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Evaluating the Brain Disease Model of Addiction & Towards Balance of Dichotomy Through Integration of Mind-Brain Intermodulatory Mechanisms

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Evaluating the Brain Disease Model of Addiction & Towards Balance of Dichotomy Through Integration of Mind-Brain Intermodulatory Mechanisms

Anum Afzal

Abstract

The way addiction is viewed by scientists, clinicians, and the public has shifted tremendously in the past two centuries. More specifically, there has been a shift from the moral model of addiction to the 'brain disease model,' in which addiction is seen as a brain disease characterized by neurobiological changes which result in compulsive and uncontrollable drug seeking behavior. In this paper, I summarize arguments from those who assert that addiction is a brain disease as well as those who find this model to be problematic. I then argue that the brain disease model is flawed and limiting for several reasons: (1) it does not emphasize the critical role of psychosocial factors and epigenetics in addiction, (2) a discrepancy exists regarding whether addicts hold some degree of behavioral control, and (3) prolonged substance use does not fatalistically lead to addiction, as this model posits. I argue that such limitations stem from the model's reductionistic emphasis on the brain unidirectionally giving rise to addiction. Therefore, I ultimately argue in favor of a strategy of moving forward from the disease model. In particular, I suggest we may be well-served to acknowledge the complex, intermodulatory relationship that exists between the brain and "mind," and that further research into it could allow us to more accurately understand addiction and to develop novel and enhanced therapeutics for it. I overall argue that a move towards this integrational perspective will further help to balance the dichotomy of the brain disease and moral models of addiction.

Keywords

Addiction, Brain Disease Model, Moral Model, Theoretical Neuroscience, Behavior, Psychology, Psychopharmacology, Philosophy of Mind, Mind-Brain Interaction, Mind-Brain Problem, Mindfulness, Metaphysics

Historically, laypeople and scientific communities alike predominantly adhered to the 'moral model' view of addiction, which explained addicts' behavior as resulting from moral deficits and lack of self-discipline. For example, the moral model would explain the behavior of an alcoholic by pointing to his or her weak character, and ultimately view the behavior as being indicative of sin and involving active choices. During the 19th century, there was a paradigm shift in which addiction began to be viewed as a disease, which historians agreed to have originated from Thomas Trotter and Benjamin Rush who first popularized this framework of addiction (Edwards 2012; Levine 1978; Meyer 1996). The

idea of addiction being a disease continued to grow, and in the late 20th century, addiction began to be seen predominantly as a *brain* disease. This new brain disease understanding of addiction had its roots in the "molecular revolution" of neuroscience that was occurring in the 1960s and 70s, during which neuroscientific links between brain physiology and addiction and its related behaviors were being uncovered (Vrecko 2010). The subsequent widespread growth and acceptance of what has become this 'brain disease' model of addiction represented a stark shift from the moral model of addiction, whereas instead of addicts being seen as morally flawed and lacking self-discipline and proper character, they were now seen largely as victims of their diseased brains, and that addiction was caused by genetic predispositions as well as neurobiological changes that occurred in the brain as a result of chronic drug use (McKim 2006). This new model also explained that these neurobiological changes result in addicts being compulsive in their drug use and unable to control their habits. The brain disease model of addiction has now become the most widely-accepted model which persists today, but it has also been a subject of great controversy.

In section 1 of this paper, I begin by discussing the perspectives of those who support the brain disease model of addiction and their arguments for doing so. In section 2, I then offer critiques of the brain disease model.[1] These critiques center on my argument that the model is highly reductionistic and overrelies on neurobiology as giving rise to addiction and its "compulsive" behaviors in a unidirectional manner. My critiques, then, are that (1) because of this unidirectional reductionism, the psychosocial factors, as well as epigenetics, critical in the etiology of addiction are not adequately

