and function of dendritic spines. Krystal et al. (2013) summarized that ketamine might function as an antidepressant by disinhibiting glutamate, sending off a signaling cascade stemming from an increase in alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and a decrease in NMDA receptors. They proposed that AMPA receptors stimulate the mammalian target of rapamycin (mTOR) pathway while decreased NMDA receptors suppress BDNF levels, and both contribute to a rapid increase in dendritic spines. Ketamine, a rising star among depression treatments, appears to enhance neuroplasticity and overcome the effects of stress on the brain.



The scientific accumulation of evidence for neurogenesis and neuroplasticity displaced the previously common conception that the structure and function of the brain was generally fixed throughout adulthood. These concepts have been applied in an attempt to explain the causes of depression, but much remains unknown. Like the monoamine hypothesis, the network hypothesis of Castrén utilizes the scientific understanding of the brain at the time to hypothesize about the nature of depression. And like Schildkraut and Coppen, Castrén has used cautious language to present the idea. As scientists gain new insights and knowledge into how the brain works, we can expect additional hypothesizing about the causes of depression.

### **2.2.9 The neuroimmunity hypothesis.**

Another recent proposal for the pathophysiological mechanism of depression involves inflammation and the immune response. Wong and Lucinio (2001) described the immune system as a “key mediator of brain-body interactions” (p. 348), and reported that cytokines, small signaling proteins created by immune cells, influence a number of basic functions that are disturbed during a depression, namely sleep, appetite, and cognition. Krishnan and Nestler (2008) summarized that cytokines appear to influence mood in humans and rodent models, but that the effect is inconsistent, and the neural circuitry and pathways to behaviour are largely unknown. Hodes, Kana, Menard, Merad, and Russo (2015) reviewed the scientific evidence from studies with humans and animal models of depression and proposed that neuroinflammation contributes to the precipitation of a mood disorder.

Michal Schwartz (2015) argued that the immune system is a central component in the functioning and homeostatic maintenance of the brain. She proposed, “Immune cells control formation of the brain’s stem cells, shape cognitive performance such as learning and memory, and affect our mood and our ability to cope with stress” (p. 13). She hypothesized that the immune system interacts with the brain during stress response and is central to fighting the neuropathology induced by chronic stress states, which includes depression and anxiety.

Schwartz (2015) argued that during acute stress, immunity is boosted in the short term, fear response is decreased, and physical/mental performance is increased. In support of this contention, she referred to research with immune deficient mice, who, after exposure to an acute stress, displayed an increased fear response and a longer lasting startle response. She equated the anxious and avoidant behaviour observed in the mice to individuals experiencing post-traumatic stress disorder (PTSD), and suggested that the immune system may play a key role in protecting an individual from developing PTSD. Further, she argued that the immune response assists the brain in restoring levels of BDNF, a protein responsible for cell growth and survival, and critically important for neurogenesis and synaptic plasticity. Thus, the immune system, under periods of acute, short-term stress, might facilitate recovery.

With regard to chronic stress, Schwartz (2015) argued that long-term, unrelenting stress disrupts the immune response by reducing the number and quality of immune cells available. She cites evidence in rodent and human studies of increased susceptibility to disease under states of chronic stress, and concludes that chronic stress creates a “vicious cycle” (p. 69) by reducing the body’s ability to recover from stress and in turn rendering the body less capable of dealing with future stressors. She suggested that restoring or improving immune response might be the key to treating depression.

The immune system plays a significant role in the brain, and inflammation and immune response may be an etiological factor in the development of depressive illness. The idea that

depression recovery could be facilitated through improving immune response and reducing inflammation is a novel approach but it is not yet clear what novel treatments this hypothesis will lead to. Implicating the immune system as among the causes of depression, and linking the immune system response to other factors in the development of depression, such as BDNF production and synaptic plasticity, appears to position the immune system as a mediator of disease and recovery in depression.

#### **2.2.10 Summary of biologically-based etiological explanations.**

Current scientific thought and research on depression etiology demonstrates that it is likely caused by a complex interaction of environmental and constitutional factors, genetic vulnerabilities, neuroplasticity, neurotransmitter functioning, endocrine functioning, and immune functioning, that are not fully understood. The hypothesis that depression is caused by a deficiency of serotonin and norepinephrine at the synapse has been displaced by more complex explanations and explorations of the biological effects of stress and antidepressant medications. Despite the accumulation of knowledge surrounding depression, much remains to be known. I agree with Kendler (2012), who described these potential causes and interactions as “the dappled nature of causes of psychiatric illness” (p. 377), and proposed that researchers must attend to the widely-distributed causes, from molecules to culture, of illnesses such as depression.

### **2.3 Additional Factors in the Etiology of Depression**

#### **2.3.1 Biopsychosocial model.**

The biopsychosocial model provides clinicians with a framework to conceptualize illnesses that have widely-distributed causes and risk factors. Engel (1977) proposed the biopsychosocial model as a way for psychiatry to integrate the biomedical model, which he argued is inadequate for understanding psychiatric presentations, with psychosocial factors. Engel argued that the reductionistic biomedical model fails to account for the presentation and subjective experience of illness, which is influenced by biological, individual, and social factors in a complex interaction. The biopsychosocial model encourages clinicians to consider multiple factors to guide treatment to the specific needs of the patient (Borrell-Carrio, Suchman, & Epstein, 2004). In the sections below, I present some of the psychological and social factors that are associated with depression.

#### **2.3.2 Psychological factors.**

In the early 20<sup>th</sup> century, thoughts in psychiatry about the etiology of depression were dominated by psychoanalytic explanations, and psychological explanations in general were more prominent throughout the century than at any other point in history (Jackson, 1986). Psychoanalytic theorists posited that melancholia or depression was caused by inadequate nurturing in infancy and childhood, and Freud (1957) described melancholia as a type of mourning for the loss of a love-object. Research conducted after the psychoanalytic heyday has since suggested that early loss in life, such as the death of a parent, especially a mother, before the age of 9, increases vulnerability to developing psychiatric disorders such as Major Depressive Disorder later in life (Agid et al., 1999). Psychological theories of the causes of depression typically follow a diathesis-stress model of illness, which posits that illness is caused by the interaction of an underlying vulnerability with stressful life events (Schotte, Van Den Bossche, De Doncker, Claes, & Cosyns, 2006).

Aaron Beck's (1979) cognitive model of depression has been extremely influential in medical discourses of depression. It contends that depression is caused by the combination of maladaptive schemas, which are patterns of thought that organize and categorize experience regarding the self, the future, and the world, automatic negative thoughts about the self, and stressful life events (Dozois & Beck, 2008). The cognitive model of depression proposes that these psychological vulnerabilities interact with precipitating stressors to produce emotional dysregulation and symptoms of depression. Cognitive Behavioural Therapy, based on Beck's model, is frequently referred to as the default psychological treatment for depression.

Another prominent evidence-based treatment for depression is Interpersonal Therapy. The interpersonal model of depression (Coyne, 1976; Evraire & Dozois, 2011) posits that individuals that are susceptible to developing depression engage in excessive reassurance seeking, i.e., repeatedly seeking affirmations from others about their worth. When others respond with support and reassurance they doubt the sincerity and continue to seek reassurance, placing a burden on the relationship, which deteriorates. Close and supportive relationships are a protective factor for depression (Evraire & Dozois, 2011). Like the cognitive model of depression, the interpersonal model constructs depression as a result of diathesis-stress.

### **2.3.3 Social factors.**

Researchers studying the link between adverse life events and depression have noted a strong correlation between serious losses, traumatic events, and other acute and chronic stressors. In a review of the research literature on the role of stress, Harkness (2008) concluded that stressful life events are strongly associated with the onset of depression, especially three to six months prior to a depressive episode, among individuals who have a genetic vulnerability, an experience of childhood adversity, and/or a cognitive vulnerability. Early life experiences such as loss of a parent, inadequate parenting, and abuse and neglect, result in a greater risk of developing depression later in life (Goodman & Lusby, 2015).

Exposure to a wide-range of social factors, often referred to as the social determinants of health, are associated with increased risk of depression. According to the Canadian Mental Health Association (n.d.), the social determinants of health in Canada include aboriginal status, disability, early life experience, education, employment conditions, food insecurity, health services, gender and gender identity, housing, income and income distribution, race, sexual orientation, social exclusion, social safety net, and unemployment and job security, with freedom from discrimination and violence, social inclusion, and access to economic resources being particularly salient for mental health. The World Health Organization (2014) has argued that improving mental health outcomes will require a reduction in social inequality, discrimination, and poverty across the lifespan of individuals.

## **2.4 Summary**

While depression appears to be caused by an interaction of multiple biological, psychological, and social factors, the idea that depression is caused by a chemical imbalance in the brain remains prominent in Canadian and American society. Next, I present the framework that guided my research and analysis (Chapter Three), and then, in Chapters Four and Five, I present my discursive analyses of talk of etiology and the chemical imbalance hypothesis that was generated in interviews with family physicians and scientists.

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## **Chapter Three: General Methods for Manuscripts 1 and 2**

### **3.1 Analytical Perspective: Discursive Psychology and Social Constructionism**

The following research is situated within the theoretical perspective of discursive psychology, with an epistemological position consistent with social constructionism (Edley, 2001; Potter, 2003). According to social constructionists such as Gergen (1985) and Burr (1995), knowledge is built and shared in social interactions; objective reality is unknowable because any form of knowing requires language and the perception of the human mind, and one can never separate oneself from the object of study. Rather than language being representative of reality or of the thoughts, beliefs, and attitudes of the speaker, language is conceptualized as a performative social action (Burr, 1995). With regard to ontology, social constructionists do not deny the existence of a reality outside of language, but instead focus upon the epistemic position that discourses construct and constrain versions of reality (Edley, 2001). This social constructionist position informs my discursive analysis.

The analytical perspective for this dissertation is located in discursive psychology, which is a discipline that applies concepts and ideas from discourse analysis to questions in social psychology (Potter, 2003; Potter & Wetherell, 1987). Discourse analysis in social psychology (DASP) involves a systematic examination of how language communicates content and performs functions, while drawing attention to contradictions and assumptions within a text (Wood & Kroger, 2000). DASP involves examining accounts for content, the style in which participants construct and present the content, and the social actions that it performs (Wood & Kroger, 2000). The goal of a DASP is to demonstrate how talk and text is structured to accomplish various effects or consequences. Consistent with social constructionism and DASP, I maintain that we are born into already-discoursed worlds and that we orient to these discourses in daily life, perhaps by agreeing with, disagreeing with, and/or nuancing the discourses. While my analysis focuses on particular statements from the interviewees, I assume that the interviewees' advocacy for a particular stance derives from their orientating to socially-available discourses.

The study of persuasive rhetoric has an ancient history. Aristotle (trans. 2007) promoted the systematic study of the art of rhetoric, which he defined as an ability to see all possible means of persuasion for a particular case, and classified rhetorical strategies as appeals to the character of the speaker (ethos), appeals to logic (logos), and appeals to emotion (pathos). Billig (1996), drawing upon the work of the ancient scholars, proposed that a rhetorical approach to social psychology involves an examination of how people construct arguments for and/or against issues of contention. Billig stated that "a basic rhetorical motive... is the motive to justify a position and ward off criticism" (p. 191). In the analyses, I make inferences about possible functions for the use of specific rhetorical strategies and means of persuasion.

#### **3.1.1 Social construction of depression.**

I rely on social constructionism to inform my perspective on the diagnosis and etiology of depression. The current diagnosis of depression is a construct created in social interaction and is historically and culturally produced. Horwitz (2011) detailed the social and contextual forces that led to the creation of the diagnosis known as Major Depressive Disorder. He noted that research-oriented clinicians gained a foothold within the American Psychiatric Association in the 1970s and displaced the traditional psychoanalytic practitioners in the decision-making processes. He also noted that the diagnoses were created during a time of competing interests from other disciplines, such as social work and psychology, and criticisms of psychiatric

diagnostic validity. Horwitz argued that the diagnostic system introduced in DSM-III was created to provide legitimacy and to align psychiatry with the other medical specialties. He argued that the consequences of this redefined diagnosis of depression were the vast proliferation of the diagnosis of depression, including the medicalization of sadness and short-lived reactions to stressors, and the rise in antidepressant use by encompassing a vast array of symptoms that responded to antidepressant medication. By aligning with this perspective, I view the diagnosis and etiological descriptions of depression as contingent upon social and contextual forces.

### **3.2 General Methods of Data Analysis**

In this section I outline my general approach to data analysis for the two studies that follow. Further details regarding the method specific to each study can be found in the respective Method sections. Here I focus on the process of the analyses and provide a description of the link between the methods of the two studies.

I honed my general approach to data analysis through reading articles and methodology texts on discourse analysis in social psychology, participating in research team meetings, and involving myself with the research of my supervisor, Dr. Linda McMullen. Dr. McMullen, along with one of her former graduate students, conducted interviews with family physicians about their diagnostic and treatment practices for depression. My introduction to the family physician interview data occurred in the context of my work as a research assistant that involved checking the fidelity of the interview transcripts, which were transcribed by a typist. I was intrigued by the way the family physicians talked about defining depression and, in particular, how the physicians described using the chemical imbalance explanation with patients. I chose to examine this talk and presented a paper as part of a symposium with Linda McMullen and fellow graduate students at the Canadian Psychological Association Annual Convention (Sigurdson & McMullen, 2010). Concurrently, I was also developing a proposal for a program of research to conduct interviews with scientists conducting neuroscientific depression research.

In the proposal phase of my study with neuroscientists, I conducted a literature review focusing on Western/English approaches to depression. I searched for review articles on depression written in high impact journals such as *Nature*, *Nature Reviews Neuroscience*, *Science*, *Neuron*, et cetera. I focused on review articles because they contained what I deemed to be an appropriate level of detail along with general statements about the state of depression research at a given time. I used some of this content in Chapter 2, *The Diagnosis and Etiology of Depression in Canada and the United States of America*. I also read articles and books critiquing neuroscience and biological psychiatry in order to hear dissenting voices and to begin to understand the main challenges and dilemmas in the fields of clinical neurosciences and biological psychiatry. Brief reviews of those writings pertinent to the research questions posed in Studies 1 and 2 are in their respective literature review sections. The literature informed my creation of a semi-structured interview schedule with follow-up prompts to interview neuroscientists for Study 2.

Analyses of both sets of data started with listening to the audio recordings and, in the case of the physician interviews, verifying the transcripts. While I had done a preliminary analysis of the family physician data presented in Study 1, it was not until after transcribing the neuroscientist interviews that I chose to return to those transcripts for further analysis. After conducting the neuroscientist interviews, I listened to the audio recordings of them several times before transcribing the interviews verbatim. I approached the listening and reading of the

transcripts broadly, noting questions or concerns that struck me as intriguing (McMullen, 2011). Several of the questions posed of the neuroscientists concerned dilemmas in research and controversies in the field with one follow-up prompt where I specifically oriented the interviewees to comment on the pervasiveness of the chemical imbalance hypothesis of depression among laypersons and clinicians. Out of all the potential directions I considered for detailed analysis, I found the responses to questions regarding the chemical imbalance hypothesis most intriguing and began noting sections of the interviews relevant to the topic. I was interested in how the interview data generated with the scientists compared to the data I had chosen to analyze from the interviews with family physicians, so before continuing the analysis of the scientist interviews, I returned to my analysis of the family physician interviews and to the complete set of audio recordings and transcripts.

I was principally interested in how the physicians and neuroscientists accounted for their use of the chemical imbalance hypothesis of depression or other explanations, the persuasive rhetorical features of the discourses, and the functions achieved by these accounts (Billig, 1996; Wood & Kroger, 2000). My analysis of the family physician data was done with printed transcripts and printed quotations, while I chose to work mostly paperless using NVivo software for the analysis of neuroscientist data. NVivo is program for qualitative researchers working with text and multimedia data to assist in the storage, organization, categorization, and visualization of data (QSI International, n.d.). I chose to use NVivo software for the analysis of the second study because it allowed for more efficiency in transitioning between specific quotations chosen for further analysis and the entire corpus of interview data, and for searching keywords within the transcripts. I employed the software in a manner consistent with the way I conducted the analysis of family physician data; for example, multi-coloured sticky tabs were replaced with NVivo “nodes.”

The analysis proceeded similarly for each set of interviews. In general, I noted sections of the transcripts related to talk of etiology and the chemical imbalance hypothesis and printed or tagged all relevant content. I read and re-read the content many times, returning to the whole transcript and occasionally the audio data in an iterative fashion. I compared and contrasted discursive patterns across participants and attended to content, style, interpretative repertoires, and forms of arguments (McMullen, 2011). I grouped the quotations into discursive themes and eventually eliminated those that I deemed did not add anything further to the analyses, such as a repetition, which was a process that developed during the writing of the analyses. I reorganized the presentation of interview extracts several times and continued writing and rewriting the analyses until I was satisfied that I had produced an account of the discourses, grounded in the interview data, that addressed my research questions (Kelley, 2002).

Supervision with Dr. McMullen and research team meetings with her and fellow graduate students contributed immensely to the analysis. Interview extracts I chose for further analysis and my interpretations and assumptions were discussed in research team meetings and in individual supervision meetings. Individual supervision also involved written commentary with suggestions for further analysis and ways to rhetorically focus the arguments I was trying to make. Discussing and defending the analyses in these socially mediated ways helped me to clarify and refine the interpretations within.

In the following two studies and general discussion, using interview data with family physicians and neuroscientists studying depression, I demonstrate the discursive resources they draw upon to construct persuasive arguments about depression and the chemical imbalance

hypothesis, and the functions achieved by such arguments. I argue that the discourses that the family physicians take up demonstrate how they utilize the chemical imbalance hypothesis to motivate their patients to take antidepressants, reduce self-blame and stigma, build knowledge in the community, and promote hope and confidence in the treatment. I argue that the discursive constructions of the neuroscientists demonstrate how the notion of a chemical imbalance in the brain can be maintained or denied by constructing the chemical imbalance in general or specific ways. Ultimately, I conclude that despite the limitations of the chemical imbalance hypothesis, the discourses espoused by scientists and family physicians suggest that there is value and veracity to maintaining some aspects of the chemical imbalance explanation, while augmenting the explanation with new ideas from the science of depression.

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## **Chapter Four: Manuscript One**

### **Explaining depression: A discourse analysis of family physicians' accounts of explanatory models and the chemical imbalance hypothesis of depression**

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## 4.1 Introduction

Depression is a common and disabling condition that affects an estimated 350 million people worldwide (World Health Organization, 2015). In terms of healthy years lost to a disability, depression is the leading cause of disability worldwide and has been described as “the biggest blight on human society – bar none” (Nature, 2014, p. 163) and a “global crisis” (World Federation for Mental Health, 2012, p. 1). A diagnosis of Major Depressive Disorder is marked by low mood, loss of interest or pleasure in activities, disturbed sleep and appetite, decreased energy, and feelings of guilt or low self-worth, that persist for at least two weeks and are accompanied by distress or impairments in important areas of functioning (American Psychiatric Association, 2013). Depression is also associated with an increased risk of suicide (Ferrari et al., 2013).

In Canada, depression is commonly diagnosed by family physicians. In 2014, there were 8.5 million office visits for depression (IMS Health, 2015). Office visits for depression grew by 60% between 1995 and 2004, which resulted in depression being the fastest rising diagnosis in Canada (IMS Health, 2004). While the rate of increase has somewhat leveled-off since 2004, depression remains the third most frequent reason for a physician visit in Canada, preceded only by hypertension and diabetes mellitus (IMS Health, 2015).

Antidepressants are a standard treatment for depression, with office-based physicians making drug recommendations in 83% of the visits for depression in Canada (IMS Health, 2015). Canadians are among the highest users of antidepressants in the developed world, with 85 daily doses taken per 1000 people (Organization for Economic Co-operation and Development, 2015); monthly antidepressant use in Canada increased 11% from 2005 to 2011 (Mamdani & Wilby, 2013). In a Canadian population-based survey, antidepressants were the leading class of medication used by women between the ages of 25 to 79, with 13.7% of respondents reporting having taken an antidepressant between 2007 and 2011 (Rotermann, Sanmartin, Hennessy, & Arthur, 2014). Overall, antidepressants are ubiquitous in the treatment of depression.

While patients report preferring psychosocial interventions to pharmacotherapy (Deacon & Abramowitz, 2005), and psychotherapy is at least as effective as antidepressants for Major Depressive Disorder (Cuijpers, van Straten, van Oppen, & Andersson, 2008) and may offer an advantage with regard to remission after discontinuation (Parikh et al., 2009), access to psychotherapy in Canada is limited (Romanow & Marchildon, 2003; Grenier, Chomienne, Gaboury, Ritchie, & Hogg, 2008; Anderssen, 2015). Physicians have reported that when considering referrals for psychotherapy, out-of-pocket expense is a significant barrier for many patients (Grenier et al., 2008). The majority of psychologists in Canada work in private practice, where patients pay through health insurance benefits, employee assistance programs, or out-of-pocket; publicly employed psychologists often have waitlists of one year or longer. Thus, while psychosocial interventions may be preferred, many Canadians do not have timely access to these types of treatments.

### 4.1.1 The Chemical Imbalance Hypothesis

The chemical imbalance hypothesis of depression claims that depression is caused by a deficiency of neurotransmitters. In 1965, Joseph Schildkraut put forth the catecholamine (i.e., epinephrine, norepinephrine, and dopamine) hypothesis of depression. He argued that the mechanism of function of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors

(MAOIs) was to increase synaptic concentrations of the catecholamines by preventing enzymes from breaking them down or preventing their reuptake back into the releasing cell. Schildkraut wrote, “some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain” (Schildkraut, 1965, p. 509). Two years later, Alec Coppen proposed that serotonin depletion was also associated with depression (Coppen, 1967). The two authors provided similar arguments from their summary of the literature: the drug reserpine markedly reduced serotonin and norepinephrine levels and appeared to cause depressive symptoms, while the antidepressants of the time increased levels of these neurotransmitters in laboratory studies and appeared to reduce depressive symptoms among patients. Serotonin later gained primacy and the Selective Serotonin Reuptake Inhibitor (SSRI) medications were invented to counter the proposed chemical imbalance of serotonin (Healy, 1997).

Healy (1997), a psychiatrist and psychopharmacologist who is known for his critique of antidepressants and pharmaceutical marketing practices, stated that the popularity of a theory does not necessarily rest on its ability to convey an absolute truth, but rather, the truth that people are looking for at the time. The chemical imbalance hypothesis of depression explained a possible mechanism by which antidepressants functioned and provided physicians with a simple narrative to explain depression and its treatment to patients. However, the hypothesis could not predict many effects. Most notable is that, while antidepressants often take two to six weeks to bring about change, monoamine levels in the brain are altered within an hour (e.g., Wong & Lucinio, 2001). In addition, a search for the biological marker of depression, such as a defective neurotransmitter system, has proven fruitless. Lately, research into the efficacy of ketamine as a treatment for depression, which acts on the glutamate system (glutamate is a wide-spread excitatory neurotransmitter involved in many physiological functions) rather than on the serotonin system, suggests that it is a more effective antidepressant than SSRIs (Healy, 2015). Additionally, while the SSRIs produce fewer side-effects and are less lethal if the patient attempts suicide by overdose, the chemical imbalance hypothesis has not resulted in a more effective antidepressant than the original tricyclic antidepressants (TCAs; e.g., Geddes, Freemantle, Mason, Eccles, & Boynton, 2000). The chemical imbalance explanation of depression, when referring to a deficiency of monoamines, does not appear to fully account for the etiology of depression.

#### **4.1.2 Chemical Imbalance: Patients**

For many years, the pharmaceutical industry promoted the position that depression is caused by a chemical imbalance in the brain that can be corrected with medication (Leo & Lacasse, 2008). While direct-to-consumer pharmaceutical advertisements no longer refer to depression being caused by a chemical imbalance (Lacasse & Leo, 2015), the effect has been a widespread adoption of the chemical imbalance explanation of depression among laypersons. The chemical imbalance hypothesis, despite a lack of scientific support (Lacasse & Leo, 2016; Schultz, 2015), is “the potentially dominant cultural story of depression” (p. 411, France, Lysaker, & Robinson, 2007). In a 2006 study, 80% of a sample of American adults who were read a vignette describing a person with Major Depressive Disorder attributed the condition to a chemical imbalance in the brain, up from 67% in 1996 (Pescosolido et al. 2010). These data suggest that the chemical imbalance hypothesis of depression is being widely endorsed by laypersons as a primary explanation.



Some individuals diagnosed with depression also report that their depression is due to a chemical imbalance in the brain. Cohen and Hughes (2011) were interested in how patients who claimed to have a chemical imbalance justified their position. They examined data from structured interviews with 22 patients that included a question about whether or not medication corrects a chemical imbalance in the brain. According to Cohen and Hughes, many respondents cited the efficacy of medication as evidence of having a chemical imbalance; others stated that they were told so by their physician, and some reported that they had conducted their own research. The authors concluded that patients will continue to draw upon the chemical imbalance explanation to make sense of their condition and their recovery.

Proponents of the biomedical model of mental illnesses have claimed that it will reduce stigma by promoting the view that mental illnesses are medical problems like any other physical disease (e.g., Andreasen, 1985; 2001). However, while biological understandings of mental illnesses are becoming more prominent, stigma has not decreased (Pescosolido et al., 2010). In meta-analyses of research articles examining biological explanations of mental illness and stigma, Kvaale and colleagues (Kvaale, Haslam, & Gottdiener, 2013; Kvaale, Gottdiener, & Haslam, 2013) concluded that biological explanations of mental illnesses were associated with reduced blaming of individuals for their condition, but were also associated with increased perceived dangerousness and a desire for social distance. Speerforck, Schomerus, Pruess, and Angermeyer (2014) reported that chemical imbalance and brain disease explanations of depression were associated with laypersons reporting an increased desire for social distance from people with depression and schizophrenia, with no beneficial effect on stigma. While the claim that biomedical explanations of mental illnesses will reduce stigma appears to be face-valid, the current data do not support the claim.

The chemical imbalance explanation of depression appears to influence patients' views of treatment and foster prognostic pessimism – the belief that one's condition is immutable and that recovery will be difficult. Kemp, Lickel, and Deacon (2014) conducted an experimental study involving undergraduate students who self-identified as having a past or current depressive episode. The researchers administered a “bogus but credible” (p. 48) biological test for depression, which involved swabbing the inner cheek of each participant and claiming to run a laboratory test to determine the participant's neurotransmitter levels. The researchers stated to half of the participants ( $n = 37$ ) that their current or past depressive episode was caused by depleted serotonin and the other half ( $n = 36$ ) were told that all neurotransmitters were in the normal range. All participants completed survey items on causal attributions of depression (e.g., life stress, negative thinking pattern, genetic predisposition, etc.), self-stigma, prognostic pessimism, mood regulation, treatment credibility and expectations, and diagnostic procedure credibility. Only participants who endorsed that they found the diagnostic procedure credible were included in the analysis. The authors reported that there were no differences between the two groups with regard to self-stigma, but stated that the chemical imbalance explanation was associated with greater prognostic pessimism – i.e., participants who received this explanation viewed their depression as more chronic and intractable than did participants who were told that their neurotransmitters were in the normal range – and decreased expectations about personal ability to regulate mood. The chemical imbalance group reported that antidepressant medication was more credible and effective than psychotherapy, while the control group rated medication and psychotherapy to be equally credible and effective. Kemp et al. (2014) concluded that depression should be explained using a biopsychosocial model to reduce the negative effects of an exclusively biological explanation. This research replicated and expanded on prior research,

which claimed to have demonstrated that the chemical imbalance explanation has a negative influence on expectations of prognosis and mood regulation ability (Deacon & Baird, 2009).

Lebowitz, Ahn, and Nolen-Hoeksema (2013) conducted a survey-based experiment with participants recruited online to determine whether providing education about the plasticity of the brain and epigenetic malleability to individuals with depression could promote prognostic optimism and agentic control over negative mood states. After participants completed a symptom checklist for depression and rated how much they endorse biomedical etiology of depression, Lebowitz et al. (2013) displayed an educational video that highlighted that environmental factors and life experiences can influence brain chemistry and genes to a third of the participants. Another third of participants watched a video on the heritability of depression and the differences in the brains of depressed and non-depressed individuals. The final third of participants received no intervention. Participants completed questionnaires assessing expectations of prognosis, agency, guilt, and future outlook. Overall, the authors concluded that endorsing biomedical etiology of depression was associated with prognostic pessimism, but that those who watched the video about the malleability of genes and brain chemistry had lower prognostic pessimism, and increased sense of agency and hope. A more holistic and comprehensive view of depression and biology might hold promise for countering the negative effects associated with the standard biomedical explanation of depression.

The chemical imbalance hypothesis might influence how people understand themselves (Fullagar, 2009; Rose, 2003). Rose (2003) theorized that advances in biotechnologies such as medications for psychiatric disorders are contributing to a “genetic and neurochemical selfhood” (p. 407), where conditions once viewed as being attributed to personality, willpower, or upbringing, are recast as diseases of the brain. Drawing upon the idea of neurochemical selfhood, Fullagar (2009) conducted interviews with a community sample of 80 women who self-identified as recovered or recovering from depression. Fullagar noted that 31 women reported that antidepressant medication was a positive force in their recovery, and she further analyzed these interviews from a critical/Foucauldian discursive perspective. In relation to the chemical imbalance hypothesis of depression, Fullagar argued that these women defined themselves as neurochemically-deficient and, as agentic biomedical consumers, sought to correct their chemical imbalance through medication. Fullagar noted that some of these women referred to the use of antidepressant medication as providing “breathing space” (p. 398) from negative self-evaluations and blame. However, Fullagar reported that the endorsement of biomedical depression discourses did not appear to reduce stigma because women still described themselves as fundamentally flawed and dependent on medication to maintain a sense of normalcy. Negotiating blame and stigma was thus complex and the women were pulled by paradoxical discourses; taking antidepressants provides users the promise of restored function and a sense of control over their lives, but also threatens agency and autonomy with notions of dependency on medication and uncertainty about the recurrence of depression.

In a follow up to her 2009 study, Fullagar and O’Brian (2013) analyzed the interviews of 43 women who reported feeling highly ambivalent about their recovery with antidepressants. The authors noted how some women who described themselves as neurochemically deficient were caught in a difficult situation when the side-effects of the medication were troubling or when multiple medications did not alleviate their depression. In essence, the women constructed the process of redefining their recovery from that of correcting a neurochemical deficiency to that of working on emotional well-being. The authors concluded that the biomedical discourses

of depression functioned to minimize or make invisible the process of working on the emotional-self.

Biological understandings of the self may also lead to neuroessentialist thinking, where a person views all psychological phenomena as dependent on the activity and structure of the brain, and that mental illnesses are associated with abnormal brains (Dar-Nimrod & Heine, 2011; Haslam, 2011; Haslam & Kvaale, 2015). It is theorized that neuroessentialist thinking can lead persons with a mental illness to view themselves as abnormal and categorically different from the rest of the population. Haslam and Kvaale (2015) advised neuroscientists, clinicians, and patients to be aware of the negative implications of viewing mental illnesses as entirely based in the brain and genetics.

#### **4.1.3 Chemical Imbalance: Physicians**

In a blog post on the website *Psychiatric Times*, psychiatrist Ronald Pies (2011), in response to critics of psychiatry and biomedical explanations of depression, described the chemical imbalance hypothesis as an "urban legend" and stated that in 30 years he had never "heard a knowledgeable, well-trained psychiatrist make such a preposterous claim, except perhaps to mock it" (para. 1). However, other psychiatrists, medical associations, pharmaceutical companies, and popular websites have promoted the biomedical explanation of depression for many years (Deacon, 2013; Hickey, 2014; Lacasse & Leo, 2015). For example, the American Psychiatric Association, in a patient information leaflet, stated "Antidepressants may be prescribed to correct imbalances in the levels of chemicals in the brain" (p. 2, American Psychiatric Association, 2005, as cited in Lacasse and Leo, 2015), and psychiatrist Charles Nemeroff stated, "There is truly a real deficiency of serotonin in depressed patients" (Nemeroff, 2007, as cited in Lacasse and Leo, 2015).

Despite the claim by Ronald Pies that the chemical imbalance hypothesis is an urban legend, physicians are likely utilizing the explanation with their patients. Among a sample of psychology students completing a survey, 46% claimed to have heard of the chemical imbalance hypothesis from a physician or medical professional (France et al., 2007). It is clear that the chemical imbalance hypothesis of depression is pervasive in the general population, and at least some physicians are using this explanation with their patients. Lacasse and Leo (2015) drew attention to a National Public Radio show from 2010 where psychiatrist Daniel Carlat talked about using the chemical imbalance hypothesis with patients, despite not believing the hypothesis to be true. He states,

I think I say that because patients want to know something. And they want to know that we as physicians have some basic understanding of what we're doing when we're prescribing medications. They certainly don't want to know that a psychiatrist essentially has no idea how these medications work (p. 207, Lacasse and Leo, 2015).

There is a lack of empirical data on the way physicians explain depression to their patients, but the above suggests that at least some are using the chemical imbalance hypothesis.

Lebowitz and Ahn (2014) were interested in the effect that biological explanations of a patient's mental illness symptoms would have on clinicians' empathy toward a patient. They recruited mental health clinicians, including psychiatrists, psychologists, and social workers. The clinicians read vignettes about patients with mental illnesses. Each vignette had two explanatory passages: one with biological factors and the other with psychosocial factors. The

vignettes and explanations were counterbalanced among participants. The clinicians then completed a measure of empathy. The authors reported that the mean empathy scores across all vignettes was significantly lower when they were paired with the biological explanatory passage. The authors posited that the lowered empathy values could be due to genetic essentialism and neuroessentialism, wherein the clinician might view the condition as immutable and the patient as abnormal. This study prescribes an etiological explanation for the situation, but it does not address how clinicians negotiate and weigh the multitude of information involved in a diagnostic interview. However, it does suggest that if a clinician views his/her patient's condition as primarily biological, the impact on the therapeutic alliance could be negative.

The biopsychosocial model is a framework to assist clinicians in considering the multiple factors involved in the presentation of mental illnesses, and is an important tool for fostering a therapeutic alliance between clinician and patient (Borrell-Carrio, Suchman, & Epstein, 2004). Lebowitz, Ahn, and Oltman (2015) examined how lay participants responded to vignettes of biologically-oriented clinicians and psychosocially-oriented clinicians on survey measures of clinician competence and warmth, and the appropriateness of the treatments the clinician would provide. The authors concluded that laypersons viewed the biologically-oriented clinicians as less warm than the psychosocially-oriented clinicians. When the participants attributed the cause of the mental illness to biological factors, they viewed the biologically-oriented clinicians as more competent. Generally, unless the participant constructed the mental illness as primarily biological in cause, the participants preferred the psychosocial clinician and viewed his or her potential interventions as more effective. The authors posited that perceiving a clinician to be less warm will inhibit the formation of a positive therapeutic alliance, which will reduce help-seeking and treatment adherence behaviours of individuals receiving treatment from clinicians they perceive to be less warm.

#### **4.1.4 Communicating a Diagnosis of Depression**

Physicians are expected to communicate knowledge and understanding; yet the etiology of depression is largely unknown, which places physicians in a difficult situation with patients who present with symptoms of depression. Blease (2014), a social scientist who focuses on medical ethics, argued,

The neglect to inform patients that: (1) the causes of depression are not fully understood; (2) the causes are likely to be complex; (3) a range of psychological and social triggers are likely to be highly significant; and (4) there is currently lack of scientific consensus on how antidepressants work, as well as the extent of their effectiveness—can be deemed as a failure to inform patients about relevant facts with regards to depression (p. 227).

This advice seems especially prudent in the context of evidence-based medicine and the responsibility of medical practitioners to provide all the information required for a patient to make an informed choice about treatment. In addition, others have further argued that physicians have a heightened duty to provide accurate information regarding depression in light of the misconceptions about what is known about depression among the lay public. Dowrick and Frances (2013) argued that physicians should inform patients about the high rates of placebo response when informing patients about antidepressants. They also suggested countering the commonly-held view that depression is primarily caused by a deficiency of serotonin in the brain by noting the relevance of social and psychological factors.

Maxwell (2005) was interested in how patients and physicians accounted for the diagnosing and management of depression in primary care. She interviewed 37 women and 20 primary care physicians and analyzed the data using a grounded theory approach. With regard to the physician data, the researchers reported that the physicians constructed the diagnosis of depression as problematic and subjective, especially for mild depression. The physicians acknowledged that they often were faced with cases that appeared to be the result of a non-medical problem in the patients' lives, but were limited in their options for treatment. As such, the physicians negotiated a dilemmatic position between understanding a patients' depression to be situationally-based, and their ethical responsibility to offer something to improve the lives of their patients, which involved providing an antidepressant. Several of the physicians stated that they were worried about a general trend of over-medicalizing mild depression and over-prescribing antidepressants. The authors concluded that primary care physicians require a more diverse range of treatment options to provide to their patients.

While there are anecdotal reports of physicians using biomedical discourse to instill confidence, reduce patient stigma, and encourage antidepressant use (Lacasse & Leo, 2015), there is a lack of research on how generalist family physicians explain depression to patients. I was interested in how family physicians, who are responsible for the vast majority of the diagnosis and pharmacological treatment of depression in Canada, described and accounted for their etiological explanations of depression in a research interview and, in particular, how they reported on their use of the chemical imbalance hypothesis to explain depression to their patients.

#### **4.2 Analytical Perspective: Discursive Psychology**

The following analysis is situated within the theoretical perspective of discursive psychology, which applies concepts and ideas in discourse analysis – the study of the performative function of talk and texts – to issues in psychology (Potter, 2003; Potter & Wetherell, 1987). Discourse analysis in social psychology involves a systematic examination of how talk and text are structured via linguistic resources, the social actions that are performed via the use of these resources, and the possible functions of these actions (Potter, 2003). I assume that language is a central component to the creation of knowledge, and that discourses have consequences and are used to accomplish social actions. As recommended by Wetherell (1998) and employed in other discourse analytic work (e.g., LaFrance, 2007), I situate the content and style of discourse and the social actions it performs within broader social discourses of depression in Canadian and American medical and lay society.

#### **4.3 Method**

The data for the present analysis were derived from 11 semi-structured interviews conducted in 2009 with family physicians on their diagnostic and treatment practices for depression. The interviews were conducted one-on-one by Dr. Linda McMullen and one of her former graduate students, Jeffery Letourneau. The University of Saskatchewan Behavioral Research Ethics Board approved this research project.

##### **4.3.1 Participants**

All family physicians (165) listed in the telephone directory of a midsized Canadian city received a letter inviting them to participate in “a program of research investigating how physicians make decisions to diagnose and treat patients for depression.” Physicians were

offered a \$150 CDN honorarium for their participation. Eleven physicians (five women) agreed to participate. They ranged in age from 33 to 73 years (median = 55 years) and had been in family practice between 3 and 46 years (median = 18 years). Six physicians were salaried and worked in publicly funded settings and 5 worked in fee-for-service practices.

#### **4.3.2 Procedures**

Each participant was informed of the purpose of the research and his or her rights both verbally and through a written, signed consent form. The interviews with physicians were conducted at the University of Saskatchewan, lasted one to two hours (median = 1.4 hours), and consisted of two parts. The first was conducted by Linda McMullen and focused on questions pertaining to how physicians went about diagnosing and treating depression. The second part was conducted by either Linda McMullen or her former graduate student, Jeffery Letourneau, and focused on whether and how patients made requests for antidepressants and how such requests influenced the physicians' diagnostic and treatment practices. There were no specific interview questions pertaining to the chemical imbalance hypothesis of depression or any other explanatory model. While there were no questions about the etiology of depression in the interview, talk of etiology was often in response to the question, "do you ever feel you need to motivate your patients to take antidepressants, and if so, how?"

The interviews were transcribed verbatim with all personally identifying information omitted. The participants were provided with a copy of the transcript and they were permitted to modify the transcript before signing a transcript release form; there were no substantial modifications to the transcripts. Jefferson transcription notation was not used because the high level of detail it provides was not required for the analysis. Instead, a more readable form of transcript notation was used (see Appendix A) and is similar to the notation used in other discursive research articles (e.g., LaFrance, 2007).

The analysis was an iterative process of reading the transcripts, listening to the audio recordings, and extracting segments of text related to the etiology of depression. These segments included talk about the biological, social, and psychological precipitants of depression and talk of how the physicians constructed the ways in which they explained depression to their patients. I compiled and organized these extracts and chose a final collection that displayed the range of talk on etiology and the biochemical explanation of depression and eliminated extracts that were similar in content and style to chosen extracts. I was principally interested in how the physicians accounted for their use of the chemical imbalance hypothesis of depression or other explanations, and the functions achieved by these accounts (Wood & Kroger, 2000).

I acknowledge that the etiological discourses presented in the following analysis are a co-construction between a physician and a clinical psychologist (or her graduate student). The analysis relies upon the reported speech of physicians who are summarizing and presenting their diagnostic and treatment practices for depression. I do not claim that the reported speech represents actual communication between patient and physician; however, for the purpose of the analysis and conclusions, I assume that the physicians draw upon similar discursive resources when speaking to patients as they did when speaking with the interviewers.

#### **4.4 Analysis**

In the following analysis, I show how family physicians accounted for their use of the biochemical explanation of depression and the beneficial functions achieved by explaining

depression in this manner (i.e., to reduce blame and stigma, increase treatment adherence, and promote depression as a brain disorder) during interviews with a clinical psychologist or one of her former graduate students about his or her diagnostic and treatment practices for depression. I present an analysis of extracts wherein physicians constructed depression as a biological, psychological, and social illness, and as lacking in available treatment options. I chose and ordered the extracts in the following analysis with the goal of presenting the diverse and nuanced ways these physicians present how they explain depression to their patients.

#### 4.4.1 Using the Biochemical Explanation to Reduce Blame and Promote Treatment

One of the positive functions of the chemical imbalance explanation of depression widely noted in the literature is to reduce or eliminate blame and personal responsibility. In extract 1, a family physician presents how the biochemical explanation is useful to help a patient overcome self-blame (in the analysis, “I” refers to line number).

##### 4.4.1.1 Extract 1.

1 Physician 11: And the other thing  
2 that some people struggle with is a  
3 concept of umm {pause} uh I just  
4 need to suck it up and get over it  
5 ... sometimes umm the motivation  
6 comes from taking it from that-  
7 their perception that this is all my  
8 fault and I just gotta do something  
9 different and it'll go away, to the  
10 more medical model in helping them  
11 kind of externalize it and that uh  
12 it's not my fault, it's because of  
13 these changes in my brain and we've  
14 just gotta fix those so that I can,  
15 move forward.

This extract is typical of the claim that a biomedical explanation of depression will reduce personal blame. The physician draws attention to a common lay expression, “suck it up and get over it” (l. 4), which is a pejorative phrase that suggests a person is responsible for moving on despite personal distress. In this phrase, the physician builds a case for the importance of countering such a negative and personally denigrating statement. She constructs her role as motivating a patient toward treatment by explaining the “medical model” (l. 10) and that the causes of depression are “changes” in the “brain” (l. 13). Her reference to “kind of externalize” (l. 11) the problem appears not to refer to locating the problem outside of one’s body; rather, it is presented as a way to provide psychological distancing from shame and blame in order to help her patient.

In the physician’s depiction of the patient’s narrative at the end of the extract (ll. 12-13), she presents that once the patient has accepted the medical model of depression he or she will accept a brain-based treatment (“we’ve just gotta fix those,” l. 13). The use of the first-person plural pronoun “we” (l. 13) is in contrast to the use of the singular pronoun “I” throughout the majority of the extract and speaks to how the physician constructs the relationship between physician and patient with regard to treatment as a collaborative one. The use of the phrase “just gotta fix those” (l. 14) presents the treatment as a simple, clear-cut intervention; i.e., the patient might need only to take care of the changes in the brain, presumably by using an antidepressant medication, to progress or “move forward” from the depression (l.15).

In extract 2, the physician responds to the question about whether she needs to motivate a patient to take antidepressant medication similarly to the physician in extract 1. However, unlike the first extract, social/psychological explanations are also implicated in reducing blame.

#### 4.4.1.2 Extract 2.

1 Physician 10: I think probably it's,  
2 it's that discussion of it, of, of,  
3 educating them that it is a biologic  
4 disease, that it's not something  
5 they brought on themselves or it's-  
6 you know, there's things they can do  
7 to help change in the ways they  
8 think but it's just so ingrained.  
9 You know, we talk a lot about the  
10 nature versus nurture and you know,  
11 how you're raised to deal with  
12 stress and most people, you know,  
13 right away say I was raised to just  
14 shove it down and so then we talk  
15 about that's how it comes out as  
16 panic attacks and things then, and  
17 then I think they, they don't blame  
18 themselves as much for it? And, and  
19 I often use the you know if you  
20 broke your leg would you fight  
21 anyone for a cast or if you had  
22 diabetes, would you say no to  
23 insulin necessarily?... and tell  
24 them that one day, we will be able  
25 to measure your serotonin or  
26 whatever marker we'll know at that  
27 time just like a thyroid blood test.

The physician starts by stating, “I think probably” (l. 1), which suggests some degree of uncertainty in her response to the question. She reports having a “discussion” (l. 2) with her patients and “educating them” (l. 3). She does not detail the content of her educational discussion with patients, but she states that depression “is a biological disease” (ll. 3-4), which positions depression fully within the medical realm. The first reference to reducing patient self-blame, “it's not something they brought on themselves” (ll. 4-5), is followed by a halt in speech (“it's-” l. 5). The halt in speech is an interruption to the utterance constructing depression as a biological disease; she adds that psychological factors – “the ways they think” (ll. 7-8) – play a role, but constructs remediating psychological factors as something that “they can do” (l. 6), effectively removing herself from such an intervention and placing the onus on the patient. She further constructs the implicating of psychological factors as immutable from the patient's view with the phrase, “it's just so ingrained” (l. 8).

Continuing the line of argument that patients view depression as social/psychological and not necessarily biological, the physician reports that they talk “a lot” (l. 9) about “nature versus nurture” (l. 10). With the phrase, “most people” (l. 12), she constructs that a typical response usually involves a patient claiming that s/he deals with stress through avoidance of the problem: “shove it down” (l. 14). Interestingly, the physician, rather than invoking a typical symptom of depression, refers instead to “panic attacks” (l. 16), but also adds the very non-descript catch-all term, “things” (l. 16). The conflation of depression and anxiety likely speaks to the high



comorbidity of the two disorders. The physician then makes a statement that the discussion results in reduced blame (ll. 17-18). However, she prefaces the statement with “I think” (l. 17) and concludes the statement with rising intonation, which functions to soften or qualify her claim.

After several lines of talk devoted to social/psychological factors, the physician returns to a biological comparison. She constructs depression as similar to a broken bone (l. 20) and diabetes (l. 22). By comparing depression to conditions with known etiologies and objective diagnostic tests, and asking the patient if s/he would refuse treatment, she constructs herself as trying to persuade her patient that treatment with antidepressants is a logical choice. Finally, she bolsters her claim that depression is a “biological disease” (ll. 3-4) by stating, “one day, we will be able to measure your serotonin or whatever marker” (ll. 24-26). Since there is no biological test for depression, this phrase reinforces the potentially problematic comparison between depression and diabetes or a broken leg. Her promise of a diagnostic marker is future oriented and indeterminate – “one day” (l. 24) – but is presented as an eventuality with the phrase, “we will be able” (l. 24).