1. In this paper, I provide a critique of the *brain disease* model of addiction, but I am not arguing against a *disease model*, per se. Indeed, although there is disagreement over whether addiction itself can be considered a '*disease*' in the broadest sense, the very definition of 'disease' remains ill-defined and definitions that exist vary widely and are inconsistent (Boyd 2000; Emson 1987; Ereshefsky 2009; Gluckman 2007; Kottow 1980; Merskey 1986; Scully 2004; Tikkinen et al. 2012). However, based off some proposed definitions, such as that of Harry Edmund Emson who states that a disease can be considered "a state…that actually or potentially disadvantages a person for survival, reproduction, or full enjoyment of life (characteristic for age), other than by sole reason of social circumstance or by temporary and reversible environmental change," we see that addiction can indeed be considered a disease in this sense (Emson 1987). This idea of addiction being a disease can further be seen when we consider the subjective state of addiction, in which addicts must take a certain amount of substance to feel normal, and if they are to stop, experience a plethora of symptoms including psychological distress, among physiological symptoms, thus fueling their continuation of the substance use (McKim 2006). Thus, in this paper, I do not argue that addiction is not a *disease*, but rather, critique the *brain disease* model of addiction, which sees addiction as being specifically caused by neurobiological aberrations which result from chronic substance use (McKim 2006; National Institute on Drug Abuse, c; Volkow, Koob, and McLellan 2016).

emphasized; (2) there is a discrepancy within the brain disease model and its proponents regarding whether addicts hold some degree of behavioral control; (3) despite the model's emphasis on addict compulsivity and 'uncontrollable' behavior as arising from neurobiological changes triggered by chronic substance use, we see evidence that addicts do hold some degree of behavioral control; and (4) we see from empirical evidence that long-term substance use does not deterministically lead to addiction, contrary to brain disease model assertions.

In section 3, I continue on to argue that to move forward from the brain disease model and its limitations, it would do us much good then to better acknowledge on a mainstream level that the brain does not *unidirectionally* give rise to states of mind and corresponding behaviors, as is emphasized in regards to addiction, but rather, that the mind and its related elements are also able to physiologically modulate the brain. In particular, I argue that the mind and brain hold an *interdependent*, *intermodulatory* relationship, which I term 'mind-brain intermodulation,' and I provide a review of the neuroscientific literature which supports the existence of such a relationship. I further argue that application of this intermodulatory principle could allow us to develop novel therapeutics for addiction, and I provide examples of recent research endeavors which have accordingly been investigating and developing such treatments which have thus far have shown much potential at allowing us to treat addiction in an enhanced way. I furthermore provide a theoretical example of how this principle could be applied to further research with the aims of developing similar therapeutics, emphasizing that although this area of research is still in its infancy, it holds much promise at allowing us to better understand and treat addiction. I argue that ultimately, turning more towards such an intermodulatory model would allow us to move past the critical limitations of the brain disease model, as well as to "balance the dichotomy" between the brain disease and moral models of addiction.

Section 1: Support for the Brain Disease Model

Today, addiction is predominantly viewed as a brain disease, and this perspective is embraced by institutions such as the National Institution on Drug Abuse (NIDA), which funds most of the research on addiction in the world (National Institute on Drug Abuse, d). Indeed, NIDA defines addiction as a "chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences" (National Institute on Drug Abuse, c). Sources that hold authority in educating clinicians

and researchers on addiction, such as the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-V*), also describe addiction as being characterized by compulsive drug use and behavior (American Psychiatric Association 2013; American Psychiatric Association. n.d.). From the use of the word *compulsive*, these sources describe addicts as having lack of control over their addiction and behaviors, and this description is what primarily defines the brain disease model of addiction today.