In extracts 1 and 2, the physicians argue that a medical explanation of depression is useful to counter the self-blame and stigma that their patients express. They make the case that convincing patients that depression is due to changes in the brain might lead them to abandon the notion that they are personally responsible for their depression. Providing this argument in the context of a question about motivating patients to take antidepressants casts the acts of persuasion as beneficial to the patients by reducing personal blame and stigma. Thus, constructing depression as a biomedical disease functions to reduce blame and set up a persuasive argument for the use of antidepressant medication.

#### **4.4.2 Using the Biochemical Explanation to Promote Treatment Adherence**

In addition to reducing blame and increasing acceptance of taking an antidepressant, using a biochemical explanation can be presented as a motivating force to encourage treatment adherence, which is notoriously problematic in depression because many patients stop taking their antidepressant medications. In the following extract, the physician notes that a value of the patient adopting the biochemical explanation of depression is in motivating the patient to continue taking the medication. The following extract occurs in an exchange about patient requests for medications.

##### **4.4.2.1 Extract 3.**

1 Physician 02: The, the reason to, to  
2 go that way with [the biochemical  
3 explanation of depression], with  
4 somebody who's depressed is for them  
5 to understand why they would need to  
6 stay on the medication when they  
7 feel better. That's when the, that,  
8 that's the payoff time for all this  
9 conversation. You know, so it's  
10 like a topic for conversation....  
11 It's just another way of us being  
12 together in the same room, me  
13 showing that I don't really want you  
14 to go immediately, that I'm still  
15 happy to spend time with you. It's

16 for me more than for- except  
17 eventually I think the knowledge  
18 grows in the community.

The physicians who were interviewed generally indicated they face a great deal of reluctance from their patients to take antidepressants. However, in contrast to extracts 1 and 2, where the biochemical explanation is presented as a motivating rhetorical device to encourage initial treatment with antidepressant medication, in extract 3 the physician reports presenting the biochemical explanation to patients to encourage medication adherence over the course of treatment. The physician talks about “the payoff time” (l. 8), suggesting that the work of explaining depression as a chemical imbalance is valuable to the physician later, when he or she can rely on this prior explanation to encourage the patient to continue taking the medication after he or she feels better. By having the patient “understand” (l. 5) that she or he has an underlying chemical imbalance, the physician can further explain that the imbalance is not corrected by the time he or she feels well. The use of the word “need” (l. 5) conveys that continued use of the medication is imperative even when the patient begins to feel better.

After the physician acknowledges this “payoff,” he further accounts for its value as “a topic for conversation” (l. 10). Family physicians are notoriously busy, and appointments typically last approximately 15 minutes on average in Canada (Irving et al., 2017). The physician reports that the explanation is useful to demonstrate that he is “happy to spend time” (l. 15) with the patient. The chemical imbalance explanation permits the physician to have a conversation with the patient that is consistent with a biomedical framework of disease. He appears to suggest that the content of the explanation is less important than communicating care and understanding when he states the explanation is “for me more than for” (l. 16) the patient. He does not explicitly state why providing the explanation is more for his benefit, but further on in his response (not presented above), he refers to talk of the biochemical explanation as “white noise” to the patient, suggesting that it is generally incomprehensible or insignificant. However, at the end of this extract (ll. 15-18), he abruptly stops his utterance “for me more than for-” to acknowledge that the explanation has an impact upon what is known about depression in the community, and this impact is constructed as beneficial and uncontroversial.

Unlike extracts 1 and 2, in this instance the physician presents the biochemical explanation of depression as a rhetorical device to motivate treatment adherence after the patient feels an improvement. The physician also notes that the biochemical explanation is valuable simply as a topic of conversation, and might contribute to building medical knowledge among the lay public. Paradoxically, he constructs the content of the explanation as insignificant or incomprehensible, while also assuming that the patient will understand and talk to others about the biochemical etiology of their depression.

#### **4.4.3 Using the Biochemical Explanation to Promote Depression as a Brain Disorder**

Many of the physician interviewees, while promoting depression as a brain-based disorder, acknowledged that treating depression involves more than medications. The following extract is part of a response to the question on motivation described above.

##### **4.4.3.1 Extract 4.**

1 Physician 09: I always say it's a  
2 chemical disorder. In part of my  
3 selling by the way is that you have  
4 a- when they have a high score this

5 is a, a brain disorder. I say brain  
6 disorder. Where- where's the  
7 disorder? Well I can, I can tell you  
8 if you want and I can show you the  
9 diagrams and I can explain it all to  
10 you, the hippocampus, all the-,  
11 cingulate gyrus and all the  
12 different parts of the brain that  
13 are involved. You know, I say, but  
14 it's a brain disorder. Your brain's  
15 not working well right now. And the  
16 chemistry of it and dopamine and  
17 serotonin, nor- norepinephrine, all,  
18 all the different stuff. And it's  
19 not working well. But to get it  
20 back, it's not just a matter of  
21 pills, you know, that's-, I-I-I I'm  
22 absolutely convinced of that.

In this extract, the physician presents how he communicates knowledge of the biology of depression to his patients, and constructs himself as having expertise in the etiology of depression. In the beginning of the extract he states that depression is a “chemical disorder” (l. 2) and a “brain disorder” (l. 5), which situates depression as a biological entity. The use of the phrase “selling it” (l. 3) constructs his explanation as an act of persuasion. He equates “high scores” on a measure of depression symptoms with evidence of brain dysfunction for the patient. In the absence of a biological test, the physician reports using a symptom tally on a questionnaire to legitimize the diagnosis and the brain-based nature of the illness.

The physician conveys expertise with the phrases, “I can tell you; I can show you; I can explain it all to you” (ll. 7-10). While there is no scientific consensus regarding depression etiology, the phrase “explain it all” indicates to the patient that he has complete knowledge about the biological underpinnings of depression. He broadly utilizes scientific language to legitimize his claim to knowledge, such as “diagrams” (l. 9), and words associated with the scientific study of depression: “hippocampus” (l. 10), “cingulate gyrus” (l. 11), “dopamine” (l. 16), “serotonin” (l. 17), and “norepinephrine” (l. 17). In this extract he does not present a detailed account of how these neuroanatomical structures and neurotransmitters are deficient, but rather provides a broad summary statement, “your brain’s not working well right now” (ll. 14-15), and a catch-all phrase, “all the different stuff” (l.18).

Despite his unequivocal commitment to the biochemical explanation at the beginning of the extract – “I always say it’s a chemical disorder” (ll. 1-2); I say brain disorder” (ll. 5-6) – he makes an equally strong unequivocal statement in lines 20 to 22 that antidepressant medication is not the only path to recovery: “I’m absolutely convinced” (l. 22). There is a congruence between depression as a disorder of brain chemistry and the use of antidepressant medication to correct the chemical deficiency. However, by stating, “it’s not just a matter of pills” (ll. 21-22), the physician emphasizes that recovery from depression requires more from the patient than simply adhering to a medication regimen, and challenges the notion that antidepressants specifically target the underlying cause of depression.

The physician in extract 4 builds his argument that depression is a brain disorder by presenting terminology related to what is known about depression in the scientific literature, while also being non-descript and broad. He claims to have complete knowledge about the

etiology of depression but simply presents a list of brain regions and neurotransmitters. The argument invokes an appeal to authority by positioning himself as an expert, despite the etiology of depression being unknown and potentially very complex.

#### 4.4.4 Depression as Biopsychosocial Illness

While some physicians talked about primarily presenting the chemical imbalance hypothesis to their patients, others presented a view of depression that included external factors. In extract 5, the physician responds to the question about the need to motivate patients to take antidepressants with an explanation of the possible causes, and suggests that the routes to influencing biochemistry are diverse.

##### 4.4.4.1 Extract 5.

1 Physician 05: I go through a little  
2 bit of the biochemical theory about  
3 what's causing depression. That  
4 their serotonin or norepinephrine or  
5 dopamine are depleted. And this may  
6 be due to, it may be partly due to  
7 some genetic factor and it may be  
8 due to external stressors. Not  
9 getting enough sleep and not getting  
10 exercise and maybe not eating  
11 properly. And say- then I- then I  
12 do say that you know, there is  
13 evidence that, that those  
14 neurotransmitters, can increase  
15 with, psychotherapy. And umm  
16 perhaps even from exercise and light  
17 exposure. But that may take quite a  
18 while. And the quickest way to get  
19 yourself feeling better is to think  
20 about combining some counselling  
21 with some medication. To take care  
22 of the biochemical side as quickly  
23 as we can.

In this extract the physician makes a statement about the biochemical basis of depression (ll. 3-5), accommodating for the contribution of genetic factors, external stressors, sleep, diet, and exercise (ll. 7-11). In the opening lines, the physician refers to the cause of depression as the “biochemical theory” (l. 2). The scientific language, i.e., “theory” (l. 2); “serotonin or norepinephrine or dopamine” (ll. 4-5); “genetic” (l. 7); “evidence” (l. 13), functions to legitimize the physician’s expertise. Similar to the previous extracts, the physician explains that depression is caused by “depleted” (l. 5) neurotransmitters.

The physician emphasizes (“I do say,” ll. 11-12) that he informs his patients about other treatments. Treatments such as psychotherapy, light exposure, and exercise are woven into the biomedical framework by implicating them as capable of (“can increase with,” ll. 14-15) and potentially capable of (“perhaps even,” l. 16) changing the chemistry of the brain. He privileges the biochemical level of explanation by reducing the efficacy of these treatments to influencing “neurotransmitters” (l. 13). He appears to elevate and prioritize the use of antidepressants when he reports that psychotherapy, exercise, and light exposure “may take quite a while” (ll. 17-18) and that adding an antidepressant is the way to “take care of the biochemical side as quickly as

we can” (l. 21-22). While the terms “quickly” and “quite a while” are not specific, these contrasting terms serve to persuasively construct antidepressants as a critical component in the most immediate route to recovery – a combination of counselling and medication (ll. 20-21). Clinical guidelines often recommend a combination of antidepressant and Cognitive Behavioural Therapy or Interpersonal Therapy as the first-line treatment for depression (e.g., Parikh et al., 2009), and this physician presents combined treatment as an option for the patient to “think about” (ll. 19-20).

In extract 6, the physician does not specifically state a position regarding the etiology of depression, but through talk of treatment recommendations, he endorses a biopsychosocial model of depression. The following extract is in response to a question about how the physician makes treatment decisions.

#### 4.4.4.2 Extract 6.

1 Physician 08: I say you know there's  
2 different ways to treat depression.  
3 Umm. There's counselling. Uh just  
4 talking about things kind of helps  
5 deal with stress and your coping and  
6 learning how to cope with situations  
7 or lifestyle depending on what the  
8 scenario is. I'd say, you know,  
9 sometimes we'll use medications and  
10 explain briefly how- restore the  
11 balance of the chemicals in the  
12 brain as briefly as you can.  
13 {chuckling} Kind of thing. De- it's  
14 all dependent on the person's  
15 knowledge. And intellect. And then  
16 I usually recommend actually a  
17 combination. If someone's,  
18 definitely got a major depressive  
19 disorder, and we're leaning towards  
20 medications I say okay well and they  
21 don't want counselling I say we can  
22 start on medications but at some  
23 stage, you have either formal  
24 counselling or he's just coming back  
25 and talking to me, is really  
26 important.

The physician responds by explaining how he approaches treatment decisions with his patients and he talks about offering counselling and medication. For counselling, he constructs it as a simple and easy intervention with the phrase, “just talking” (ll. 3-4). However, he also states that it “kind of helps” (l. 4), which constructs the effectiveness of the intervention as partial. He acknowledges external factors, e.g., “stress” (l. 5), “situations” (l. 6), and “lifestyle” (l. 7), and psychological factors, e.g., “coping” (l. 5) and “learning” (l. 6) involved in the treatment of depression.

With regard to medication, the physician reports, “sometimes we'll use medications” (l. 9). The use of the word “sometimes” constructs the practice of prescribing medications as an occasional occurrence rather than routine. Paired with the introduction of medications as treatment, the physician alludes to the chemical imbalance hypothesis of depression (ll. 10-12).

He abruptly stops his utterance, “explain briefly how-” (l. 10), and chuckles after “as briefly as you can” (l. 12). There is a clear contrast between the complexity of depression etiology and the need to provide an explanation to a patient in a short amount of time. The physician adds that the explanation is “all dependent on the person’s knowledge. And intellect” (ll. 14-15), which suggests that he presents more or less information to different patients based on his perception of their ability to understand the content, and that the explanation might be too difficult to comprehend for some of his patients.

When recommending treatment, as in extract 5, the physician endorses a combination of counselling and an antidepressant. The use of the term “actually” (l. 16) emphasizes the recommendation of combined treatment as somewhat surprising or unusual. The physician then constructs a situation where his patient “definitely” (l. 18) has a diagnosis of major depressive disorder and both he and the patient are collaboratively “leaning towards” (l. 19) antidepressant treatment. In this scenario, he adds that the patient is not interested in counselling, and he states that the patient has two options: “either formal counselling” (ll. 23-24) or “talking to me” (l. 25). While the physician constructed a collaborative path to treatment, counselling or, at minimum, talking to the physician, is presented as imperative and non-negotiable.

In extracts 5 and 6, the physicians endorse a biopsychosocial view of depression. When talking about discussing treatment options with their patients, they describe a collaborative path toward deciding on treatment. A combination of talk therapy and medication is presented as the optimal treatment, which might or might not be accepted by the patient.

#### **4.4.5 Biopsychosocial Model and Treatment Options**

In the following extracts, the physicians acknowledge an incongruence between illness model and treatment. Endorsing a biopsychosocial model of depression does not necessarily mean that psychological and social interventions are available. Extracts 7 and 8 are from the same physician. The following extract is in the context of an interview question about whether or not depression is over-treated and/or under-treated in the population.

##### **4.4.5.1 Extract 7.**

1 Physician 04: So yeah, I mean, the  
2 people who are, who have bad life  
3 circumstances, they don't have money  
4 to pay for depression medication so  
5 if they're on it, it's probably  
6 because someone told them to go on  
7 it. And it's futile because they're  
8 not depressed because they have low  
9 serotonin, they're depressed because  
10 uh things are happening to them, so  
11 it's, it's sort of stupid to think  
12 that a drug is going to treat that  
13 but we do anyways. Yeah, so, we're  
14 over-treating with drugs, under-  
15 treating with the other modalities,  
16 if you want to look at it that  
17 way.... If somebody's depressed  
18 because crappy things are happening  
19 in their life, why not take care of  
20 the crappy things and odds are  
21 {chuckling} you won't need the

22 drugs. You won't need to intervene  
23 any more than that. But I, I, you  
24 know, I feel like I have  
25 surprisingly little power in that  
26 regard.

In the opening of extract 7, the physician begins to construct an argument regarding the over-prescription of antidepressant medications. His use of the term "people" (l. 2) is vague and might refer to many individuals, but the term broadly constructs it as a widespread phenomenon. He again uses a vague term, "someone" (l. 6), to describe the person who initiated the antidepressant treatment, but one can assume that the physician is referring to another physician because physicians are the gatekeepers of prescription medications. He subtly indicts the "someone" by describing the treatment with antidepressant medication in these particular cases as "futile" (l. 7) and "sort of stupid" (11). By using the term "we" (l. 13), which he most likely uses to refer to the profession of family physicians, he extends the indictment to himself and his profession as a whole ("we do anyways," l. 13; "we're over-treating with drugs" (ll. 13-14)). With these phrases he constructs medication as a resource likely to be used by physicians even when it is unlikely to be useful.

The physician in extract 7 constructs a distinction between two types of depression: depression as caused by a deficiency of "low serotonin" (ll. 8-9) and depression as caused by "bad life circumstance" (ll. 2-3). Rather than reduce the non-biological factors involved in depression to biochemistry as was done in extract 5, he appears to present the biochemical explanation as existing independently of life circumstances. He states, "they're not depressed because they have low serotonin, they're depressed because uh things are happening to them" (ll. 7-10). This statement evokes the distinction between endogenous and reactive depression that was prevalent prior to DSM-III.

The physician acknowledges the lack of correspondence between illness model and treatment recommendations (ll. 17-22). He presents a rhetorical question, "why not take care of the crappy things" (ll. 19-20), which suggests treatment should correspond directly to the perceived cause of the depression. He chuckles as he states the answer, "odds are you won't need the drugs" (ll. 20-22). The chuckle appears to acknowledge the absurdity of not following what he constructed as a simple and direct relation between cause and intervention. However, in lines 23 to 26, he articulates a counter position and defends his own practice as constrained. The physician laments the lack of power he has to improve the lives of his patients. It is unclear why he refers to this as 'surprising' (l. 25), but it does speak to the lack of congruence between an illness model like the biopsychosocial model of depression and the available interventions to target the perceived causes. Access to counselling, financial resources, and social supports are limited, especially in private practice clinics, and writing an antidepressant prescription might be the only immediate intervention available to the physician.

In the following extract, similar to extract 5, the physician again separates biological depression from situational depression in the context of a response about treatment decisions. Despite acknowledging that antidepressants are not always a preferred treatment, they are presented as a standard, fallback treatment.

#### 4.4.5.2 Extract 8.

1 Interviewer: You mentioned just a  
2 few minutes ago that if you sense

3 that there's something organic going  
4 on. So how do you make that  
5 determination?  
6 Physician 04: It's a diagnosis of  
7 exclusion. So if you, if you're  
8 depressed and I can't tease out an  
9 obvious cause in your life, you  
10 know, marital conflict, lost your  
11 job, somebody died. If you can't  
12 find any other reason then you're  
13 sort of left with the conclusion  
14 that boy, it must be something  
15 organic, serotonin deficiency. The  
16 other interesting thing is you'll  
17 see a lot of depression in people  
18 with other medical conditions....  
19 And because of all the limitations  
20 that are placed on his life he'll  
21 become depressed as a reason, as a  
22 result. I don't find in that  
23 situation that treating him with uh-  
24 I'll offer it to him obviously. But  
25 I don't find medications are very  
26 useful in that case because the  
27 depression isn't from a deficiency  
28 of serotonin, it's because bad  
29 things are happening in his life.

In this extract, we see again a separation of the social causes of depression from biochemical causes through the “diagnosis of exclusion” (l. 6-7). The physician excludes life stressors from the diagnosis of depression (“marital conflict, lost your job, somebody died” ll. 10-11), which he might otherwise diagnose as an adjustment disorder or bereavement in DSM-IV nosology (current at the time of the interview). The physician makes the assumption that a depression that occurs without any obvious stressors is “organic” (l. 15) in cause and in these cases it is appropriate to treat the patient with antidepressant medication. The physician alludes to an endorsement of the chemical imbalance hypothesis of depression when he refers to such depression as a “serotonin deficiency” (l. 15).

The physician continues his line of reasoning on the diagnosis of exclusion with an example of people with medical conditions who also display symptoms of depression. He constructs the depression as being caused by lifestyle “limitations” (l. 19) as opposed to an organic deficiency. Interestingly, the physician begins to state that he does not find antidepressants useful in these situations, but interrupts his statement to add, “I’ll offer it to him obviously” (l. 24). The use of the term “obviously” seems to construct the practice of prescribing antidepressant medication as standard and routine, but it could also suggest that the physician constructs the interviewer as somebody who might expect him (as a physician) to provide biomedical treatment. Offering medication, even when he does not “find medications are very useful” (ll. 25-26), places the decision about whether or not to use them as the responsibility of the patient. The physician again reinforces the chemical imbalance hypothesis of depression when he adds that antidepressant treatment is not useful when there is no “deficiency of serotonin” (ll. 27-28) to correct.



Extracts 7 and 8 exemplify the limitations of the biopsychosocial model of depression when making treatment recommendations in primary care. The physician constructs offering antidepressant medication routinely and laments his lack of influence into the social lives of his patient. A full range of treatment options is constructed as limited and incomplete and an antidepressant prescription might be the only option that this physician has to offer his patient.

#### 4.4.6 Social Causes and Treatment Options

In the following two extracts, the physicians do not talk about the underlying biochemical etiology of depression, but instead focus on the social factors involved in depression. In extract 9, the physician responds to a question about whether antidepressants are over-prescribed, under-prescribed, or appropriately prescribed at the population level.

##### 4.4.6.1 Extract 9.

1 Physician 01: That prescription I'm  
2 never in favour of it unless there's  
3 no choice left....  
4 Everybody doesn't need  
5 antidepressant. If somebody needs a  
6 chit-chat or needs exercise or help  
7 or financial thing, how is the  
8 antidepressant prescription enough  
9 if they have a financial problem and  
10 I prescribe them seventy-dollar drug  
11 for a month? It's, it's, compounding  
12 their problem. It's not helping  
13 their problem. So it's a question  
14 of what is, what the background  
15 problem is there.  
16 Interviewer 2: Okay. Any final  
17 comments or questions about my  
18 questions ... or anything else you  
19 think we might want to know?  
20 Physician 01: I think laughter is a  
21 good medicine. People should  
22 actually uh laugh a little bit more.  
23 And you, you improve your chemicals  
24 by laughing more as well.

The physician begins his response by stating that he regards antidepressants to be a last-choice option. He argues that he is “never in favour of” (l. 2) antidepressant drugs “unless there’s no choice left” (ll. 2-3). The use of the term “never” in his utterance constructs his position as an absolute but he qualifies his position with the term “unless.” During several lines of text omitted from this extract, the physician does acknowledge that antidepressants are under-prescribed in some cases and that people who are very depressed need antidepressants. However, he returns to state that all depressed patients, i.e., “everybody” (l. 4), do not require antidepressants. He lists “chit-chat,” “exercise,” “help,” and “financial” assistance as potential “needs” (ll. 5-7) of his patients. The term ‘need(s)’ positions these factors as essential and necessary targets of treatment.

This physician poses a rhetorical question: “how is the antidepressant prescription enough” (l. 7-8). The use of the term “enough” suggests that antidepressants are insufficient on their own in such cases, but does permit their inclusion in a treatment plan. He continues the

rhetorical question, adding “if they have a financial problem” (l. 9) paired with “seventy-dollar drug for a month” (l. 10). The link between the cost of the drug and the financial problem serves to construct the treatment with antidepressant drugs in this scenario as absurd and irresponsible. He answers the question by stating that such treatment would be “compounding” (l. 11) rather than “helping” (l. 12) the problem. Unlike the physician in extracts 7 and 8, who added that he treats with or offers antidepressants even when he does not think it will be helpful, this physician does not make a similar utterance, which reinforces his earlier statement that antidepressants are his last option.

While the physician makes the claim that he eschews routine antidepressant treatment for his patients, at the end of the extract, he talks about improving “chemicals” (l. 23) through “laughing more” (ll. 23-24), which speaks to the power and pervasiveness of the chemical imbalance explanation in shaping etiological understandings of depression. The phrase “improve your chemicals” (l. 23) indirectly suggests that there is a chemical deficiency in patients with depression. Similar to the physicians in extracts 4 and 5, where they constructed alternative treatments to medications as also influencing brain chemistry, this physician appears to endorse the chemical imbalance etiology of depression and multiple routes to treating the underlying imbalance.

The final extract occurs in the context of a conversation about the addiction, poverty, and mental health issues prevalent among this physician’s patients.

#### 4.4.6.2 Extract 10.

1 Interviewer: And is it your sense  
2 that there’s- again, I don’t want to  
3 put words in your mouth but that  
4 there isn’t the kind of coordinated  
5 effort around that or even the  
6 resources really to-  
7 Physician 03: Well, I think often  
8 you don’t want to treat the symptom  
9 of depression without- it’s a  
10 symptom. You don’t get into the  
11 root cause of it. So if you just  
12 treat someone with an  
13 antidepressant, and nothing changes  
14 otherwise, then you can be just  
15 numbing their feelings, not lifting  
16 their mood. I don’t think that’s  
17 very healthy.