Many theories on the 'brain disease' of addiction, which focus primarily on the neurobiology as well as genetics of drug addiction, are widespread today; most agree that addiction to substances involves physiological changes in the brain, which alter the way that the brain's motivational system functions (McKim 2006). Research has shown that this motivational system, called the *mesolimbic system* (involving brain structures such as the *ventral tegmental area* and the *nucleus accumbens*), is activated during drug use, and plays a role in reward and reinforcement (Kauer and Malenka 2007; Le Moal and Koob 2007; McKim 2006). It has also been demonstrated that chronic drug use can alter this system as well as other brain systems on a neurobiological level (Le Moal and Koob 2007; McKim 2006; Volkow, Koob, and McLellan 2016). It is not fully understood how drugs specifically alter these systems, although several theories, such as the incentive sensitization and hedonic dysregulation theories, offer possible explanations (Belin et al. 2013; Hyman, Malenka, and Nestler 2006; McKim 2006). Overall, these findings that prolonged substance use and addiction result in neurobiological changes are often cited as evidence that addiction is truly a brain disease, and this perspective demonstrates a tremendous shift from the moral model of past centuries, which asserted that addiction was caused by moral deficits and weak character (Le Moal and Koob 2007; Leshner 1997; Levine 1978; McKim 2006; Volkow, Koob, and McLellan 2016; Vrecko 2010).

Due to these research findings that support the notion of addiction being a brain disease, the brain disease model has gained wide prominence today. Furthermore, it is widely accepted by those who hold authority in the field of addiction neuroscience. Dr. Alan I. Leshner, a former director of NIDA, for example, directly compared addiction to medical conditions such as lung cancer and clogged arteries:

> This unexpected consequence of drug use is what I have come to call the oops phenomenon. Why oops? Because the harmful outcome is in no way intentional. Just as no one starts out to have lung cancer when they smoke, or no one starts out to have clogged arteries when they eat fried foods, which in turn usually cause heart attacks, no one starts out to become a drug addict when they use drugs. But in each case,

> though no one meant to behave in a way that would lead to tragic health consequences, that is what happened just the same, because of the inexplicable, and undetected, destructive biochemical processes at work. While we haven't pinpointed precisely all the triggers for the changes in the brain's structure and function that culminate in the "oops" phenomenon, a vast body of hard evidence shows that it is virtually inevitable that prolonged drug use will lead to addiction. From this we can soundly conclude that drug addiction is indeed a brain disease. (McKim 2006)

From Leshner's quote, we can see that viewing addiction as a brain disease is not only supported with scientific evidence—it is also the dominant way of thinking about addiction. We can further see this dominance of the brain disease model in the mainstream perspective through the discussions of Dr. Nora Volkow, the current director of NIDA. Dr. Volkow, too, is a proponent of the brain disease model, and similarly to Dr. Leshner, emphasizes that it is caused by chronic substance use which results in neuroadaptations which give rise to addiction, as well as trigger the "cycle" of addiction (Volkow and Koob 2015; Volkow, Koob, and McLellan 2016).

Beyond the citation of neuroscientific research in defense of the brain disease model of addiction, as well as the model's evident prominence in and dominance of the mainstream perspective today, many argue that this model is beneficial for both addicts and society as a whole. For example, Leshner (1997) explains how viewing addiction as more similar to a chronic, "organic" illness, such as diabetes, has positive implications, such that healthcare professionals do not have unrealistic expectations when trying to treat addiction, which Leshner explains to be "chronic, relapsing [brain] disease" (Leshner 1997). Rather, he says, the expectations for treatment teams can shift from total abstinence to more of an "illness management" approach, such as striving towards long periods of abstinence which will tend to have occasional relapses accompanying them (Leshner 1997). Leshner also explains that it is a sign of progress to view addiction as a brain disease, as it affects how we view addicts when it comes to criminal justice. Specifically, he says that by viewing addicts as having such a disease, we can focus efforts on treating them rather than simply incarcerating them, which he describes as being futile, as the recidivism rates for both drug use and crime are very high if addicts are not treated in prisons (Leshner 1997). In contrast, if addicts are provided treatment options while in prison, due to the acknowledgment of their "brain disease," they would be less likely to return to crime and substance use when they are released (Leshner 1997).