In the opening of extract 10, the interviewer tentatively reflects some content from earlier in the conversation, focusing on the lack of “coordinated effort” (ll. 4-5) or “resources” (l. 6) toward addictions treatment and poverty reduction strategies. The physician responds but abruptly stops her utterance at “symptom of depression without-” (ll. 8-9). The halt in this utterance, and the subsequent exclamation, “it’s a symptom” (ll. 9-10), suggests that considering depression to be a symptom is not typical or self-evident. Indeed, the rhetoric regarding depression in medical discourse is typically that depression is a disease entity, rather than a symptom.

The physician states that the “root cause” (l. 11) of depression is not treated by antidepressants, which suggests that she is resisting the discourse that depression is caused

principally by a chemical imbalance in the brain. She claims that treating a patient with an antidepressant alone is “just numbing their feelings” (ll. 14-15) and not “very healthy” (l. 17). These claims construct such treatment as ineffective and potentially irresponsible, since physicians are expected to improve the health of their patients. While the term ‘antidepressant’ suggests that the medication will prevent or alleviate depression as a disease (Moncrieff, 2008), the physician counters this notion when she states that antidepressants on their own do not “[lift] their mood” (ll. 15-16).

The physicians in extracts 9 and 10 construct some cases of depression as caused by social factors. Antidepressants are described as counter-productive in instances of financial difficulty, and as ineffective for treating the underlying social causes of depression. While the physician in extract 9 refers to laughter also improving chemicals in the brain, the physician in extract 10 constructs an alternative to the notion that antidepressants correct an underlying chemical imbalance, insisting instead that antidepressants treat depression by numbing a patient’s feelings. Both physicians indicate that antidepressant treatment in cases where social causes are present is irresponsible.

Throughout the entire corpus of data, there was no mention that scientific knowledge of depression is incomplete or that the mechanisms of antidepressant action are not fully understood. That is not to say that the physicians would disagree that depression and antidepressants are not completely understood, but this omission is in contrast to statements found on depression information websites and by pharmaceutical companies. For example, WebMD, a popular website for health information, states “Depression is an extremely complex disease. No one knows exactly what causes it, but it can occur for a variety of reasons” (para. 2, WebMD, n.d.); and the information pamphlet for the popular drug Prozac, states “Although the exact mechanism of PROZAC is unknown, it is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin” (p. 20, Eli Lilly and Company, 2014). The physicians instead focused on explaining depression based on the presumed mechanism of action of antidepressants and/or by focusing on salient stressors in the patients’ lives.

## **4.5 Discussion**

### **4.5.1 Uses of the Biochemical Model**

The physician participants in this study presented the utility of the biochemical explanation as a positive discursive device to (a) motivate patients to take and stay on antidepressants, (b) reduce self-blame and stigma, (c) contribute to building knowledge among laypersons that depression is a biological disease, and (d) instill hope and confidence that the condition is understood. In addition, many physicians talked about using a biopsychosocial model to understand and guide their treatment of depression, but were limited by available treatment options.

#### **4.5.1.1 Motivating patients.**

When the physician participants talked about the biochemical explanation of depression, it was often in response to the question, “do you ever feel you need to motivate your patients to take antidepressants?” The etiological model they presented when motivating their patients to take an antidepressant was that depression is caused by an imbalance/deficiency of neurotransmitters. While this discursive move is not entirely surprising given that the chemical imbalance hypothesis is a pervasive and persuasive explanation of depression (France et al.,

2007), and that the pharmaceutical advertising supporting this claim is widespread (Leo & Lacasse, 2008), physicians who use this explanation are arguably not upholding the principles of informed consent.

According to Blease (2014), a social scientist who focuses on medical ethics, physicians diagnosing and treating depression should inform their patients that depression is not fully understood, the causes are multifactorial and complex, and that there is a lack of scientific consensus about how antidepressants work. However, the physicians in the course of our interviews did not make statements to suggest that they routinely present depression to their patients as not fully understood or that antidepressant mechanisms of action and efficacy is lacking scientific consensus. Arguably, presenting depression and antidepressants as not fully understood could undermine the perceived benefit of communicating to the patient that his/her condition is diagnosable and treatable. In addition, the chemical imbalance narrative offers a quick and simple description that dovetails with a description of antidepressant medications as neurotransmitter reuptake inhibitors that can correct a chemical imbalance in the brain. Patients are more likely to accept a treatment as valid and credible when it matches the etiological description (Iselin & Addis, 2003).

The physician participants did talk about depression as a complex condition with biological, psychological, and social inputs, but several physicians delineated biological depression from depression symptoms in the presence of external factors (e.g., the death of a loved one or financial hardship). Depression in the absence of external factors was presented as a legitimate condition of neurotransmitter deficiency. The “diagnosis of exclusion,” as one physician described his diagnostic routine, is reminiscent of the classification of depression as endogenous versus reactive, which was popular before the advent of the DSM-III. In practice, the distinction between depression caused by biological versus psychological/social factors could have unwanted effects; physicians diagnosing a depression they construct as predominately biological might display less warmth and empathy toward their patients (Lebowitz & Ahn, 2014).

#### **4.5.1.2 Reducing self-blame and stigma; building knowledge in the community.**

The benefits of the biochemical model with regard to mitigating self-blame and reducing stigma and to contributing to building knowledge about the biological causes of depression in the community are not straightforward. The physicians constructed their biochemical explanation with patients as a positive factor in moving the patients from viewing their depression as a character flaw or something that they should be able to control, to accepting that they are not at fault for their own depression and to externalizing the problem. However, while Deacon and Baird (2009) reported that self-blame decreased among undergraduate students who imagined they were depressed and were told their depression was caused by a chemical imbalance, Kemp et al. (2014) reported no change in self-blame among undergraduate students who had personally experienced depression and were told their depression was caused by a chemical imbalance. Thus, it is unclear whether physicians succeed in reducing self-blame in their patients by telling them their depression is caused by a chemical imbalance. While the biochemical explanation might or might not reduce self-blame, the tradeoff is that patients expect a worse prognosis and view psychosocial interventions as ineffective (Deacon & Baird, 2009; Kemp et al., 2014). In addition, while the biological causes of mental illness have gained prominence in recent decades, overall stigma has not decreased (Pescosolido et al., 2010; Schomerus et al., 2012).

Scholars have theorized that the biological explanations of mental illnesses lead to neuroessentialist thinking, i.e., that the primary way to view psychological phenomena is through the activity and structure of the brain, and that mental illnesses are associated with abnormal brain activity (Dar-Nimrod & Heine, 2001; Haslam, 2011; Haslam & Kvaale, 2013). The biochemical explanation of depression can lead to attributions of uncontrollability, positioning depression like any other physical disease over which we have no control and thus reducing blame. However, it can also lead to neuroessentialism, which can increase other aspects of stigma, including a perception that those with mental illness are inherently different and possibly dangerous, that mental illnesses are resistant to intervention, and that for treatments to be effective they must target the brain directly (Haslam & Kvaale, 2013).

If the biochemical explanation does not significantly reduce self-blame among affected individuals and has not contributed to a reduction of depression stigma in the population, then there is little value in building knowledge about the biochemical causes of depression in the community. In addition, given that the chemical imbalance hypothesis of depression has been widely discredited and abandoned in the scientific and psychiatric communities (Healy, 1997), continuing to promote this hypothesis contributes to the misunderstanding of depression with unintended consequences.

As Lebowitz et al. (2013) suggested, the negative effects of neuroessentialism, such as prognostic pessimism, might be countered by information emphasizing the plasticity and non-deterministic aspects of genes and the brain, and by promoting the notion that all behaviour, e.g., socializing, exercising, laughing, etc., can influence the chemistry in the brain. While they did not talk of epigenetics and neuroplasticity, some physicians in the current study did report that they informed their patients that many different interventions could influence the brain. Given that these interviews were conducted in 2009, it is highly likely that research on epigenetics and neural plasticity in mental illnesses had not been effectively translated to clinical practice.

#### **4.5.1.3 Instilling hope and confidence.**

Family physicians are in a difficult position. In the absence of consensus on the etiology of depression, the chemical imbalance hypothesis offers a simple and compelling medical explanation for a patient's symptoms. Family physicians, who diagnose and treat the majority of depression cases, are generalists who are required to be familiar with a wide range of presenting problems; they are not psychiatric specialists. While psychiatrists might not routinely explain to patients that their depression is caused by a chemical imbalance (Pies, 2011), many family physicians in our study described using this explanation, especially when recommending antidepressants. While physicians constructed this discursive move as a way to communicate with their patients that their condition is understood and that treatments are available, if the chemical imbalance hypothesis leads to prognostic pessimism, then the narrative of instilling hope and confidence in recovery is undermined. In addition, there is much controversy surrounding the chemical imbalance hypothesis and the efficacy of antidepressants. After consulting their physician, patients might search the Internet about their condition and find that what their physician told them is disputed, which might affect trust in the physician-patient relationship. Searching "depression chemical imbalance" in Google brings up a number of articles, opinion pieces, and depression FAQs that refer to the complexity of depression and the lack of scientific evidence that depression is caused by a simple chemical imbalance (e.g., Angell, 2011; Arkowitz & Lilienfeld, 2014; Harvard Health Publications, 2009; Moncrieff, 2014; Mukherjee, 2012; Pies, 2011). As Blease (2014) suggested, presenting depression as

complex, multifaceted, and not fully understood has the potential to permit the patient to make an informed choice about treatment; such openness and transparency has the potential to exert a positive effect on the therapeutic relationship (Street, Makoul, Arora, & Epstein, 2009).

#### **4.5.2 Biopsychosocial Model of Depression: Treatment Limitations**

Physicians are trained to view depression as a multifactorial condition and many endorsed using the biopsychosocial model of depression in their practice. However, pragmatics of treating patients overruled any link between model and treatment recommendations. For example, the physicians' accounts contained references to antidepressant medications being offered regardless of perceived effectiveness for the given situation, and some physicians expressed feeling powerless to make substantial impact into the personal and social lives of their patients and being constrained by limited access to counselling and social assistance resources.

Access to social, psychological, and other mental health services is limited in primary care in Canada (Romanow & Marchildon, 2003; Grenier et al., 2008; Anderssen, 2015). Some participants stated they are "lucky" and "fortunate" to work in salaried positions at community and university clinics where they have time and ready access to mental health professionals such as counsellors, social workers, clinical psychologists, and mental health nurses. However, these types of clinics are rare and are available only to certain populations (e.g., students at the university). Primary universal health care, touted as the ideal model of care in Canada, is often unattained because access to mental health care providers is not universally accessible.

The Mental Health Commission of Canada (2012) has published a broad-based mental health strategy for improving mental health services in Canada. One of six strategic directions is aimed at improving access to services, treatments, and supports. To this end, the Commission recommended increasing the capacity of primary healthcare workers to address mental health concerns of a large number of people. The Commission recommended increasing resources and capacity of community-based care, including improved access to psychotherapy and standards for wait times. The Commission also recommended better social supports, such as housing and employment assistance. In 2016, the Mental Health Commission of Canada released a five-year action plan document to improve mental health services. This document was created following consultations with stakeholders and citizens, and it outlined 17 specific recommendations in the areas of leadership and funding, promotion and prevention, access and services, and data and research (Mental Health Commission of Canada, 2016). Implementation of these recommendations would permit and encourage family physicians to make treatment recommendations that are congruent with the biopsychosocial model of depression that many of them espoused.

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## **Chapter Five: Manuscript Two**

### **Explaining depression: A discourse analysis of neuroscientists' accounts of explanatory models and the chemical imbalance hypothesis of depression**

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## 5.1 Introduction

The clinical features of depression have been described similarly for over two millennia, with many predisposing and precipitating factors proposed over the years (Healy, 1997; Jackson, 2008). While biological research and theories into its causes abound, depression has an unknown etiology. Currently, investigations into the etiology of depression are occurring in the field of neuroscience, a hybrid scientific discipline focused on the brain and nervous system, with origins in molecular biology, chemistry, genetics, and anatomy and physiology (Abi-Rached & Rose, 2010; Abi-Rached, Rose, & Mogoutov, 2010). Current explanations in clinical neuroscience propose that its causes and correlations are manifold, with social factors, psychological factors, genetic vulnerabilities, and impairments in neuroplasticity, neurotransmitter functioning, endocrine functioning, and immune functioning all implicated in some form (Kendler, 2012; Krishnan & Nestler, 2008; Wong & Lucino, 2001).

While the etiological understanding of depression is complex and incomplete, the idea that depression is caused by a chemical imbalance in the brain remains pervasive and persuasive in Canadian and American society (e.g., Pescosolido et al., 2010; Sigurdson, 2019, unpublished manuscript). Until recently, pharmaceutical advertising promoted depression as a simple chemical imbalance in the brain that can be corrected with medication (Leo & Lacasse, 2008). While pharmaceutical advertisements no longer refer to depression being caused by a chemical imbalance (Lacasse & Leo, 2015), there is widespread espousal of the chemical imbalance explanation of depression among laypersons (Cohen & Hughes, 2011; France, Lysaker, & Robinson, 2007; Pescosolido et al. 2010). In the following section, I summarize the major biologically-based etiologies of depression, including the chemical imbalance explanations and contemporary ideas in neuroscience literature.

### 5.1.1 Biologically-Based Etiologies of Depression

#### 5.1.1.1 Humoral explanations.

For many years, human illnesses, including what we now refer to as depression or major depressive disorder, were conceptualized within the humoral system of medicine (Jackson, 2008; Healy, 1997). In the humoral system, diseases were thought to be caused by imbalances of the four humors, i.e., blood, phlegm, yellow bile, and black bile. The humoral conception of illness was prominent from the time of Ancient Greece up until the 18<sup>th</sup> century (Healy, 1997). Melancholia, meaning black bile (“Melancholia,” n.d.), is an historical term for severe depression which was thought to be caused by an excess of black bile in the blood (Jackson, 2008). The spleen, thought to be responsible for filtering black bile that originated in the liver, was the site of pathology in this system. Treatment of melancholia according to the humoral system typically involved bloodletting and purging, which was believed to remedy the excess of black bile built up in the body (Healy, 1997).

#### 5.1.1.2 Mechanical explanations.

In the 18<sup>th</sup> century, mechanical and hydrodynamic explanations were proposed to explain the etiology of melancholia and began to displace the humoral explanation. Jackson (2008), psychiatrist and medical historian, summarized the mechanical explanations as being first vasocentric, with symptoms of melancholia thought to be caused by sluggish blood or reduced circulation, and later neurocentric, with symptoms of melancholia thought to be caused by sluggish nerve fluid or depleted energy levels in the brain. By the 19<sup>th</sup> century, the vasocentric

and neurocentric explanations merged, and symptoms of melancholia were posited to be caused by impaired blood circulation within the brain, effecting nerve cells, as well as hereditary factors (Jackson, 2008). At this time, mental disorders, including what we now call depression, were increasingly viewed as brain diseases rather than diseases of the soul (Healy, 1997). Jackson (2008) concluded that, while the mechanical explanations diverged from explanations derived from the humoral system, treating depression continued to involve bloodletting and purging. In the 20<sup>th</sup> century, the advent of drugs that became known as the antidepressants made an impact upon the etiological explanation of depression.

### **5.1.1.3 Influence of antidepressants and the monoamine hypotheses.**

The discovery of the drugs classified as antidepressants led to a new conceptualization of depression. In the late 1950s, Roland Kuhn and Nate Kline independently reported their observations that two drugs appeared to have mood lifting properties (Healy, 1997). Roland Kuhn (1958) reported that imipramine, an antihistamine, appeared to have “potent antidepressant action” (Kuhn, 1958, p. 464) and Loomer, Saunders, and Kline (1957) described iproniazid, used to treat tuberculosis, as a “psychic energizer” (p. 129). The observations that certain drugs seemed to have antidepressant properties spurred research examining their mechanisms of action. Schildkraut (1965) proposed that the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) function by increasing the concentrations of monoamine neurotransmitters in the synaptic cleft, specifically the catecholamines (epinephrine, norepinephrine, and dopamine), by either preventing enzymes from breaking them down or by preventing their reuptake into the releasing cell. Coppen (1967) further argued that a lack of serotonin, another monoamine neurotransmitter, at important receptor sites in the brain was responsible for depression. Both Schildkraut and Coppen argued that reserpine, a drug thought to induce a depressed state, functions by reducing levels of monoamine neurotransmitters available in the synaptic cleft.

The shortcomings of the monoamine hypothesis of depression have been well documented (e.g., Bentall, 2009; France, Lysaker, & Robinson, 2007; Healy, 1997; Kirsch, 2010; Leo & Lacasse, 2008; Valenstein, 1998; Whitaker, 2010). The most significant challenge to the monoamine hypothesis of depression is the observation that antidepressant drugs influence neurotransmitters within hours but treatment response of antidepressants takes several weeks (Wong & Lucinio, 2001). Kirsch (2010), a psychology researcher known for his controversial claim that antidepressant effects are due to the placebo response, provided a comprehensive argument against the tenability of the chemical imbalance hypothesis. Kirsch (2010) argued against the monoamine hypothesis by citing research that was available to Coppen and Schildkraut; he noted that reserpine does not deplete monoamines, does not cause symptoms of depression at a high rate, and inhibits reuptake of serotonin and norepinephrine, similar to imipramine. Kirsch also argued that upwards of 90 experiments have been unsuccessful in causing depression by depleting monoamines in healthy people. Review articles summarizing the biological bases of depression provide a nod toward depleted monoamines but ultimately come to the same conclusion as Kirsch with regard to veracity of the monoamine hypothesis. For example, Wong and Lucinio (2001) wrote, “Thirty years of research have revealed some serious gaps and limitations in the monoamine hypothesis” (p. 347), and Krishnan and Nestler (2008) wrote, “The cause of depression is far from being a simple deficiency of central monoamines” (p. 895). Current ideas regarding the biological bases of depression are complex and there is no unifying etiological model for depression.

#### **5.1.1.4 Genetics and heritability hypotheses.**

While heritability is estimated at approximately 40% (American Psychiatric Association, 2013), genetic variants associated with increased risk for depression have not been consistently replicated. The most extensively studied gene potentially related to depression is 5-HTTLPR. This gene is responsible for promoting the coding of the serotonin transporter protein, which is responsible for the reuptake of serotonin at synapses. Caspi et al. (2003) posited that depression is caused by an interaction of stressful life events and a genetic vulnerability in 5-HTTLPR. Subsequently, much research was devoted to studying the relationship between 5-HTTLPR and stressful life events, with some researchers replicating these results (e.g., Kendler, Kuhn, Vittum, Prescott, & Riley, 2005) and others failing to do so (e.g., Risch et al., 2009). In an attempt to settle the conflicting results, Culverhouse et al. (2017), working as a large consortium of scientists who had previously published on the topic, reanalyzed a large corpus of published and unpublished data. They reported that there was no evidence for an interaction between stressful life events and 5-HTTLPR genotype. They concluded that future research into the topic be curtailed, given the lack of a strong, robust association.

#### **5.1.1.5 The neuroendocrine hypotheses.**

Stressful life events are associated with an increased risk of developing symptoms of depression. Stress produces a response in the hypothalamic-pituitary-adrenal (HPA) axis in the body, culminating with the release of cortisol. The HPA axis is central to the body's sympathetic, or fight-flight response. Sustained elevated activity of the HPA axis can lead to hypercortisolemia, which is associated with disturbances in anxiety regulation and monoaminergic systems, cognitive impairments, and volume reductions in limbic brain structures, similar to those observed in depressed individuals (de Kloet, Joels, & Holsboer, 2005). Among the correlational data for stress as a risk factor in the etiology of depression is the impaired suppression of cortisol following an injection of dexamethasone, a synthetic form of cortisol. Once thought to be a potential diagnostic biomarker for depression, the dexamethasone suppression test lacked the specificity to differentiate depression from comorbid conditions such as Alzheimer's disease, alcohol withdrawal, obsessive compulsive disorder, and schizophrenia (Nierenberg & Feinstein, 1988). After a comprehensive meta-analysis of studies assessing depression and stress hormones, Stetler and Miller (2011) concluded that HPA hyperactivity in depression varies across patient groups and depression subtypes, with the greatest effect observed in older patients with more severe symptoms. The data on stressful life events and their impact upon the endocrine system are robust but correlational, and the search for a reliable biomarker has so far been inconclusive.

#### **5.1.1.6 The neuroplasticity hypotheses.**

In the past two decades, neuroplasticity has shaped much debate and theorizing about the brain and behaviour, including depression. Neuroplasticity is an umbrella term that describes the brain's ability to adapt and change, functionally and structurally, to environmental stimuli and experiences throughout the lifespan (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). A central problem with the monoamine hypothesis of depression was the observed delay between elevated synaptic concentrations of monoamines and the therapeutic effect of antidepressants, and mechanisms underlying neurogenesis were purported to account for the delay (e.g., Castrén, 2005; Krishnan & Nestler, 2008). Castrén (2005) proposed that brain derived neurotrophic factor (BDNF), which plays a role in the maintenance of neurons and the survival of new

neurons, was a possible mechanism for altering activity-dependent neural plasticity. Krishnan and Nestler (2008) summarized the support for the role of BDNF in depression, noting that scientists have measured reduced postmortem hippocampal BDNF in people who were depressed, reduced BDNF expression following chronic stress in animal models of depression, and increased BDNF expression following antidepressant treatment in animal models of depression. A potential rapid-acting antidepressant, ketamine, appears to increase synaptic plasticity (Berman et al., 2000; Krystal, Sanacora, & Duman, 2013; Li et al., 2010). While neurogenesis and synaptic plasticity hold promise for the future of understanding the etiology of depression, much remains to be known.

#### **5.1.1.7 The neuroimmunity hypothesis.**

Finally, the immune system appears to play a role in the onset and course of depression. Cytokines, which are small signaling proteins created by immune cells, influence a number of basic functions that are disturbed during a depression, namely sleep, appetite, and cognition (Wong & Lucinio, 2001). Krishnan and Nestler (2008) summarized that cytokines appear to influence mood in humans and rodent models, but that the effect is inconsistent and the neural circuitry and pathways to behaviour are largely unknown. Hodes, Kana, Menard, Merad, and Russo (2015) reviewed the scientific evidence from studies with humans and animal models of depression and concluded that neuroinflammation contributes to the precipitation of a mood disorder. Schwartz (2015), in her book on neuroimmunity, posited that the immune response to acute stress facilitates recovery by restoring levels of BDNF and improving neuroplasticity. She also argued that under chronic stress, the immune response is disrupted, and the body is less able to recover to homeostasis. She proffered that improving immune response in cases of chronic, long-term stress, might improve outcomes for people with depression.

#### **5.1.1.8 Summary of biologically-based etiological explanations.**

Overall, depression appears to be associated with a number of factors that are not fully understood. The idea that depression is caused by a chemical imbalance of monoamine neurotransmitters in the brain has been displaced by theories implicating genetics, the neuroendocrine system, the immune system, and neuroplastic mechanisms in the brain. While the exact causes of depression are still unknown and no reliable biological markers currently exist, we seemingly know more about depression and the nervous system than ever before and neuroscience is at the forefront of this research.

While serotonin and the serotonin transporter may still be implicated among the causal mechanisms of depression, the current research that scientists are conducting with regard to depression is complex, nuanced, and manifold when compared to the chemical imbalance explanation as espoused by laypersons. The discrepancy between the pervasiveness and persuasiveness of the chemical imbalance hypothesis in lay society and the lack of conclusive scientific evidence to support the hypothesis in scientific literature led to the following research question: How do scientists working on the biological understanding of depression account for the use of the chemical imbalance hypothesis and structure arguments for and/or against it? The following analysis and discussion has the potential to add to the literature critical of the chemical imbalance hypothesis by adding the voice of scientists who are researching the mechanisms underpinning depression. It also has the potential to inform future directions on clinician-patient communication strategies for depression by articulating contemporary scientific views of the etiology of depression and the potential arguments for and against these explanations.



## 5.2 Analytical Perspective: Discursive Psychology

Discursive psychology applies concepts and ideas from discourse analysis to questions in psychology (Potter, 2003; Potter & Wetherell, 1987). Consistent with social constructionist epistemology, I assume that multiple versions of an event, person, and/or object are available to individuals through language, and those versions are created and shared between people. As a methodology, discursive psychology guides a systematic examination of how talk and text relevant to questions of psychological significance are structured via linguistic resources, the social actions that are performed via the use of these resources, and the possible functions of these actions (Potter, 2003). As recommended by Wetherell (1998) and employed in other discourse analytic work (e.g., LaFrance, 2007), I situate the content and style of discourses and the social actions they perform within broader social discourses of depression in Canadian and American medical and lay society.

## 5.3 Method

The data for the present analysis were derived from semi-structured interviews conducted in 2013 and 2014 with 10 neuroscientists working in the field of depression research. The interviews contained a broad range of questions regarding the science of biological psychiatry in general and depression in particular. The University of Saskatchewan Behavioral Research Ethics Board approved this research project.

### 5.3.1 Participants

Potential participants were first identified as authors who published review and opinion articles in the journals *Nature* (including *Nature Reviews Neuroscience*) and *Science* and who appeared, from website biographies, to be principal investigators of research programs on the neuroscience of depression. Further, a convenience sample of neuroscientists (also principal investigators) geographically close was solicited to participate. Finally, snowball sampling was used to identify additional scientists. Twenty-six potential participants were e-mailed a letter inviting them to take part in an hour-long interview about the science of depression (Appendix G). Ten scientists agreed to participate. I conducted one-on-one interviews with these scientists, either in-person ( $n = 4$ ) or by telephone ( $n = 6$ ).

The ten participants (seven males) ranged in age from 34 to 66 years (median = 53) and had worked as a researcher for 3 to 38 years (median = 24.5). Seven participants had PhD degrees (three in psychology, one in cell biology, one in neuroscience, one in biological psychiatry, and one in pharmacology/medicine); two participants had MD/PhD degrees; and one had an MD degree. All participants had advanced training as postdoctoral researchers ( $n = 8$ ) or psychiatric fellows ( $n = 1$ ), or both ( $n = 1$ ). All participants ran laboratories with multiple postdoctoral researchers and/or graduate students. Reported yearly grant funding for the laboratories ranged from approximately \$40,000 to \$1,000,000 USD (median = \$250,000; one participant did not disclose funding).

### 5.3.2 Procedures

Each participant was informed of the purpose of the research and his or her rights both verbally and through a written, signed consent form (Appendix B). Participants who were interviewed over the telephone received a copy of the consent form in advance by e-mail and provided verbal consent. Consent was also obtained to e-mail completed transcripts (Appendix C). The interview began with collecting demographic information (Appendix D). Interviews

with scientists lasted approximately one hour (range = 50 to 80 minutes; median = 59 minutes). The interviews were guided by a semi-structured schedule (Appendix E). The interview schedule contained questions and prompts regarding defining and studying depression, the challenges and controversies present in depression research, and the future of depression research.

The interviews were audio-recorded and transcribed verbatim by the author with all personally identifying information omitted. Consistent with University of Saskatchewan research ethics guidelines, the participants were provided with a copy of the transcript and they were permitted to modify, delete, or add to the transcript before releasing the transcript for purpose of analysis (Appendix F). One participant modified his transcript for clarity, but did not significantly alter the content. Jefferson transcription notation was not used because the high level of detail it provides was not required for the analysis. Instead, a more readable form of transcript notation was used (see Appendix G), and is similar to the notation used in other discourse analysis in social psychology research articles (e.g., Lafrance, 2007).

The analysis was an iterative process of reading the transcripts, listening to the audio recordings, and extracting segments of text related to the etiology of depression. These segments included talk about the chemical imbalance hypothesis of depression and alternative explanations regarding the mechanism of depression and purported causes. I compiled and organized these extracts using NVivo software (QSI International, n.d.) and chose a final collection of extracts that included responses from each participant related to the chemical imbalance hypothesis. I was principally interested in how the scientists accounted for the chemical imbalance hypothesis of depression and other explanations, and the functions achieved by these accounts. To this end, I drew upon analytic concepts in discourse analysis in social psychology: I paid attention to the way I and the interviewees constructed arguments in content and style and the similarities and differences among accounts (Wood & Kroger, 2000); I also paid attention to rhetorical features of justifying a position and warding off criticism utilized by myself and the interviewees (Billig, 1996). In the analysis, I make inferences about the possible motives and functions of specific rhetorical strategies.

## 5.4 Analysis

In the following analysis, I show the varied responses of the scientists to the question of whether the chemical imbalance hypothesis of depression is controversial or has impaired scientific and/or clinical progress in the understanding of depression. I then present extracts regarding alternative etiological models of depression.

### 5.4.1 Depression and the Chemical Imbalance Hypothesis

#### 5.4.1.1 Chemical imbalance as a general problem with brain function.

Some scientists argued that since depression involves altered function of the brain and brain circuit function involves chemical transmissions, the chemical imbalance hypothesis, while simplistic, is not controversial.

##### 5.4.1.1.1 *Extract 1a.*

1 SCIENTIST J: I think that uh if you  
2 look at, um, brain imaging or if you  
3 look at the responses to  
4 psychotropic medications there's

5 little doubt that these are  
6 alterations in brain circuit  
7 functioning, and that changes in  
8 functioning of the brain circuits  
9 have to do with the  
10 neurotransmitters, neurochemicals.  
11 And so hence the neurochemical  
12 imbalance or altered function, makes  
13 perfect sense. But that imbalance,  
14 may be different in different  
15 people. That is the problem. That  
16 is something that needs more  
17 attention.  
18 I: right  
19 SCIENTIST J: the fact that something  
20 must be going awry in the brain, I  
21 don't think there are issues about  
22 that.

In extract 1a, the scientist presents an argument in support of a general chemical imbalance hypothesis of depression. He begins his response by outlining the logic to arrive at a conclusion that depression involves a neurochemical imbalance. He appeals to the interviewer generally, “if you look at” (ll. 1 & 2), and he suggests that brain imaging and medication responses leave “little doubt” (l. 4) that neurochemical changes are occurring in the brain (ll. 5-9). The phrase “little doubt” constructs depression as almost certainly a neurochemical problem with the brain. He reinforces his argument with the statement, “makes perfect sense” (ll. 11-12), which constructs his conclusion as both realistic and evident. The scientist qualifies his conclusion with the phrase, “but that imbalance may be different in different people” (ll. 12-14), which acknowledges the lack of specificity regarding chemical imbalances in the brain – “that is the problem” (l. 14). He contends that “the problem” (l. 15) with knowing the etiology of depression lies in the variance seen across persons with depression. However, he argues, “something must be going awry in the brain” (ll. 17-18). The use of the term “something” is non-descript but he does suggest that the etiology of depression has a basis in dysfunctional brain chemistry and circuits. A brain-based etiology is presented as a “fact” (l. 17), bolstering his argument as a certainty, and he argues that from his viewpoint it is uncontroversial; i.e., “I don't think there are issues about that” (ll. 18-19). Extract 1b continues directly from extract 1a.

#### **5.4.1.1.2 Extract 1b.**

1 I: right. But it's, you know it's  
2 overly simplified to say that, you  
3 know depression is caused by a lack  
4 of serotonin or, or norepinephrine  
5 in the brain.  
6 SCIENTIST J: yes, so that becomes  
7 like the lay language.  
8 I: yes, and this is the language  
9 that, you know a lot of general  
10 practitioners are using as well.  
11 SCIENTIST J: exactly. And so, I  
12 mean not that, they're necessarily  
13 right, but, sometimes when you're  
14 dealing with laypeople, to be able  
15 to let them understand that there

16 might be something that's going awry  
17 in brain chemistry, I think it's a  
18 good thing. Because that's, we all  
19 agree that, that there is, that  
20 underpinning, at play.  
21 I: yes  
22 SCIENTIST J: but the use of a  
23 description of it, may be overly  
24 simplistic. And, and, not correct.

In extract 1b, I provoke the scientist to consider that the chemical imbalance is “overly simplified” (l. 2). The scientist responds by stating that it becomes a “lay language” (l. 7), which functions to distance the explanation from scientific discourses. When I state that general practitioners are also using the language, expanding on the claim that the chemical imbalance hypothesis is a lay discourse, the scientist agrees (ll. 8-11). He argues that while physicians who explain depression as a deficiency of neurotransmitters are not “necessarily right” (l. 12), the overall message that is communicated, i.e., “there might be something that's going awry in brain chemistry” (ll. 15-17), is valuable. This appears to be an example of a consequentialist ethical position, as the end result is positioned as more important than the fidelity of the explanation. With the phrase, “there might be” (l. 15), the scientist does construct his position as a possibility rather than an actuality, but then states, “we all agree” (l. 18) that abnormal brain chemistry is the “underpinning” (l. 20), or the foundation for the etiology of depression. It is unclear who he is referring to with the pronoun “we” (l. 18) but he is arguably referring to the general group of depression scientists and perhaps also to clinicians. I reply “yes” in agreement with his general statement that brain chemistry is implicated in depression (l. 21), thus including myself within the group he may be referring to. While I am suspicious of the veracity and primacy of the chemical imbalance hypothesis, as the interviewer I am aligning myself with the interviewee in this moment. I construct the position I took here as one of conversation facilitator rather than interrogator. The scientist, also taking up a socially mediated position in response to my provocation, then reiterates my utterance that the chemical imbalance hypothesis is “overly simplistic” (l. 23) and adds that it is “not correct” (l. 24).

Scientist J maintains a consistent position that depression is a brain-based disorder and that this position is generally accepted as fact by scientists in the field of depression research. While the idea of a serotonin deficiency in depression is acknowledged as an incorrect construction, he contends that communicating to patients that depression involves abnormal brain activity is beneficial. Thus, the value of the chemical imbalance hypothesis as an explanation for depression is maintained by its overall ability to construct depression as a brain-based disorder.

In extract 2, Scientist E presents an argument that our brains and bodies function through chemical interactions and depression likely involves a dysregulation of brain functioning.

#### **5.4.1.1.3 Extract 2.**

1 SCIENTIST E: We have you know, our  
2 neurons they work on, basically our  
3 bodies, it's a chemical body. So  
4 the interaction that we have, both  
5 physical and psychological, are  
6 transmitted through chemical, made  
7 into- transduced into chemical

8 interactions. So um, is there a  
9 dysregulation of um, brain function?  
10 Probably yes. But is that the  
11 primary, culprit of the disease? I'd  
12 say it isn't clear. We still don't  
13 know.

The scientist begins her response by stating that the human body is a “chemical body” (l. 3). The use of the term “basically” (l. 2) constructs the chemical nature of the human body as a fundamental property. The word “interaction” (l. 4) is vague and appears to be utilized in a broad sense to encompass all behaviour, “physical and psychological” (l. 5). She builds on this argument by adding that these ‘interactions’ are “transduced into chemical interactions” (ll. 7-8). The parallel construction of physical/mental interactions and chemical interactions within the brain serves to reinforce her claim that chemical interactions in the brain are fundamental. She constructs all interactions, i.e., those external and internal to the body, as associated with chemical messaging within the nervous system. She asks rhetorically, in the overall context of talk about depression, “is there a dysregulation of brain function?” (ll. 8-9). Given her premise that the human body is a chemical body, and functions via chemical transduction, she concludes that the answer is “probably yes” (l. 10). The word “probably” leaves some room for doubt but communicates that it is almost a certainty. Then, she interjects with another question: “is that the primary, culprit of the disease?” (ll. 10-11). She appears to be referring to the specific chemical imbalance hypothesis as the etiological mechanism of depression and she answers, “it isn't clear” (l. 12). Thus, similar to the scientist in extract 1, she contends that depression is associated with a dysregulation of brain function, but rather than stating the chemical imbalance hypothesis is incorrect, she constructs its status as “the primary culprit” as unknown.

By arguing that all ‘interactions’ involve a corresponding chemical interaction in the brain, Scientist E constructs the conditions for depression to be associated with a chemical dysregulation. However, by proposing that chemical changes in the brain may not be a primary precipitating mechanism, she positions her support in line with the prevailing understanding of depression: that the etiology is currently unknown.

In extract 3a, Scientist G argues that there is enough truth to the chemical imbalance hypothesis to warrant its current use.

#### **5.4.1.1.4 Extract 3a.**

1 SCIENTIST G: so you know, there's  
2 always an attempt to say, oh we've  
3 left the monoamine or the  
4 neurotransmitter hypothesis. Well  
5 there are neurotransmitters they do,  
6 you know cross synapses, we do know  
7 that serotonin transporter plays an  
8 important role, we do have, genetic  
9 data about differences in, um,  
10 promoter regions of the serotonin  
11 transporter, in some groups, um, the  
12 problem is that if you do the same  
13 study twice you don't actually know  
14 if you've recruited the same type of  
15 depressed people into, the two  
16 studies. So you may find something

17 with um, a promoter region in one  
18 study that you don't find in the  
19 other and maybe you just recruited a  
20 different, subtypes of depression in  
21 each study.

The scientist begins his response by addressing the dismissing of the monoamine hypothesis of depression (ll. 1-4). He then lists truth claims that are consistent with the hypothesis. He states in very simple terms, “well there are neurotransmitters” (ll. 4-5) that “cross synapses” (l. 6). This line of argument is similar to the previous extracts wherein the scientists argued that all behaviours or interactions involve chemical transmissions in the brain. He also claims the serotonin transporter, a protein that functions to move serotonin out of the synaptic cleft and back to the originating neuron, “plays an important role” (ll. 7-8). He emphasizes this claim as truth with the phrase “we do know” (l. 6). The serotonin transporter protein functionally reduces synaptic levels of serotonin and is the target of most antidepressant drugs, such as the SSRIs. To bolster his argument he argues that “we” (l. 6), presumably the scientific community, have “genetic data” (ll. 8-9) regarding differences in the genes that code for the serotonin transporter. The genetic data on serotonin transporter in depressive disorders are mixed, and he acknowledges this with the qualifying statement, “in some groups” (l. 11).

He shifts from a claim about the importance of the serotonin transporter to address “the problem” (ll. 11-12) in replicating data. He constructs the problem in the science as one of diagnosis and recruitment, arguing that depression encompasses a diverse range of individuals with different “subtypes of depression” (l. 20). The problem is a significant one in psychiatric research, which bases clinical diagnoses on clusters of symptoms that meet a defined threshold, rather than biological markers of disease. Thus, the truth claim that the genes that promote the encoding of the serotonin transporter protein play an important role is maintained by claiming that it occurs in a particular, but unknown, subtype of depression. Extract 3b continues directly from extract 3a.

#### **5.4.1.1.5 Extract 3b.**

1 I: so, just getting back to this,  
2 would you find it uh, you know  
3 controversial with, you know, a  
4 family physician telling a patient  
5 that they're, they're depressed  
6 because they have a chemical  
7 imbalance in the brain?  
8 SCIENTIST G: uh, would I find it  
9 controversial?  
10 I: mmhm  
11 SCIENTIST G: no I would find it um,  
12 simplistic but you know, there's  
13 nothing wrong with simple messaging  
14 if that has some legitimacy and if  
15 uh, it actually has some relevance  
16 to treatment.

In the extract, a direct continuation from extract 3a, I ask the scientist if the chemical imbalance explanation is controversial. The scientist responds to my prompt with a short response. He states that the chemical imbalance explanation is “simplistic” (l. 12). He sets up two qualities that substantiate the acceptability of the simple explanation: that it has “some

legitimacy” (l. 14) and “some relevance to treatment” (ll. 15-16). By using the word “some” (l. 14; l. 15), he qualifies the level of accuracy required to justify the use of the explanation. Stating that there is “nothing wrong” (l. 13) with the simple explanation, which is an extreme case formulation, appears to contradict the ethical position espoused by Blease (2014) if, for example, the explanation is not also prefaced with a statement that the etiology of depression is not fully understood.

In extracts 3a and 3b, Scientist G constructs an argument in partial support of the chemical imbalance hypothesis. Similar to previous extracts, the scientist builds a logical argument that brain chemistry and genetics play an important role in the etiology of depression and refers to current knowledge in support of this claim. While the scientist later stated that he would use an alternative explanation with patients (see Extract 12), he clearly reported that simple messaging is valid when there is some truth to the explanation and when it is related to the treatment being offered. The argument serves to reinforce the received views in biological psychiatry that the brain is a neurochemical signaling mechanism, that behavioural and affective dysfunction involves disruption of certain brain circuits, and that antidepressant treatments are effective.

#### **5.4.1.2 Chemical imbalance as a specific problem with serotonin function.**

When arguing against the chemical imbalance hypothesis, scientists constructed the chemical imbalance hypothesis as a specific problem with serotonin function, while maintaining that depression likely involves problems in brain function. In extracts 4a and 4b, Scientist I supports the idea of dysfunctional brain chemistry in depression, but also argues for the eschewal of the simple messaging of the chemical imbalance hypothesis.

##### **5.4.1.2.1 Extract 4a.**

1 SCIENTIST I: yeah, I mean I guess it  
2 depends on how you call, I mean, the  
3 idea of a chemical imbalance is,  
4 hhh, I would guess that there's  
5 something, probably, dysfunctional  
6 with the brain chemistry of someone  
7 who has full-blown depression.  
8 Like, I would guess that there's  
9 something that's not functioning,  
10 the way that it should be. But. I  
11 think that the way that the drug  
12 companies have spun, a chemical  
13 imbalance like a sad neuron having  
14 less serotonin and a happy neuron  
15 having more serotonin, has really  
16 permeated the public quite a bit  
17 and, even the medical community I  
18 would say yes, that's true as well  
19 with physicians, because that's the  
20 way they learn about it and I think  
21 that's really, impaired, progress in  
22 the field.  
23 I: mmhm

The scientist opens his response by beginning to articulate the boundaries of the chemical imbalance hypothesis. He states, “I guess it depends on how you call” (ll. 1-2), which opens a

discursive space for multiple interpretations of the chemical imbalance hypothesis. He audibly exhales (l. 3) when talking about the chemical imbalance hypothesis, which could be interpreted or received as a sign of exasperation. In support, he constructs, albeit somewhat hesitantly – i.e., “guess” (l. 4) and “probably” (l. 5) – that there is a dysfunction of brain chemistry. The use of the term “something” (l. 4) is vague and imprecise, and leaves the chemical imbalance open to a number of chemically-based mechanistic possibilities.

Further delineating the boundaries of a valid chemical imbalance hypothesis of depression, the scientist, emphasizing the word “But” (l. 10) with a halting intonation, indicates there are things that he does not agree with. The use of the phrase “the way that the drug companies have spun” (ll. 10-11) directly implicates the pharmaceutical industry as having crafted a particular interpretation of the data to present to the public. He constructs the spin used by the pharmaceutical industry with the aid of an evocative simile: “like a sad neuron having less serotonin and a happy neuron having more serotonin” (ll. 12-14). The simile constructs the chemical imbalance hypothesis as told by the pharmaceutical industry as very simplistic, and anthropomorphizes neurons as emotive beings. This simile functions to delegitimize the direct-to-consumer advertising of antidepressants as unscientific. The scientist also implicates the pharmaceutical industry in influencing physicians’ understanding of depression when he states, “because that’s the way they learn about it” (ll. 18-19). The statement functions to absolve physicians of responsibility for using the chemical imbalance explanation of depression with patients and to place the blame on pharmaceutical companies. Further, the scientist states that the simple chemical imbalance spin by the pharmaceutical industry as was widely adopted has “impaired progress” (l. 20) in the science of depression, denigrating its continued use.

Continuing his argument in extract 4b, the scientist builds a case against the simple chemical imbalance explanation of depression.

#### **5.4.1.2.2 Extract 4b.**

1 SCIENTIST I: Because people look at  
2 things in this very simplistic view,  
3 and I just don't understand like  
4 whenever I try to talk to someone  
5 about it at a public level I just  
6 say well, I mean if it was, if it  
7 was as simple as that how come the  
8 second you take Prozac you wouldn't  
9 improve? Because within minutes  
10 Prozac is going to elevate synaptic  
11 levels of serotonin so, if it was  
12 just, a sad neuron doesn't have much  
13 serotonin, then as soon as you boost  
14 it you should immediately feel  
15 better and that's definitely not  
16 what the clinical course of  
17 antidepressant treatment is.

The scientist argues that the lay public views depression in simple terms; by using the term, “people” (l. 1), he initially constructs the issue as occurring broadly, but further refines with the phrase “public level” (l. 5). The use of the term ‘public’ suggests that he may speak differently when talking to a lay audience than when speaking privately with colleagues. His statements, “I just don’t understand” (ll. 2-3) and “whenever I try” (ll. 3-4) construct the



chemical imbalance story as incredulous and suggest that he may be met with resistance when talking to a layperson about depression. The scientist then describes his retort as simple: “I just say” (l. 5). An often-cited phenomenon that is incompatible with the chemical imbalance hypothesis of depression is that patients must take antidepressants for several weeks before they might report symptom improvement despite rapid increase of synaptic monoamines such as serotonin. The scientist draws upon this shortcoming of the hypothesis and presents a rhetorical question he uses in conversation (ll. 6-8). To solidify his argument, he constructs an extreme case formulation within the question with the phrase, “the second you take” (l. 7), referring to the time it takes for the antidepressant to influence brain chemistry. The scientist describes a simple logical argument to refute the idea that “a sad neuron doesn’t have much serotonin” (ll. 11-12). The scientist positions himself as a credible expert by talking about “synaptic levels of serotonin” (l. 10) and by claiming knowledge of the “clinical course of antidepressant treatment” (ll. 15-16).

In extracts 4a and 4b, Scientist I delineates the chemical imbalance explanation as (1) a general explanation of brain function, which, consistent with previous extracts, is deemed likely to be credible, and (2) the chemical imbalance hypothesis as presented in pharmaceutical advertising, which is deemed to be simplistic and fallible. Constructing the explanation using the terms “sad neuron” and “happy neuron” functions to distance the simple explanation from scientific discourse. The scientist presents how he talks to a layperson who might believe that depression is caused by a chemical deficiency of serotonin, presenting a common retort to the hypothesis in a logical and credible manner.

Next, in extracts 5a and 5b, Scientist D rejects the chemical imbalance hypothesis and claims that depression scientists have moved beyond this explanation of depression.

#### **5.4.1.2.3 Extract 5a.**

1 I: uh you talk to someone on the  
2 street today, and you say, you know  
3 what is depression? Oh it’s a  
4 chemical imbalance, you know it’s a  
5 chemical imbalance in the brain.  
6 Uh, even physicians, you talk to  
7 physicians and they’ll say well,  
8 yeah it’s caused by a chemical  
9 imbalance. You see pharmaceutical  
10 advertisements, it’s a chemical  
11 imbalance. Um, you know it’s a very  
12 simplistic view of things it’s  
13 SCIENTIST D: see I would never say  
14 that. I would never call depression  
15 a chemical imbalance.