Others have agreed that viewing addiction as a brain disease has benefits that accompany it. For example, William Wilbanks (1989) discusses how brain disease model advocates, similarly to Leshner, argue that the model allows for addicts to receive greater help since they are seen as victims of their brains rather than being morally flawed or "choosing" to become addicted (as the past moral model claimed) (Wilbanks 1989). Furthermore, he explains how this model garners more financial support for addiction treatment as well as research that seeks to find novel and effective neurobiological treatments. Similarly, Dr. Volkow discusses how understanding addiction as being a brain disease legitimizes it in eyes of health insurance companies, and therefore allows addiction treatment to be more widely covered and subsequently for addicts to be able to receive greater help without as many barriers (Volkow and Koob 2015; Volkow, Koob, and McLellan 2016). Wilbanks further explains how addicts rarely overcome their addictions on their own, and often do need help; however, addicts would not seek help if they personally believed the cause of their addiction to be bad habits or moral flaws. In this way, the brain disease model encourages addicts to seek help, works towards their eradication of self-stigma, and allows them to receive greater coverage by insurance companies if they seek or are receiving treatment (Wilbanks 1989).

In short, advances in addiction research have demonstrated that there are neurobiological and genetic underpinnings to addiction, and many cite these findings as evidence that addiction is indeed a brain disease (Belin et al. 2013; Hyman, Malenka, and Nestler 2006; Le Moal and Koob 2007; McKim 2006; Volkow and Koob 2015; Volkow, Koob, and McLellan 2016). Proponents of the brain disease model also describe the benefits that the model has brought forth for addicts and society, such as how this model enables healthcare professionals to have more realistic expectations for addicts when trying to treat them (Leshner 1997). Other argued benefits include that the brain disease model allows for greater criminal justice for addicts, decreases the stigmatization of them, allows them to receive greater help, as well as garners more financial support for addiction treatment and research (Leshner 1997; Wilbanks 1989). Despite these benefits that proponents discuss, the brain disease model of addiction has some critical flaws and limitations, and I turn to these challenges next.

Section 2: Limitations of the Brain Disease Model

Despite the benefits of the brain disease model which its proponents describe, there are several flaws and limitations which I argue the model holds. Such limitations

include: (1) the brain disease model overrelies on neurobiology as being a unidirectional causal factor for addiction, and subsequently does not adequately emphasize the critical importance of psychosocial factors and epigenetics in the etiology of addiction, (2) the brain disease model and its proponents often contradict themselves regarding whether addicts hold some degree of behavioral control, while empirical evidence indicates that they do, and (3) prolonged substance use does not fatalistically lead to addiction, which is demonstrated by how a relatively small amount of chronic pain patients who are prescribed and use opioids long-term become addicted to them – further contradicting the brain disease model's assertion of how chronic substance use leads to brain changes, which inevitably give rise to addiction.

Section 2.1: The Brain Disease Model as Being Overly Reductionistic and Unidirectional as an Explanatory Model, & Subsequent Neglect of Psychosocial Factors and Epigenetics

The brain disease model of addiction, as described by those such as Drs. Volkow and Leshner, emphasizes that brain changes, or "neuroadaptations" occur when one persistently consumes addictive substances. It further describes such neuroadaptations in a manner which emphasizes that they give rise to addiction and its related "compulsive" and "uncontrollable" behaviors in a unidirectionally causal way, and I argue that this view is problematic and leads to many of the model's limitations (Leshner 1997; McKim 2006; National Institute on Drug Abuse, c; Volkow and Koob 2015). An example of such a limitation is the model's neglecting to emphasize the critical importance of psychosocial factors and epigenetics implicated in the etiology of addiction, which abundant research has indeed demonstrated as playing a critical role in both the onset and reinstatement of addiction.