Extract 5a occurs within the context of an exchange regarding the chemical imbalance hypothesis of depression wherein the scientist agrees that the explanation has dominated the scientific field for decades. I then construct the chemical explanation of depression as pervasive among laypersons and “even physicians” (l. 6), which functions to provoke a response regarding the chemical imbalance explanation of depression. My use of the word “even” functions to acknowledge that it might be surprising that physicians also report depression to be caused by a chemical imbalance. Finally, I cite “pharmaceutical advertisements” (ll. 9-10) and make the claim that the explanation is “a very simplistic view” (ll. 11-12). The scientist responds to this

argument by distancing herself from the explanation: “see I would never say that” (l. 13). She uses the word “see” to communicate that her response is different than those who might uphold the argument as constructed by me. Her response is brief and she uses repetition – “I would never... I would never” (ll. 13-14) – to affirm her position that depression is not a chemical imbalance. Her use of the word “never” functions to construct her position as an absolute, but by using the first-person pronoun “I,” she constructs the statement as a personal opinion rather than a scientific declaration; e.g., ‘depression is not caused by a chemical imbalance.’ In the following extract, she continues her argument against the chemical imbalance hypothesis, before opening up a possibility that chemical imbalance could mean many different things.

#### 5.4.1.2.4 Extract 5b.

1 SCIENTIST D: I think in this example  
2 [the chemical imbalance hypothesis]  
3 you’re right, that wasn’t- well, I  
4 mean maybe, maybe the argument is  
5 that it’s just a hypothesis that  
6 took a really long time for people  
7 to get past. But I think we are  
8 past it because I don’t think there  
9 is anybody in the field who would  
10 agree that that’s, related to  
11 depression.  
12 I: Right, but the effects are still  
13 lingering.  
14 SCIENTIST D: I guess it depends on  
15 what you mean by chemical imbalance  
16 too, because chemical imbalance  
17 could mean all different kinds of  
18 things.  
19 I: Right. So specifically saying  
20 the serotonin hypothesis.  
21 SCIENTIST D: Right, well that’s  
22 clearly not the case in depression.  
23 At least not in my mind.

The scientist initially agrees with me that the chemical imbalance hypothesis is controversial, but stops short of restating the particular point with which she agrees: “that wasn’t-” (l. 3). Instead, she formulates an argument that “maybe” (l. 4) it was “just a hypothesis that took a really long time for people to get past” (ll. 5-7). Within this utterance she uses the phrase “just a hypothesis,” which functions to contrast with my assertion that the hypothesis has had broader societal implications on the lay understanding of depression. By using the word “people,” rather than an inclusive word such as ‘us,’ she distances herself and perhaps her specific discipline from those who maintained the chemical imbalance hypothesis. Then, she uses the pronoun “we” (l. 7) to argue that she and her discipline have moved beyond the hypothesis, and claims that it is her understanding – “I don’t think” (l. 8) – that no one in her field would contend that the hypothesis explains depression. Setting up that it is her understanding creates a space that distances her from making a declarative truth claim. However, she does construct an extreme case to bolster the truth claim when she states that there is not “anybody in the field” (l. 9) that would agree with the chemical imbalance hypothesis.

I prompt the scientist to comment on the broader implications of the hypothesis (ll. 12-13), but she continues by raising doubt about the way I specifically construct the chemical

imbalance hypothesis: “I guess it depends on what you mean” (ll. 14-15). The scientist argues that the term ‘chemical imbalance’ is extremely vague when she claims that it “could mean all different kinds of things” (ll. 17-18). This utterance appears to unite with the argument made by the scientists above when they stated that depression is a brain-based disorder, and that since the brain functions through chemical signaling, depression might be considered as being caused by a general chemical imbalance. However, she does not outline what these “different” (l. 17) things could be, to which I respond by defining it specifically as a deficiency of serotonin. She responds with an unequivocal statement, “that’s clearly not the case” (ll. 21-22), but again hedges by personalizing this position: “at least not in my mind” (ll. 23).

Scientist D’s arguments function to construct the chemical imbalance hypothesis as an idea that is no longer supported by herself or other scientists in her immediate field. She distances her position from laypersons and clinicians who might state that depression is caused by a chemical imbalance. She does open the possibility that there is some truth in stating that depression is associated with a chemical imbalance if the parameters are defined broadly enough; however, she unequivocally rejects that depression is caused by a deficiency of serotonin.

#### **5.4.1.3 Chemical imbalance and the science of depression.**

Scientists argued that the chemical imbalance hypothesis of depression and related ideas have had an impact upon scientific research. In extract 6, Scientist B argues that a problem with the specific chemical imbalance hypothesis is that it hinders depth and breadth of understanding.

##### **5.4.1.3.1 Extract 6.**

1 SCIENTIST B: Right now the, the only  
2 approved medications we have, are  
3 things that target monoamines, these  
4 chemicals that are presumably  
5 imbalanced within the brain. And I,  
6 and I just don’t think that’s the  
7 whole story and I don’t even think  
8 that that’s the majority of the  
9 story I think there’s probably a  
10 number of underlying causes to the  
11 disease and that when we start  
12 thinking about it as just purely a  
13 chemical imbalance, it doesn’t  
14 really get us any more specific.

The scientist begins by providing a time context, “right now” (l. 1), indicating the present day (the interview took place in early 2014), and states that “the only” (l. 1) medications for depression are ones that “target monoamines” (l. 3). The term “approved medications” (l. 2) provides a space to accommodate a drug such as ketamine, which acts differently to the current antidepressants, since it is not yet an approved medication for depression. The scientist expresses doubt regarding the chemical imbalance hypothesis in several ways. He defines monoamines as “chemicals that are presumably imbalanced” (ll. 4-5), with the word ‘presumably’ functioning to convey doubt and to distance him from the idea. He states, “I just don’t think” (l. 6), and the use of the adverb “just” (l. 6) functions to emphasize his statement that the chemical imbalance explanation is not the “whole story” (l. 7); the use of the adverb “even” (l. 7) functions to emphasize that it is also not the “majority of the story” (ll. 8-9).

He argues that depression is “probably” (l. 9) caused by a “number of underlying causes” (l. 10), with the term “probably” functioning to cast his statement as very likely but leaves room for doubt. He chooses the word “disease” (l. 11) to refer to depression, as opposed to ‘disorder.’ In the DSM, the word ‘disease’ is reserved for those conditions with a known underlying pathology, such as Alzheimer’s disease; the scientist’s use of the term ‘disease’ does function to construct depression as a legitimate medical diagnosis, in spite of the uncertainty with respect to etiology.

The scientist provides a critique of the chemical imbalance hypothesis. He states that when “we” (l. 11), depression scientists, think about depression “as just purely a chemical imbalance” (ll. 12-13), it does not “get us any more specific” (l. 14). The terms “just purely” (l. 11) function to acknowledge that a chemical imbalance might be associated with depression but that other aspects or mechanisms must be considered. Ultimately, he constructs the goal of the scientific endeavour in depression research to increase specificity.

In extracts 7a and 7b, Scientist H expresses disbelief when presented with a question about the use of the chemical imbalance hypothesis by laypersons and medical professionals, before arguing that it should not be completely eliminated from scientific research.

#### **5.4.1.3.2 Extract 7a.**

1 I: What do you think about, um the  
2 use of the chemical imbalance  
3 hypothesis of depression? um, both  
4 by medical professionals and as well  
5 as laypersons, given that the  
6 science of depression has most moved  
7 quite a, you know a distance past  
8 this simplistic, what depression is  
9 caused by.  
10 SCIENTIST H: do people really talk  
11 about that still? (laughs)  
12 I: they sure do yes.  
13 SCIENTIST H: I guess in my community  
14 they’re not really. I mean I guess  
15 there are, there are definitely  
16 people who just like to hang onto  
17 things but

Extract 7a opens with my question regarding the use of the chemical imbalance hypothesis. As seen in previous extracts, I pose a provocative position and construct the hypothesis as passé by calling it “simplistic” (l. 8) and state that the science of depression has moved on. The scientist responds with a short utterance and uses laughter to express her disbelief. The question “do people really talk about that still?” (ll. 10-11) functions to convey that she is either not aware that the chemical imbalance hypothesis is still prevalent or as a rhetorical question that denigrates the hypothesis. After I affirm that people still do talk about it, she reaffirms her own stance by making the claim that in her “community” (l. 13), presumably research scientists, they are not talking about depression as a chemical imbalance. Then she backtracks slightly by opening the argument that there are “definitely people” (l. 15) who “just like to hang on to things” (l. 16). The term “people” is vague, but presumably she is still talking about scientists in the field of depression. The phrase, “just like to hang on” is a derisive utterance that constructs the other as archaic and not progressive. In extract 7b, she furthers this

line of argument and she concludes with a statement which suggests that depression is potentially caused by a chemical imbalance and it should not be completely ruled out.

#### 5.4.1.3.3 Extract 7b.

1 SCIENTIST H: Um, I don't think, I  
2 don't think it's- as long as people  
3 don't hang on, I mean theories,  
4 theories are useful constructs, um  
5 but like, Tim Minchin says, you  
6 should, you know opinions, and  
7 theories, I use the word theories  
8 instead of opinions, we got to  
9 examine them every day. Look at our  
10 data, look at our theory, and refine  
11 them. So, is there a chemical  
12 imbalance? Well, maybe there is and  
13 maybe there isn't in a subset, but I  
14 wouldn't necessarily throw it out.  
15 I think people need to be open.

While in extract 7a, the scientist states that she and her community do not talk about depression as being caused by a chemical imbalance, in extract 7b she adds more nuance to her argument about the chemical imbalance hypothesis. She begins with a repeated utterance, “I don't think” (ll. 1-2) and then halts her utterance to begin a new line of argument. She argues, “theories are useful constructs” (ll. 3-4). The use of the term ‘theory’ suggests that her argument applies to all scientific hypotheses that have been verified by empirical means and are believed to have a greater probability of being correct. She cites the comedian Tim Minchin (l. 5), who has stated that people need to be hard on their opinions and evaluate their prejudices and biases in their beliefs. She appropriates this argument and applies it to the process of science. She argues that theories must be examined “every day” (l. 9), which suggests that the testing and refining of theories is a continual and common practice.

Once she has laid out the argument that theories must be examined every day, she returns to the topic of the chemical imbalance etiology of depression by presenting a simple question, “So, is there a chemical imbalance?” (ll. 10-11). She answers with equivocation, “maybe there is and maybe there isn't” (l. 12), which functions to present herself as neither holding on to a theory nor completely refuting it. By adding, “in a subset” (l. 13) she adds further nuance to the argument, suggesting that depression might have different causes in different people. She concludes that she “wouldn't necessarily throw it out” (ll. 13-14). In contrast to her derisive statement that some people “hang on” (l. 3) to ideas, she constructs openness as an ideal and necessary quality of a scientist with the statement, “I think people need to be open” (ll. 14-15). Thus, while she claims to not talk about depression as being caused by a chemical imbalance, she constructs herself as open-minded and willing to examine the data to refine the theory.

In extract 7a and 7b, Scientist H moves from expressing disbelief that clinicians and laypeople are still talking about the chemical imbalance hypothesis of depression, to expressing that the explanation might still be true and warrant further examination. Through this, she positions herself as an ideal scientist who is open to ideas and willing to engage with the data to refine a theory.

In extract 8, Scientist C alludes to the chemical imbalance hypothesis and describes it as a problem stemming from excessive reductionism.

#### 5.4.1.3.4 Extract 8.

1 SCIENTIST C: Neuroscientists,  
2 usually we are quite reductionistic  
3 and that's not good. We try to  
4 simplify things to ah, I don't say  
5 to go from molecules to behaviour,  
6 but it's almost so. Then you find  
7 an alteration in your molecule that  
8 correlates with an alteration in  
9 behaviour, you made a common mistake  
10 of oh, then the alteration of this  
11 molecule is that one that causes  
12 that behaviour.  
13 I: mmhm  
14 SCIENTIST C: that happened with  
15 antidepressants  
16 I: right

In this extract, the scientist does not directly reference the chemical imbalance hypothesis, but instead presents a “common mistake” (l. 9) made in neuroscience. He begins by making the claim that neuroscientists are “reductionistic” (l. 2). Indeed, methodological reductionism is a central component of most neuroscience research, where scientists attempt to explain phenomena at the most primary level possible. While reductionism might be a common goal among most neuroscience researchers, he states, “that’s not good” (ll. 2-3). He dampens the statement, “go from molecules to behaviour” (ll. 4-5), an extreme case formulation, by introducing it with, “I don’t say” (l. 4). However, he constructs the extreme case as close to truth when he adds, “it’s almost so” (l. 5). He provides a simple, general example that fits with the extreme case formulation, and constructs it as a “common mistake” (l. 9), which suggests that causation is frequently erroneously assumed with correlational evidence. Finally, the scientist alludes to the chemical imbalance hypothesis when he states, “that happened with antidepressants” (ll. 13-14). While the scientist does not state that he is talking about the chemical imbalance hypothesis directly, it is commonly known that depression as a chemical imbalance was hypothesized in light of observational evidence of clinical improvement of depressed patients with antidepressant medication treatment, the depressive effect of the drug reserpine, and the chemical effect of the TCA and MAOI medications.

Making an assumption of causation based on correlational data is a fallacy. In extract 1, for example, Scientist J makes the claim that depression is associated with altered brain circuit function based on evidence from brain imaging data and medication response, and, from this evidence, he concludes that abnormal functioning in the brain must cause depression. While this relation is potentially correct, the argument relies on correlational data. Scientist C in extract 8 warns that neuroscientists are prone to making this mistake and alludes to the chemical imbalance hypothesis, which was derived in an attempt to explain the action of antidepressants.

In extract 9, the scientist presents a similar argument against the way the chemical imbalance hypothesis was created.

#### 5.4.1.3.5 Extract 9.

1 SCIENTIST A: you know people call me  
2 depression researcher but I don't  
3 want to call- be called depression

4 researcher because I don't think we  
5 are investigating that. So we're  
6 investigating how the drugs act.  
7 And ah that I think is not- it's a  
8 different thing.  
9 I: mmhm  
10 SCIENTIST A: I mean, and I think  
11 it's dangerous and and you know even  
12 though I'm doing you know I have to  
13 say I'm doing that thing myself, as  
14 well, but it's dangerous.  
15 I: how so?  
16 SCIENTIST A: I mean, hhh, it's you  
17 know, so the fact that if if you  
18 know that the drugs do something,  
19 then it's very easy to assume that  
20 the disorder is caused by the  
21 opposite. So if there is an  
22 increase in BDNF by these drugs then  
23 people think that depression is  
24 caused by a lack of BDNF. Ah, or  
25 serotonin for that matter, the same  
26 way. And I think it's it's not  
27 proper logic to to think that way.

The scientist states that he does not want to be called a “depression researcher” (ll. 3-4). Rather, he positions himself as a researcher “investigating how the drugs act” (l. 6). He argues that conflating research on how antidepressants function with depression research is “dangerous” (l. 11). However, separating research on antidepressants from research on depression is difficult given their close relationship, and the scientist acknowledges that he is “doing that thing” (l. 13) himself, i.e., conflating antidepressant drug effects with the etiology of depression. Thus, while the scientist is interested in depression, he is careful in how he constructs his identity as a researcher lest he be trapped into going beyond the data regarding the effect of an antidepressant drug to commenting on the nature of depression.

I prompt the scientist to clarify how conflating antidepressant research and depression research is dangerous (l. 15) and the scientist argues that it is “very easy to assume” (l. 19) the cause of depression based on the action of an antidepressant, which is similar to the argument in the previous extract where the scientist called it a “common mistake.” He furthers his argument with a more specific example: BDNF (brain-derived neurotrophic factor; ll. 21-24). The scientist argues that the hypothesis that a lack of BDNF causes depression was based on a faulty assumption and is the same as what happened with serotonin and the chemical imbalance hypothesis of depression. The extract closes with his statement, “I think it's it's not proper logic to think that way” (ll. 27). The scientist, as opposed to other “people” (l. 22) who may make ‘dangerous’ assumptions about causation, positions himself as thinking responsibly and logically about the data.

In extract 9, Scientist A distances himself from controversy surrounding the construction of depression via indirect means, i.e., defining depression based on the actions of antidepressants. By denying that he is a depression researcher *per se*, and claiming that it is easy to make the assumption that depression etiology is the opposite of an observed mechanistic effect of an antidepressant, he constructs himself as a responsible researcher. Similar to how the

scientist in extract 9 argues against assuming causation from correlational data, in extract 10 he also argues that those who make such assumptions are committing a logical fallacy.

Extract 10 is a long passage of talk broken into three extracts, wherein Scientist A voices criticism of the chemical imbalance hypothesis.

#### **5.4.1.3.6 Extract 10a.**

1 SCIENTIST A: Yeah it's, you actually  
2 are right. I mean it is something  
3 which is very much uh penetrated  
4 popular press and uh and and also  
5 even you know, I've been to meetings  
6 with with clinicians and if you go  
7 to the poster they show something  
8 and you talk with these people and  
9 they would say they would say that  
10 well of course it's not, we know  
11 it's not that simple as this and  
12 it's sort of more multidimensional  
13 problem and blah blah blah. But uh  
14 if you sort of you know if you  
15 scratch the surface a little bit you  
16 would find out in the deep in their  
17 mind they think that it is about  
18 serotonin after all (slight  
19 chuckle).  
20 I: mmhm, yes  
21 SCIENTIST A: So this is- it is it is  
22 uh it is I think uh, depressing.  
23 (both laugh)

The scientist responds in an affirmative way to my prompt regarding the adoption of the chemical imbalance hypothesis as an explanation for depression by laypersons and clinicians, and emphasizes this affirmation with the word, “actually” (l. 1). The use of the word ‘actually’ might be received by the listener as conveying surprise or signaling an unexpected admission. He states that the chemical imbalance hypothesis has “penetrated popular press” (ll. 3-4), which constructs the hypothesis as a powerful force capable of infiltrating the media. The term ‘popular press’ typically refers to media intended for the general public, as opposed to academic books and journal articles.

The scientist then moves to clinicians and provides an anecdotal example of interactions he has had with clinicians at academic conferences, which functions to bolster his claim with evidence. The use of plural, e.g., “clinicians” (l. 6), “they” (l. 7), “people” (l. 8), constructs the anecdotal report as having occurred multiple times with different clinicians. He uses reported speech of the clinicians to construct his argument that the chemical imbalance hypothesis is an idea that some clinicians support, which again functions to reinforce his argument. He uses repetition – “of course it's not, we know it's not” (l. 10) – to emphasize that clinicians assert that they do not construct the etiology of depression as simply a chemical imbalance of serotonin, but then diminishes and dismisses the reported speech of the clinicians with the phrase, “blah blah blah” (l. 13). The phrases “scratch the surface” (ll. 14-15) followed by “deep in their mind” (l. 16) construct the viewpoints that depression is a “multidimensional problem” (l. 12) as superficial and that depression is a problem with “serotonin” (l. 17) as entrenched. The scientist



uses humour to convey his disagreement, employing the word “depressing” (l. 21) in a conversation about the etiology of depression.

**5.4.1.3.7 Extract 10b.**

1 SCIENTIST A: I find it's uh you  
2 know, uh and this is one of- these  
3 are among the things that that sort  
4 of hold back, progress in in the  
5 field, that people don'- people  
6 aren't open minded to looking at  
7 the-. You know it could be that,  
8 I'm not saying that, it might very  
9 well turn out that that depression  
10 is about a problem with serotonin in  
11 the end. But I don't think it is in  
12 such a simple manner that people are  
13 thinking about it at the moment. So  
14 I think what the- there would be a  
15 lot of important nuances there. So  
16 yeah you're right and what, it is  
17 sort of not, and you know  
18 pharmaceutical industry definitely  
19 has their have their hands in the  
20 fact that this has penetrated the  
21 popular press  
22 I: yes  
23 SCIENTIST A: and sort of sort of  
24 layman understanding so so deeply.

The scientist continues by arguing that adherence to the chemical imbalance hypothesis of depression has a negative effect on the science of depression. He constructs his argument with a claim that “people aren't open minded” (ll. 5-6). The general and vague term “people” positions the problem as occurring among others. He halts his utterance about open-mindedness (l. 6) to interject with the possibility that depression “is about a problem with serotonin in the end” (ll. 9-10). While in the midst of constructing an argument for being open-minded, the scientist stops to present himself as being open-minded by acknowledging that serotonin may in fact be a causative agent for depression, pre-emptively countering any claim against his openness to ideas, which is consistent with the talk of several of the scientists. With the use of the phrase, “at the moment” (l. 13), the scientist presents the problem of the widespread use of the chemical imbalance hypothesis as occurring in the present. The scientist begins a couple unfinished utterances as he attempts to articulate his position (ll. 16-17), and ends up indicting the pharmaceutical industry as responsible for the translation of the chemical imbalance hypothesis to the mainstream media and lay understanding of depression. The phrase, “have their hands in” (l. 19), suggests purposeful action by the pharmaceutical industry in promoting the hypothesis.

**5.4.1.3.8 Extract 10c.**

1 SCIENTIST A: We don't have  
2 unfortunately- I mean a part of it  
3 is that the story is very  
4 compelling. I mean it's it is  
5 simple  
6 I: mmhm

7 SCIENTIST A: and uh, and it's not  
8 something that is uh, as you know  
9 the format of the story is not new,  
10 because if you think about if you  
11 think about Hippocrates he was  
12 thinking about depression as an as  
13 an excess of black bile,  
14 I: mmhm  
15 SCIENTIST A: which is very much the  
16 same kind of thinking. I would say  
17 that you just changed the you know  
18 the pluses plus to minus. You would  
19 say that there is, it's not about  
20 too much black bile it's too little  
21 serotonin.  
22 I: yes  
23 SCIENTIST A: so, in a sort of, the  
24 kind of context is very similar. So  
25 this has been with us, you know two  
26 and a half millennia. So I'm not  
27 surprised that it's, you cannot  
28 change these things overnight.  
29 Plus, we don't have anything, simple  
30 to offer.

Turning to the reasons why the chemical imbalance explanation persists, the scientist begins his claim that scientists studying depression do not have a simple alternative to offer. He halts his utterance at “unfortunately-” (l. 1) and does not return to it until the final line in the extract. He interjects to describe the “story” of depression as a chemical imbalance as “compelling” (l. 3), “simple” (l. 4), and “not new” (l. 8). The scientist does not elaborate upon how it is compelling, but he does compare the chemical imbalance hypothesis to “Hippocrates” (l. 10) and humourism. Hippocrates, the ancient Greek physician known as the father of medicine, proposed that the balance of four bodily fluids influenced health and temperament, with one of the four humors, black bile, being associated with a melancholic temperament. The scientist argues that it is “very much the same kind of thinking” (l. 14), and by comparing the chemical imbalance hypothesis to humourism, he constructs the fundamental principle of the hypothesis as archaic. He presents the comparison as simple when he states, “just” (l. 16) change the “plus to minus” (l. 17). He argues that depression has been considered a chemical imbalance, of black bile or serotonin or BDNF, for “two and a half millennia” (ll. 24-25). The time reference functions to construct the chemical imbalance explanation as extremely persistent and he draws on that persistent construction to explain that he is “not surprised” (l. 25) that it remains. Finally, he appears to continue the utterance started at the beginning of this extract when he states, “we don't have anything simple to offer” (ll. 27-28). Thus, the scientist argues that the chemical imbalance hypothesis has persisted because it is a simple explanation, consistent with long-held conceptualizations of depression, and because of the absence of simple alternative explanations.

Across extracts 10a to 10c, Scientist A develops an argument against the chemical imbalance hypothesis and the influence on science and practice. He agrees that clinicians espouse the chemical imbalance hypothesis and he proposes that the persistence of this idea limits the production of novel ideas regarding the etiology of depression. He argues that others may not be open-minded to new and alternative ideas, which also inhibits progress. He

implicates the pharmaceutical industry in spreading the message to a lay and clinical audience. However, he acknowledges that the explanation will need to be replaced by something and that scientists do not currently have a simple explanation for depression.

As demonstrated in the analysis of accounts and arguments above, the scientists interviewed for this research project formulated a range of arguments for and against the chemical imbalance hypothesis of depression. In defense of the chemical imbalance hypothesis, scientists utilized a rhetorical construction of depression as a brain-based disorder and the brain as functioning through chemical transmissions. Arguing against the chemical imbalance hypothesis, scientists constructed the chemical imbalance hypothesis specifically as a deficiency of serotonin and drew attention to the shortcomings of the hypothesis, most notably the observation that serotonin levels are rapidly increased and yet depression symptoms do not abate for several weeks. Some of the scientists implicated the hypothesis in affecting the progress of science and presented themselves as good scientists who are open to novel ideas. Overall, constructing the distinction between a general chemical imbalance and a specific serotonin deficiency allowed for the maintenance and support of the assumption that depression is a brain-based disorder across arguments for and against.

#### **5.4.2 Alternative Explanatory Models**

If depression is not caused by a simple chemical imbalance, such as a deficiency of serotonin or norepinephrine in the brain, what might physicians tell their patients instead? Some scientists argue that the chemical imbalance hypothesis, in a broad way, is accurate enough for physicians to continue to use it to explain depression to their patients. Others argue that it should be abandoned in its specific form, i.e., that low levels of neurotransmitters such as serotonin and norepinephrine cause depression, and suggest that an explanation involving reduced neural plasticity in depression may be more in-line with the current understanding of depression. However, they express skepticism that physicians would use such a description and that laypersons would understand. While no scientist explicitly states that physicians should tell their patients that the causes of depression are unknown, several scientists state that we do not understand the causes of depression. The following extracts are a selection of talk on alternative explanatory models.

##### **5.4.2.1 Modifying the chemical imbalance explanation.**

In the first extract on alternatives, Scientist G argues for the use of the chemical imbalance hypothesis with the addition of information about brain circuits.

###### **5.4.2.1.1 Extract 11.**

1 SCIENTIST G: I think we personally  
2 would be more likely to talk about,  
3 um, how, neurotransmitters and if  
4 you want to call it brain chemicals,  
5 influence the way um, circuits work  
6 in the brain, to regulate mood,  
7 sleep, appetite, sexual interest,  
8 thinking, concentration, and  
9 equally, hopelessness, suicidal  
10 ideation, um, various other issues.  
11 I: mmhm

12 SCIENTIST G: So I think you can  
13 weave them together, it's not an  
14 either-or, kind of model.

The scientist in extract 11 continues a defense of the use of the chemical imbalance hypothesis by physicians. He uses the pronoun “we” (l. 1), which may refer to himself and other collaborators in his research group. The phrases “I think” (l. 1) and “more likely” (l. 2) may be received by the listener as qualifying statements signaling that he is not entirely certain how his colleagues describe depression. He states that “neurotransmitters” (l. 3), which could also be simplified to “brain chemicals” (l. 4), “influence the way circuits work in the brain” (ll. 4-5). This adds some complexity to the explanation while maintaining simplicity, and is consistent with the talk of other interviewees who constructed neurotransmitters as having a general influence on various circuits in the brain.

He continues his explanation by linking talk of brain circuits to specific symptoms involved in depression, from “mood” (l. 6) to “suicidal ideation” (l. 9). This talk fits with the assumption that neural circuits regulate behaviour and that mental illnesses are associated with disruption or dysregulation of the circuits. Finally, the scientist argues that the explanation described above and the chemical imbalance explanation can be used in conjunction with each other, i.e., “you can weave them together” (ll. 12-13). By stating that it is not an “either-or kind of model” (ll. 13-14), the scientist presents an alternative to the simple chemical imbalance hypothesis that adds a level of complexity while maintaining simplicity.

Overall, Scientist G argues for retaining the chemical imbalance hypothesis, while adding that neurotransmitters influence circuits in the brain that regulate mood and behaviour. Underpinning this explanation is the assumption that all behaviour is associated with the functioning of neurotransmitters and brain circuits.

#### **5.4.2.2 Replacing the chemical imbalance explanation.**

If the chemical imbalance hypothesis is inadequate, what alternative explanations are possible? Some of the scientists presented neuroplasticity and neuroimmune dysfunction as possible explanations.

##### **5.4.2.2.1 Extract 12.**

1 SCIENTIST D: exposure to chronic  
2 stress really what it does is  
3 dampens the brain's ability to be  
4 plastic. So our brain is constantly  
5 changing and adapting to everything  
6 that we're doing.... So, the  
7 question is what is the specific  
8 mechanism and that's where we fail  
9 because we don't have the answer....  
10 But what I can tell you without any  
11 doubt, is that the depressed brain  
12 is less plastic.  
13 I: Right, okay  
14 SCIENTIST D: Uh, I don't know if,  
15 family physicians will start saying  
16 that because it doesn't sound nearly  
17 as good as you have a chemical  
18 imbalance.... You tell them your

19 brain is like quiet or not plastic  
20 or whatever and they're going to be  
21 like, oh my god, you know, and how  
22 can a pill fix that?

The scientist states that “chronic stress” (l. 1), which she had previously constructed as a precipitant of depression, reduces neuroplasticity. She defines a “plastic” (l. 3) brain as one that is capable of “changing and adapting to everything” (ll. 4-5), which constructs plasticity as a basic, fundamental feature of a healthy brain. She does state that the mechanism underlying plasticity is unknown (ll. 6-9), but follows that with a statement of certainty, “without any doubt” (l. 10), that depression is associated with reduced plasticity. Despite the earlier claim that plasticity is reduced under conditions of chronic stress (ll. 1-3), she chooses the word “depressed” (l. 11), which draws upon the assumption that at least some depression is precipitated by chronic stress.

She argues that physicians might not be willing to adopt the plasticity explanation. She indicates that the plasticity explanation “doesn’t sound nearly as good” (ll. 15-16). She does not elaborate on how the chemical imbalance hypothesis sounds good, but she does seem to suggest that the way the explanation sounds to the patient is important. She goes on to question the effect on patients. She constructs the potential plasticity explanation in its simplest terms, i.e., “your brain is like quiet or not plastic or whatever” (ll. 18-19), and imagines that the patient would react with shock – “oh my god” (l. 20) – and despair – “how can a pill fix that?” (ll. 20-21).

This scientist initially presents neuroplasticity as a potential explanation for depression that is more accurate than the chemical imbalance explanation. While she is unequivocal in her support for the brain being less plastic under chronic stress and while in an episode of depression, she does not talk favourably about it being used to explain depression to patients, arguing that physicians will not like the explanation and that it could have a negative effect on patients’ view of their condition.

In extract 13, Scientist I also questions whether a plasticity explanation could replace the chemical imbalance explanation.

#### **5.4.2.2.2 Extract 13.**

1 I: Maybe, plasticity, would, you  
2 know allow for some, you know some  
3 sort of, broader view some more  
4 options? Um  
5 SCIENTIST I: Mhm, yeah, that’s  
6 definitely possible I think it’s  
7 just, hhh, plasticity is a bit more  
8 of a loaded gun because it’s already  
9 a term that’s less, that the public  
10 is less familiar with so, it  
11 requires some sort of base knowledge  
12 of what the concept of  
13 neuroplasticity even is. I mean  
14 chemical imbalance is an easy sell  
15 because you can just say there are  
16 chemicals in the brain. And in  
17 people who are depressed there’s an

18 imbalance in these chemicals.  
19 (chuckle)

I prompt the scientist to consider plasticity as an alternative explanation. The scientist initially agrees, stating, “that’s definitely possible” (ll. 5-6), but he audibly exhales (l. 6) and calls plasticity a “loaded gun” (ll. 7-8), which is an evocative phrase that suggests it is an accident waiting to happen. Thus, while he supports the explanation in principle, he constructs it as potentially very dangerous. He argues that it is dangerous because it is not a common concept with which laypersons are familiar, and would require “some sort of base knowledge” (ll. 11-12), which implies that the plasticity explanation would be too complicated for a physician to explain in a short appointment. He contrasts the plasticity explanation with the chemical imbalance explanation. He states the chemical imbalance explanation is “an easy sell” (ll. 13-14), which identifies the importance of persuasive rhetoric on the part of physicians. As opposed to plasticity, he constructs the chemical imbalance explanation as simple, e.g., “just say” (l. 14), because it only requires knowing “there are chemicals in the brain” (ll. 14-15) and “there’s an imbalance in these chemicals” (ll. 16-17). The scientist chuckles, potentially because the explanation is so simple and that there is no definitive scientific evidence that chemicals are imbalanced in depression.

Scientist I initially agrees that plasticity may be an alternative explanation for depression, but he also argues that an explanation of depression involving neuroplasticity might not be accepted as an alternative explanation. He constructs the plasticity explanation as potentially dangerous, and cites a lack of knowledge among the public about the concept of plasticity and reluctance among physicians to replace a simple explanation with a more complicated explanation as reasons why it might not be possible to replace the chemical imbalance explanation.

In extract 14, the scientist denigrates the specific chemical imbalance hypothesis by suggesting that it is potentially responsible for increasing the stigma of depression, and then presents an alternative conceptualization.

#### **5.4.2.2.3 Extract 14.**

1 SCIENTIST B: Um, and and it [the  
2 chemical imbalance hypothesis]  
3 probably does kind of, further the  
4 stigma associated with it.... And  
5 there’s a clear correlation between,  
6 um, the immune system an-  
7 dysregulation of the immune system  
8 and depression and anxiety and other  
9 psychiatric illnesses. And I think  
10 when you start talking to people  
11 about those types of data,  
12 comforting in some ways and those  
13 types of data could destigmatize it  
14 because it’s not about some vague  
15 general chemical imbalance that  
16 causes this vague general cluster of  
17 behavioural symptoms, it’s about an  
18 underlying disease that could be  
19 targeted therapeutically to correct  
20 a symptom.

While the scientist does use hedging statements, “probably” (l. 3) and “kind of” (l. 3), he argues that the chemical imbalance hypothesis might “further the stigma” (ll. 3-4) of depression. This argument is consistent with the research on stigma and the chemical imbalance hypothesis of depression, which generally suggests that understanding depression as being caused by a chemical imbalance in the brain is associated with higher perceived stigma of the disorder (e.g., Deacon & Baird, 2009; Haslam & Kvaale, 2015; Kemp, Lickel, & Deacon, 2014; Pescosolido et al., 2010; Schomerus et al., 2012). The scientist then begins to talk about an alternative conception of depression, linking “dysregulation of the immune system” (l. 7) with depression and other mental illnesses. He halts his utterance to add the word “dysregulation” (l. 7), which conveys that he is talking about an impairment in the body’s ability to control or maintain proper functioning. His use of the phrase ‘immune system’ is a powerful reference to the body’s ability to counter infections and diseases. It is important to note that the scientist describes this link as a “clear correlation” (l. 5), rather than causation.

He returns to the concept of stigma by stating that data on the dysregulation of the immune system in depression is “comforting in some ways” (l. 12) and “could destigmatize it” (l. 13). He contrasts the talk of immune system data with the chemical imbalance explanation, calling it a “vague” (l. 14) and “general” (l. 15) imbalance that causes “vague” and “general” (l. 16) symptoms. This contrast casts the immune system data as indicating a specific and precise cause, despite being correlational data. Further, while never suggesting that the immune system is the culprit of depression, the scientist does construct the immune system data as an indicator that there is “an underlying disease” (ll. 17-18). He constructs the disease as amenable to pharmacological treatment when he states that the disease could be “targeted therapeutically” (l. 19). Finally, the singular term, “a symptom” (l. 20) contrasts with the plural term, “cluster of... symptoms” (ll. 16-17). Earlier in the interview, this scientist discussed moving away from DSM nosology in research in favour of the Research Domain Criteria (RDoC), which focuses on discrete symptoms rather than syndromes. His use of the term, “a symptom” is consistent with his preferred approach to defining depression for research purposes.

Overall, he argues that an explanation that includes the data regarding immune system dysregulation could benefit patients by reducing the stigma associated with depression and the chemical imbalance hypothesis. His construction of depression as a disease involving the immune system functions to further legitimize depression as a biological pathology.

#### **5.4.2.3 Depression etiology as an unknown.**

Many scientists stated that the etiology of depression is unknown. Indeed, some scientists stated that their interest in depression research is due to the fact that it remains a mystery. The following extract is an example of how one scientist talked about depression and its unknown etiology.

##### **5.4.2.3.1 Extract 15.**

1 SCIENTIST A: So if you, if you're  
2 asking more about, about what I  
3 think about depression, what  
4 depress- so I think that, the short  
5 answer is we have no idea. I don't  
6 think that we really know, and this  
7 is ah, many people think that we  
8 know and sometimes it's uh, I've

9 been wondering whether it is more  
10 dangerous, you know, that we don't  
11 know, is it more dangerous that we  
12 don't know or, or the fact that we  
13 think we do,  
14 I: right  
15 SCIENTIST A: do know. And it's  
16 almost better I think that if if  
17 you, if you, if you know that you  
18 don't know, then then you have to  
19 sort of then you're curious about  
20 what might be happening. If you  
21 think you know, ah, that you know,  
22 then, then you're not interested in  
23 alternative, uh  
24 I: mmhm, right  
25 SCIENTIST A: alternative ideas. And  
26 I think that you know the former is  
27 true, I don't think we really know  
28 what what what depression is about.

The scientist clarifies my question about depression etiology (ll. 1-3), and provides what he calls the “short answer” (l. 4), which is, “we have no idea” (ll. 4-5). The term ‘short answer’ qualifies the statement as being the endpoint of what could potentially be a long answer. Indeed, there are many potential leads about the causes of depression with many ongoing investigations. However, the phrase “we have no idea” functions to construct the nature of depression as absolutely unknown. The scientist is careful in his statements to express that it is his opinion, (i.e., “I think” (l. 3); “I don't think” (l. 5)), which is not universally shared (i.e., “many people think that we know” (ll. 6-7)). He is not clear who he is referring to by the vague term “people” (l. 6), but it might be argued that in the context of an interview about the science of depression that he is talking about other scientists. By acknowledging that there are “many” who think otherwise, the scientist is positioning himself as a person who is “curious” (l. 18) and “interested in alternative...ideas” (ll. 21-23).

The scientist continues to present himself as inquisitive with the statement, “I've been wondering” (l. 8), and argues that constructing depression as having known etiology is potentially as “dangerous” (l. 9) as not knowing the etiology of depression. While he does not explicitly say so, not knowing the etiology of depression could have negative consequences, especially for those who suffer from depression and for whom the available treatments do not work. However, he concludes, “it's almost better” (l. 14) to “know that you don't know” (l. 16). The phrase “almost better” concedes that it would still be better to know the etiology of depression, but he concludes that if a scientist thinks he or she knows what depression is, then she or he will not be as “curious” (l. 18) and will not be interested in “alternative ideas” (l. 23). The argument relies on his stated assumption that we do not know “what depression is about” (l. 26). Thus, while there are scientists working to understand the etiology of depression and following several different lines of explanation, this scientist warns about the dangers of prematurely concluding that the etiology of depression is known.

While the chemical imbalance hypothesis did not have the widespread support of all the scientists who were interviewed for this project, there is little that they offered with regard to modifying or replacing the explanation. Scientist G supported the use of the chemical imbalance hypothesis but added additional details to the explanation, such as talk about the role of



neurotransmitters in the function of circuits in the brain. While Scientist A in extract 15 made an argument in favour of acknowledging that we do not know the etiology of depression, he appeared to be referring to scientists rather than clinicians, since the benefit of acknowledging the unknown etiology was to spur creative and novel ideas about underlying cause(s). The other scientists who talked about plasticity as an alternative explanation did so hesitantly and were reluctant to suggest it could supplant the chemical imbalance hypothesis as a more accurate description of depression because of the convenience and simplicity of the latter. Scientist B (Extract 6) referenced the immune system as implicated in depression, and argued that such an explanation could be comforting to the patient, presumably because it leverages the legitimizing force of the immune system to cast depression as a veritable biological disease state. Overall, depression was constructed by the interviewees as a complex brain-based disorder with no simple explanation.

## **5.5 Discussion**

The etiological explanations for depression have shifted, along with the received views of the way the brain and body function, from an excess of black bile to impaired neuroplasticity and neuroimmune functions (Jackson, 2008; Krishnan & Nestler, 2008). The chemical imbalance hypothesis was proposed at a time when scientists had recently accepted that the brain functions using chemical messengers between neurons (Coppen, 1967; Schildkraut, 1965). The chemical imbalance hypothesis, specifically a deficiency of serotonin and other monoamines, led to the creation of the SSRIs and the chemical imbalance explanation reached a wide audience through pharmaceutical promotion and direct-to-consumer advertising of SSRIs and related antidepressants (Leo & Lacasse, 2008). In the five decades since the chemical imbalance hypothesis was proposed, there have been significant developments in how scientists understand the functioning of the brain. Alternative explanations for depression are being studied experimentally, and the research literature is vast and accumulating daily. However, the etiological understanding of depression is complex and incomplete, and the purported mechanisms underlying depression might not be possible to explain in a brief television advertisement, such as was done with the chemical imbalance hypothesis in 15 seconds in a Zoloft commercial (<https://youtu.be/twhvtzd6gXA>), or in a short office visit with a family physician. The chemical imbalance hypothesis remains a pervasive discourse among laypersons and clinicians.

### **5.5.1 Arguments in Defense of the Chemical Imbalance Explanation**

Scientists defended the chemical imbalance explanation for depression by constructing a chemical imbalance as a general concept rather than a specific deficiency of serotonin. They argued that neurotransmitters are integral to the function of circuits in the brain, and circuits in the brain are responsible for behaviour, so functional and behavioural impairments in depression must result from a dysfunction or dysregulation of chemical messengers in brain circuits. While defining chemical imbalance as a general concept of brain functioning bolsters the argument that depression is caused by a chemical imbalance, the lack of evidence for a specific serotonin deficiency threatens to undermine the explanation. The scientists acknowledged that the specific serotonin deficiency explanation was incorrect but argued that it is more important to communicate to patients that their depression is a biological illness than to try to articulate the exact state of scientific understanding, which is complex and incomplete. The argument involves a persuasive appeal to pathos, evoking sympathy for sufferers of depression who face stigma and self-blame.

For many people, depression is viewed as a character flaw or a sign of being weak, and biological explanations are purported to reduce stigma and self-blame (e.g., Andreasen, 1985; 2001). Appealing to relieve the sufferer of guilt and shame through a biological explanation is a persuasive defense of the chemical imbalance hypothesis, but biological explanations for depression, such as the chemical imbalance hypothesis, might not be the route to reduced stigma and self-blame. For example, Pescosolido et al. (2010) analyzed survey responses to vignettes about depression and other mental health diagnoses. They described increased public endorsement of neurobiological causes between 1996 and 2006, with no effect upon stigma. The authors concluded that relying exclusively on neurobiological explanations “is at best ineffective and at worst potentially stigmatizing” (p. 9). Kemp, Lickel, and Deacon (2014) reported that understanding depression to be caused by a chemical imbalance had no significant association with self-blame, but was associated with increased prognostic pessimism and decreased expectations regarding mood regulation ability. The argument that the chemical imbalance explanation will improve patient outcomes rests upon the assumption that biological explanations reduce stigma and self-blame; however, equating a person’s distress to the action of molecules in the brain might have negative effects. While efforts should continue to focus on reducing stigma and self-blame among persons with depression and in society, the general chemical imbalance explanation might actually reify discourses that stigmatize depression.

### **5.5.2 Arguments in Opposition to the Chemical Imbalance Explanation**

While constructing the phrase chemical imbalance as a general dysfunction or dysregulation of neurotransmitters in brain circuits permitted a compelling defense of the chemical imbalance explanation of depression, scientists also argued against the explanation by constructing it in terms of a specific deficiency of serotonin. The separation allowed the scientists to maintain the presentation of depression as a brain-based disorder while also countering a specific hypothesis prevalent in lay and medical discourses.

One way of arguing against the specific chemical imbalance explanation was to draw attention to incompatible evidence, such as the observation that while antidepressants increase synaptic concentrations of monoamines immediately, therapeutic effects are delayed. The therapeutic delay is one of the most problematic observations not explained by the specific serotonin deficiency hypothesis, and while others have outlined several problems with the hypothesis (e.g., Healy, 1997; Kirsch 2010), no scientists referred to those additional inconsistencies in the course of the interview.

Another line of argument involved critiquing past scientific endeavours. Reductionism, a hallmark of scientific inquiry, was implicated in the erroneous inference of depression causality when attempting to explain the mechanism of antidepressant action. Openness to ideas and a willingness to test and refine theories to fit the data was presented as an ideal position, and was coupled with denigrating those who still held fast to the chemical imbalance hypothesis. The scientists taking up this argument defended themselves against potential counter-arguments that they are not open to ideas by presenting themselves as willing to accept depression as caused by a problem with serotonin. The hallmark of a good scientific hypothesis is falsifiability, and these scientists positioned themselves as good scientists by presenting their ideas tentatively and acknowledging the possibility of serotonin being a major etiological factor in depression.

### **5.5.3 Possible Alternative Explanations**

In the current study, several scientists described depression as associated with problems of neuroplasticity, but expressed skepticism regarding physicians' and patients' willingness and ability to utilize and understand an explanation based on neuroplasticity. Their skepticism may be due to the communicative power and pervasiveness of the chemical imbalance explanation. The idea that depression is caused by a chemical imbalance has permeated lay and medical discourses, and it can be leveraged as a persuasive rhetorical device to influence medication adherence.

In an attempt to counter the negative effects associated with the chemical imbalance hypothesis, Lebowitz, Ahn, and Nolen-Hoeksema (2013) played an educational video which highlighted that environmental factors and life experiences can influence brain chemistry and genes for a subset of participants. They concluded that endorsing a biomedical etiology of depression was associated with prognostic pessimism, but that those who watched the video about the plasticity of genes and brain chemistry had lower prognostic pessimism and increased sense of agency and hope. In addition to the concepts of epigenetics and neural plasticity, the concept of neuroimmunity may be a persuasive explanation that contributes to the construction of depression as a legitimate illness rather than a deficit of character or personal strength. By promoting the knowledge that the brain is malleable and capable of changing under a variety of stimuli, e.g., medication, exercise, and talk therapy, we might one day augment or replace the chemical imbalance explanation for depression.

### **5.5.4 Conclusion**

The present study highlights how the chemical imbalance hypothesis of depression, while simple and incomplete, can be maintained by defining chemical imbalance in a general manner. The study also highlights that many scientists have moved past the chemical imbalance hypothesis when thinking about depression and its causes, and that they consider depression as of unknown etiology with multiple potential causes. A unified theory of depression that accounts for all predisposing and precipitating factors and all known therapeutic interventions is likely to be elusive, and in time, depression, as we know it, might be divided into a number of different disorders or diseases with unique etiologies. The study raises several questions: What role do neuroscientists have in providing and promoting explanations of depression to medical professionals and the lay public? What level of scientific explanation is acceptable to physicians and patients? And, what type of explanation, if any at all, is most beneficial to a patient's recovery? These questions might be productively explored in a variety of ways – quantitatively and qualitatively – in future research.

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## Chapter Six: General Discussion

The research questions that directed the individual analyses and overall project originated with the observation that there was a discrepancy between the scientific literature and the general talk among laypersons regarding the etiology of depression. Of interview data with family physicians and scientists, I asked the following research questions: How do family physicians, who are responsible for the vast majority of the diagnosis and treatment of depression in Canada, describe and account for their etiological explanations of depression and what discursive resources do they use to explain depression to their patients? And, how do scientists who are working toward a biological understanding of depression account for and construct arguments for or against the chemical imbalance hypothesis of depression? In this general discussion, I bridge the conclusions of the two studies and offer commentary on additional questions left unanswered.

### 6.1 The Chemical Imbalance Hypothesis: Challenges and Opportunities

Does the chemical imbalance hypothesis need a replacement? From the data I analyzed and presented in these research projects, it is apparent that at least some physicians are utilizing the chemical imbalance hypothesis as a persuasive rhetorical device to motivate patients toward treatment, to attempt to minimize self-blame and stigma, to instill hope and confidence in the treatment, and to contribute generally to scientific knowledge among patients. However, from a read of the literature on stigma and prognostic pessimism associated with the chemical imbalance hypothesis of depression, reducing stigma and instilling hope is not as self-evident as the physicians suggested (Deacon & Baird, 2009; Fullagar, 2009; Fullagar & O'Brien, 2013; Kemp, Lickel, & Deacon, 2014; Kvaale, Gottdiener, & Haslam, 2013; Kvaale, Haslam, & Gottdiener, 2013; Pescosolido et al., 2010; Schomerus et al., 2012; Speerforck, Schomerus, Pruess, & Angermeyer, 2014). Further, there is an ethical responsibility of the clinician to provide sufficient information for a patient to make an informed decision regarding treatment (Blease, 2014). The scientists interviewed for this study were somewhat reluctant to endorse any one alternative etiological account of depression, and some maintained the chemical imbalance narrative by describing the brain as functioning through chemical signals that they argue are impaired in states of depression.

While the chemical imbalance explanation was defended by these scientists, it was also evident that they had a sophisticated understanding of the brain and how it adapts as we interact with our environment. The scientific method in neuroscience is fundamentally reductionistic, but the scientists avoided neuroessentialist talk that might be evident among laypersons (e.g., Dar-Nimrod & Heine, 2001; Haslam, 2011; Haslam & Kvaale, 2013). Some family physicians also talked about stating to their patients that many things can alter the chemical composition of the brain. These learned individuals have a nuanced view of depression that might be difficult to communicate to a layperson in a brief exchange. Building knowledge of the brain and depression among laypersons in the community is an important step toward reducing stigma and building awareness of available treatments. However, it is also important to aspire to achieving a relatively sophisticated and contextualized understanding of how the brain works in concert with the environment. If neuroessentialist thinking promotes prognostic pessimism and stigma, then explanations that include a description of environment-dependent factors, such as epigenetics and neuroplasticity for example, might promote prognostic optimism and reduce the tendency for a person to construct mental illnesses as dangerous and immutable.



When considering a replacement for the chemical imbalance hypothesis, it is important to consider the knowledge and understanding that is already held by laypersons and clinicians. Steven Polgar (1962), a medical anthropologist, wrote of the *fallacy of the empty vessel*. The metaphor conveys that laypersons already have constructions of illnesses and new knowledge might not be readily accepted. Some scientists drew attention to this general notion when they expressed their expectation that a new explanation for depression, such as reduced neuroplasticity, would not be readily accepted by laypersons and clinicians. However, as some scientists demonstrated, a rhetorical construction of the brain as a chemical signaling mechanism in general can maintain the notion that depression is associated with a chemical imbalance. Since a majority of laypersons likely already endorse that depression is caused by a chemical imbalance, it may be fruitful to augment the explanation, rather than to expect it to be displaced by an entirely new explanation. The arguments in defense of the chemical imbalance hypothesis can scaffold the creation of a more complex and nuanced explanation for depression – one that builds upon the knowledge already prevalent in the talk of laypersons and physicians. Thus, augmenting, rather than replacing, the chemical imbalance hypothesis might be most favourable.

There are several potential routes to constructing discourses of depression that encompass the gamut of potential explanations among clinicians and laypersons. Trainee medical students learn that illnesses are often biopsychosocial, and among the sample of family physicians, several endorsed biopsychosocial explanations of depression. Encouraging family medicine students to explain that depression is not well understood but likely involves brain chemistry and structure that is malleable might build knowledge among laypersons with depression without the detrimental effects noticed with pure chemical imbalance explanations. Kandel (1998) called for the specialized training of psychiatrists to emphasize the structure and function of the brain and how the body interacts with its environment. Bringing forth current knowledge and debates in neuroscience to clinical training programs could result in increased translation of basic science to clinical application.

A brief educational video for patients with depression might be an effective intervention to increase feelings of personal agency and prognostic optimism. For example, Lebowitz, Ahn, and Nolen-Hoeksema (2013) successfully reduced self-report ratings of prognostic pessimism and increased self-report ratings of personal agency through a six-minute educational video explaining epigenetics and experience-dependent plasticity, followed by an instruction to write a persuasive letter to a person with depression using the information in the video. A similar intervention might be utilized in an office-based visit for depression, either through an educational video or simply by taking the time to explain depression's many potential causes within the body, in the environment, and in the interaction between the two.

Scientists studying pre-clinical models of depression might also contribute to the public discourses regarding depression. Several Canadian scientists I interviewed talked about the Canadian Depression Research and Intervention Network (CDRIN, 2015). The CDRIN project connects scientists across the country and beyond, and includes laypersons living with depression in the hopes of improving clinical outcomes. This network provides a platform for scientists to share their work more broadly and encourages the involvement of people living with depression in basic research. Such initiatives have the potential to add to public discourses about the causes of and treatments for depression.

## 6.2 The Intersection of Neuroscience and Clinical Practice

The research project is an example of research conducted across disciplinary lines. I employed a qualitative, social science approach to studying social/psychological research questions involving clinicians and neuroscientists. The research was not interdisciplinary per se, but I was principally concerned with how both clinicians and scientists viewed depression and the chemical imbalance hypothesis. The discipline concerned with the intersection between clinical and neuroscience research is termed translational neuroscience. Ultimately, the goal is to translate basic research into improved clinical outcomes for patients.

Of the interview data generated as part of these research projects, what did clinicians say about scientists? And what did scientists say about clinicians? I analyzed the scientist interview data with regard to translational science for a paper presentation at the 2016 Qualitative Research on Mental Health conference (Sigurdson & McMullen, 2016). I present three quotes below to highlight the intersection of neuroscience and clinical practice.

When searching the family physician interview transcripts, there was only one instance of a physician talking about scientific research related to depression etiology. In the context of talking about communicating the neurochemical basis of depression to his patients when prescribing antidepressants, this physician stated, “There’s some trust... from our scientists.... People tell us that this is how it works and we believe that.” The term “people” is vague, but could include scientists, other clinicians, professors, and pharmaceutical advertising/representatives. The word “it” most likely refers to antidepressant medication given the context surrounding the statement. By talking about trust in scientists, this physician acknowledges that the explanation he provides to his patients relies upon a confidence in the scientific community. Translation of clinical research to clinical practice has many potential routes, but from interview data with the sample of physicians, it appears to be lagging behind the current discourses in depression science.

By comparison, scientists talked about clinicians significantly more. Several scientists in the sample described their work as translational and talked about the necessity of engaging with clinicians. For example, one scientist stated,

We need more interaction between basic scientists and clinicians. Um, you know I need to talk to clinicians so I understand that clinical situation. And they need to talk to me so that they are abreast of research and new ideas and new ways of thinking.

This scientist makes the point that cross-talk between scientists and clinicians is important for both researchers and scientists alike. She makes the assumption that talking will lead to understanding and new ways of thinking.

However, scientists also drew attention to limitations to translation. The language of scientists and clinicians was often cited as a barrier to translating science to practice. Another scientist stated,

I think that, as a field... it’s taken us a long time to, be able to speak um, I wouldn’t even say a common language but I’d say a language that, um, people who do different work can respect. And what do I mean by that?... The, lack of understanding or awareness of gene environment interaction, led to people having uh, well is it a psychological depression or is it a biological depression? Which in our field today would be nonsense because people understand, levels of analysis.

The scientist makes the claim that while the two groups have not reached a consensus or a common language, there is more mutual regard for the other's way of working and speaking about depression. He goes on to provide an example of the historical division of reactive vs. endogenous depression in psychiatry. In our previous interviews with family physicians, many of them still referred to depression in the absence of external factors as a true medical/biological depression. Such division, in the words of this scientist, is nonsense.

I observed several key assumptions within the talk of scientists when speaking on translational science. Translation of neuroscience research into practice was routinely constructed as a necessity, even by those scientists who were not directly engaged with clinicians in their work. There was an assertion that the research literature might already hold key findings that could improve the outcomes of patients with depression but that research is not being translated to clinical interventions. In addition, clinicians and scientists differ in the language they use, and this difference was constructed as a limiting factor that must be overcome. There was an assumption that, if two groups are brought together, they will reach a common ground and/or develop insights into the worldview of the other. To examine this assumption, Brosnan and Michael (2014) conducted an ethnographic study of a laboratory/clinic designed to foster cross-talk between clinicians and scientists concerned with Parkinson's disease. The space included a medical clinic and a neuroscience research laboratory in close proximity. Brosnan and Michael (2014) concluded that the two groups, scientists and clinicians – with the exception of the group leader – were still very divided in their work and vision. Narrowing the gap between science and practice as observed in the talk of scientists and clinicians, while a commendable pursuit, is likely to remain complicated and fraught with barriers.

### **6.3 Limitations and Directions for Future Research**

I acknowledge that my analysis is one of many potential interpretations of the data. I included large extracts of interview text and referred specifically to the text for each analytic claim. Doing so allows the reader to evaluate the analysis and also to bring his or her own knowledge to bear on the selected extracts. Since an “analysis is never complete” (p. 208, McMullen, 2011), including large sections of text is likely to spur other research questions and interpretations of the data.

Both sets of interviews contained wide-ranging questions related to depression. This general approach produced interview data that covered a wide-range of potential research questions. The approach has benefits and limitations. A benefit is that the general questions allowed for many research questions to be asked of the data. For example, because of the general questions related to the diagnostic practice of family physicians, I observed many utterances regarding the chemical imbalance hypothesis and could ask a research question not conceived of when the interview schedule was created. A limitation is that the focus of the interview might go in a different direction than it would if the chemical imbalance hypothesis was the focus of the conversation. Additionally, the interviews produced a vast amount of data that will go unanalyzed unless specific research questions are asked. To further the research related to explaining the causes of depression, future researchers could formulate specific questions to narrow the scope of the interviews or utilize surveys and quantitative methods.

Interview data can be potentially problematic, as they are a co-construction between interviewer and interviewee. For example, when interviewing scientists, I often referred to the chemical imbalance hypothesis as “simple” or “simplistic” when prompting for further

discussion from the scientists. With regard to the physician data, it would be very interesting to obtain direct recordings of physicians explaining depression to their patients. While “naturalistic records” (p. 301, Potter & Hepburn, 2005) – data generated without significant researcher involvement – might be ideal for many research questions, such records would be extremely difficult, if not impossible, to obtain ethically. Despite this limitation and the potentially complicated physician recruitment and ethics approval process, future researchers might want to partner with physicians to record and analyze the diagnostic and treatment communications between physician and patient. The data and analysis will contribute to the understanding of the communication of depression.

Further, the interviews were conducted by a clinical psychologist and clinical psychology graduate students. It is conceivable that this had an effect upon the interview data produced. For example, it might have prompted the physicians/scientists to talk more about psychological treatments than they otherwise would have if they were speaking with a peer. Future researchers building upon this work will need to remain mindful that the interviews were a situated encounter between psychologists and physicians/scientists.

New developments in science and practice will affect the discourses of depression over time. The latest biomedical treatment for depression is ketamine infusion. Ketamine continues to be studied for its antidepressant efficacy, but because it is a medication already approved for use with human patients, it is currently being used to treat depression in some clinics. Scientists are unsure as to why it appears to have an antidepressant effect, but they have observed that ketamine starts a signaling cascade in the brain that promotes the growth of dendritic spines, ultimately enhancing neuroplasticity and the number of connections between neurons. Thus, while the effect is achieved by a chemical process in the brain, it results in a change in structure. It is likely that now, or in the near future, family physicians will be referring their patients to ketamine clinics. When that happens, how will these physicians explain depression and the ketamine treatment to their patients? Will the chemical imbalance narrative survive or will talk of enhanced neuroplasticity replace or augment the chemical imbalance explanation for depression? What effect will an explanation of depression involving ketamine treatment have on the explanation of how SSRIs and related medications work? As ketamine treatment becomes more common, it will be interesting to examine and compare explanations for depression among laypersons and medical professionals as they relate to treatment.

#### **6.4 Reflexivity**

The analysis and discussion presented here are dependent on my position as a researcher. I acknowledge that the analysis is a co-construction involving my own perspectives, background, and knowledge which I brought to bear upon the data generation and data analysis. In the interview data with scientists, I followed a semi-structured interview schedule that I created from my reading and understanding of the scientific literature. However, I focused most on review articles in neuroscience rather than original research. I read that literature through the lens of a trainee in clinical psychology. As such, I was principally interested in the broad constructions of depression and its causes, rather than the detail-oriented focus that is often prevalent in neuroscience research. I focused on a general question: what do we know about depression from scientific studies?

Despite my clinical focus, I attempted to immerse myself in neuroscience. I gained a great deal of perspective on neuroscience research from discussions with neuroscience graduate

students about their work. I attended a Society for Neuroscience Annual Meeting. Here, in addition to one formal interview, I was able to have informal conversations with researchers and students studying depression.

As I reflect upon the analysis and interview data in general, I acknowledge that this research has had an effect upon how I talk about depression. While conducting psychotherapy with individuals with depression, it is not uncommon to hear, “My depression is a chemical imbalance,” or to be asked, “Do you think I have a chemical imbalance?” Knowing that a pure chemical imbalance explanation of depression might be associated with prognostic pessimism and might potentially undermine the perceived effectiveness of psychotherapy, I have become careful to explain depression first as not completely understood but to also utilize the argument by the scientists in support of the chemical imbalance hypothesis. By explaining that the brain functions by chemicals known as neurotransmitters and adding there are many routes to changing the structure and functioning of the brain, I hope to augment the explanation without undermining the clinician who potentially described depression as a chemical imbalance. When I first embarked on this journey, I would have been more inclined to be silent with my position on the chemical imbalance hypothesis because I constructed it to be erroneous and outdated. I aspire to present depression in a way that is consistent with the scientific literature, recognizes the held-view of the person experiencing depression, and fosters prognostic optimism.

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## Appendix A

### Invitation to Participate Email

Dear [Name],

I am a PhD student at the University of Saskatchewan in Canada and I am writing to invite you to participate in a research study entitled “The Neuroscience of Depression: A Discourse Analysis of Scientists’ Accounts of Knowledge Generation.” You were identified as an expert in the field of depression research who has made significant contributions to the understanding of the science of depression.

Neuroscience is a relatively new discipline emerging as an important and pervasive contributor to the understanding of mental illness. The objective of the proposed research is to contribute to a broader understanding of how such knowledge generation is understood by scientists who are experts in the field.

Involvement in the project includes participating in a 1 to 1 ½ hour individual interview. [I will be attending the Society for Neuroscience 2013 Annual Meeting in San Diego, California, and will be conducting face-to-face interviews on-location. Alternatively, if you are not attending this meeting and would like to participate, we can arrange a telephone interview.] [Personalized message]

All interviews will be audio-recorded and transcribed verbatim. All identifying information will be removed from the transcripts and data will be reported in the form of quotations using a pseudonym. In the analysis, I will summarize the themes of the interview and conduct a detailed examination of the text, which will include, for example, how interviewees employ language categories, frame arguments, and construct metaphors about the neuroscience of depression. The data will be used in a student thesis, published in peer-reviewed journals, and presented at academic conferences.

If you are interested in learning more about this project, please contact Kristjan Sigurdson at 306-966-2322 or at [kristjan.sigurdson@usask.ca](mailto:kristjan.sigurdson@usask.ca) and more details will be provided. The project is supervised by Dr. Linda McMullen ([linda.mcmullen@usask.ca](mailto:linda.mcmullen@usask.ca); 306-966-6666). For information about ethics board approval, please call the Ethics Unit at the University of Saskatchewan (306-966-2084).

Sincerely,

Kristjan J. Sigurdson

Graduate Student in Clinical Psychology



## Appendix B

### Consent Form



### *Participant Consent Form*

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**Project Title:** The Neuroscience of Depression: A Discourse Analysis of Scientists' Accounts of Knowledge Generation

**Researcher(s):** Kristjan J. Sigurdson, Graduate Student, Department of Psychology, University of Saskatchewan, (+1) 306 966-2322, kristjan.sigurdson@usask.ca

**Supervisor:** Dr. Linda McMullen, Department of Psychology, University of Saskatchewan, (+1) 306 966-6666, linda.mcmullen@usask.ca

#### **Purpose(s) and Objective(s) of the Research:**

- The purpose of the proposed research is to contribute to an understanding of knowledge generation practices and the epistemological foundations employed by eminent behavioural neuroscientists working toward a biological understanding of depression.
- The objectives of the research are to study how neuroscientists:
  - define and make sense of the science of depression in biological psychiatry, including etiological claims, and epistemology and methodology in research.
  - contend with controversy over (a) the use of the chemical imbalance hypothesis of depression by medical and lay persons despite a lack of scientific support, and (b) the failure of psychotropic medications, including antidepressants, to reduce the burden of mental illness despite increased use of these medications.
  - define the challenges and dilemmas faced by scientists and the field of neuroscience regarding biological research of depression.
  - account for the historical and recent promises by scientists and biological psychiatrists for innovation and a greater understanding of depression.

#### **Procedures:**

- Participating in this research involves taking part in an individual interview lasting approximately 1 to 1.5 hours.
- The interview will be conducted face-to-face at the Society for Neuroscience annual meeting, 2013, or via telephone.
- I will interview up to a maximum of 15 scientists.

- The interview will be recorded with a digital audio recorder and transcribed verbatim.
- Once the interview is transcribed, you will have a chance to read the transcript and sign a transcript release form.
- Please feel free to ask any questions regarding the procedures and goals of the study or your role.

### **Potential Risks:**

- There is potential for a breach of confidentiality in email and telephone interactions. In particular, for participants living in the United States, the US Patriot Act allows authorities access to the records of Internet and telephone service providers.
- You may choose to have the transcript of your interview sent to you via email in a password-protected document or you may choose to have a hard-copy of the transcript mailed to an address of your choice.

### **Potential Benefits:**

- The research has the potential to contribute to our understanding of the state of knowledge regarding neuroscience of biological psychiatry for depression.
- There is no guarantee that you will personally benefit from this research.

### **Confidentiality:**

- Measures will be taken to ensure the confidentiality of all participants.
  - Data will be reported in the form of written quotations (i.e., interview audio will not be presented).
  - All directly identifying information will be removed from the interview transcripts (i.e., locations, names, employers, etc.)
  - Pseudonyms will be used in the place of real names.
- Because the participants for this research project have been selected from a relatively small group of people, it is possible that you may be identifiable to other people on the basis of what you have said.
- **Storage of Data:**
  - After the interview, the audio file of the interview will be saved as an encrypted, password protected file on Kristijan Sigurdson's computer and the original file deleted from the audio recorder. Backup files will be stored with Linda McMullen.
  - The electronic transcript files will be password protected in Microsoft Word.
  - The paper transcripts will be stored in a locked filing cabinet in a university office.

- The transcripts and interview recordings will be stored with Linda McMullen for a minimum of 5 years after the final publication of research results.

**Right to Withdraw:**

- Your participation is voluntary and you can answer only those questions that you are comfortable with. You may withdraw from the research project for any reason, at any time without explanation or penalty of any sort.
- Should you wish to withdraw from the research, the audio recording and transcript data will be deleted at your request.
- Your right to withdraw data from the study will apply until results have been disseminated. After this date, it is possible that some form of research dissemination will have already occurred and it may not be possible to withdraw all of your data.
- The researcher will advise you of any new information that could influence your decision to participate in the ongoing parts of the study.

**Follow up:**

- Once the study is complete, a summary of the results will be available to participants upon request.

**Questions or Concerns:**

- Contact the researcher using the information at the top of page 1.
- This research project has been approved on ethical grounds by the University of Saskatchewan Research Ethics Board. Any questions regarding your rights as a participant may be addressed to that committee through the Research Ethics Office [ethics.office@usask.ca](mailto:ethics.office@usask.ca) (306) 966-2975. Out of town participants may call toll free (888) 966-2975.

**Signed Consent (for face-to-face interviews):**

Your signature below indicates that you have read and understand the description provided; I have had an opportunity to ask questions and my/our questions have been answered. I consent to participate in the research project. A copy of this Consent Form has been given to me for my records.

\_\_\_\_\_  
Name of Participant

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher's Signature

\_\_\_\_\_  
Date

*A copy of this consent will be left with you, and a copy will be taken by the researcher.*

---

**Oral Consent (for telephone interviews):**

I read and explained this Consent Form to the participant before receiving the participant's consent, and the participant had knowledge of its contents and appeared to understand it.

\_\_\_\_\_  
Researcher's Signature

\_\_\_\_\_  
Date

## Appendix C

### Transcript Consent

### Transcript Review

There is potential for a breach of confidentiality in email and telephone interactions. In particular, for participants living in the United States, the US Patriot Act allows authorities access to the records of Internet and telephone service providers. You may choose to have the transcript of your interview sent to you via email in a password-protected document or you may choose to have a hard copy of the transcript mailed to an address of your choice.

via email

via mail

Name: \_\_\_\_\_

Address: \_\_\_\_\_

\_\_\_\_\_

Postal Code: \_\_\_\_\_

Email address: \_\_\_\_\_

Would you like a summary of the results when the project is completed:

No, thank you

Yes, by mail

Yes, by email

**Appendix D**

**Demographic Form**

Participant Number: \_\_\_\_\_

Gender: \_\_\_\_\_

Age: \_\_\_\_\_

Degree(s): \_\_\_\_\_

Additional training/ specialization: \_\_\_\_\_

\_\_\_\_\_

Length of time in research: \_\_\_\_\_

Annual grant funding: \$ \_\_\_\_\_

## Appendix E

### Interview Questions

- Please describe your current work and how you came to have expertise in the area of the science of depression.
- What interests you most about depression research?
- How do you define depression? How do you study depression? Are there differences between how you think about depression in the context of your work as a scientist and how you might employ the word ‘depression’ in your everyday encounters outside of the context of your work?
- What are the challenges and dilemmas that scientists and the field of neuroscience face with regard to the biological understanding of depression?
  - Prompt for (a) the defining of depression in psychiatry and the lack of a biological test, (b) the modeling of depression in research, (c) the limited understanding of the neurobiology of mental health and illnesses, and (d) the funding of psychiatric research.
- What are the major controversies in the science of depression?
  - Prompt for (a) the use of the chemical imbalance hypothesis of depression by medical professionals and lay–persons, (b) the controversy regarding the effectiveness of antidepressants, and (c) the data suggesting that the advent of psychotropic medications has not reduced the overall burden of mental illness.
- How successful has the neuroscience of biological psychiatry been? Where has it contributed and where has it fallen short?
- What do you foresee for the future of the science of depression? Are we on the right path to help sufferers of this illness? If you had the power to control all depression research funding, how would you allocate the resources?

Appendix F

Transcript Release



TRANSCRIPT RELEASE FORM

**Neuroscience of depression: A discursive analysis of scientists' accounts of knowledge generation**

I, \_\_\_\_\_, have reviewed the complete transcript of my personal interview in this study, and have been provided with the opportunity to add, alter, and delete information from the transcript as appropriate. I acknowledge that the transcript accurately reflects what I said in my personal interview with Kristjan Sigurdson. I hereby authorize the release of this transcript to Kristjan Sigurdson to be used in the manner described in the Consent Form. I have received a copy of this Data/Transcript Release Form for my own records.

\_\_\_\_\_  
Name of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Signature of researcher



## Appendix G

### Transcription Notation

Symbol	Use
,	Indicates a brief pause in utterance
-	Indicates an abrupt halt or interruption in utterance
.	Indicates falling pitch or a stopping intonation
?	Indicates a rising, questioning intonation
hhh	Audible exhale
...	Intentionally omitted text