Richard E. Ashcroft (2004), in support of the argument that the brain disease model overrelies on neurobiology as an explanatory factor for addiction, discusses his criticism of cocaine vaccines, a proposed treatment which was trying to be developed in light of the idea that addiction is a brain disease, and that therefore it could theoretically be treated by specifically targeting the neural and biological 'underpinnings' of addiction. He argues that this sort of vaccine would be an inadequate stand-alone treatment, as there are many other factors implicated in addiction:

> …treatment and prevention approaches focus far too much on identifying simple biomedical mechanisms, and too little on why

> people seek to use drugs, how their patterns of use are socially shaped, and what the triggers or deficits in their personal or social situation may be that make drug use "rational." (Ashcroft 2004)

The brain disease model's over-reliance on neurobiology as being a deterministic, unidirectional explanatory factor for addiction is problematic, because as Ashcroft describes, it results in addiction research and treatment being targeted heavily from one angle (e.g. an overly neurobiologically-focused perspective). This is a more limited approach to undertake when trying to determine the causes of and effective treatment for addiction, as addiction is complex and multi-faceted. Due to this complexity, it needs be examined thoroughly through its multiple components, including the psychosocial factors which contribute to addiction, which research has indeed demonstrated to play a critical role.

For example, much research has shown that various types of psychological trauma and chronic stressors (such as social isolation or abandonment, parental divorce and conflict, and physical and emotional abuse) increase one's vulnerability to addiction (Khoury et al. 2010; National Institute on Drug Abuse, b; Sinha 2008). It has also been shown that the greater the accumulation of such stressors, the higher the risk is for a victim of such stress or trauma to develop an addiction (Sinha 2008). In addition to this, research has shown that social factors, such being surrounded by peers who use substances, are predictors of substance use (Bahr, Hoffmann, and Yang 2005; Smith 2012). These examples provide support for the argument that psychosocial factors play a critical role in addiction in various ways, which is contrary to the brain disease model's emphasis on how addiction is *primarily* a neurobiological disease, in which the direct causes of addiction are aberrant neurobiological processes which unidirectionally give rise to addiction and its behaviors.

A further example of how psychosocial factors play a critical role in addiction is seen by the psychological process of learning. Milton & Everitt 2012 discuss how learning, and more specifically, *classical conditioning* and *instrumental conditioning*, is a large factor that is involved in the development and reinstatement of addiction (Milton and Everitt 2012). They emphasize how the transition from occasional substance use to addiction is shaped by various types of reinforcement, and how this type of learning (i.e. conditioning) is accompanied by neurobiological changes that occur in various parts of the brain. Such learning processes, consisting of goal-directed behavior becoming habitual, are generally normal and productive; however, addiction can be seen as an "aberrant engagement of [these] normally adaptive learning processes" (Milton and Everitt 2012).

Darke 2012 also describes how learning can play a role in the development of addiction, and he more specifically discusses the *Self-Medication Hypothesis (SMH)*. According to SMH, those who experience unpleasant psychological states, such as distressing affect which could occur as the result of psychological trauma, may subsequently turn to substance use as a way to "self-medicate," or alleviate such distress (Darke 2012). The alleviation of these psychological symptoms in turn becomes negatively reinforcing, which is an example of instrumental conditioning; the individual learns that there is relief that accompanies the use of the substance, which promotes additional use of the substance in the future (Darke 2012; Milton and Everitt 2012). In this manner, learning is an example of a psychosocial factor that plays a prominent role in the development of addiction.

In addition to learning playing a role in the development of addiction, it has also been shown to play a role in relapse. Stress is a well-documented predictor of relapse, and Milton & Everitt describe how learning processes, such as instrumental conditioning, play an important role in these stress-induced relapses (Milton and Everitt 2012). They explain, similarly to Darke, how the use of substances is negatively reinforcing when it alleviates one's psychological distress. Such reinforcing effects subsequently lead to cravings of the substance when one experiences a similar type of stress again and he or she is not currently using the substance, as he or she has learned the association between psychological relief and his or her use of this substance. As the individual experiences these cravings, due to learned associations, he or she may experience a relapse if he or she does not have other adaptive ways to cope with that psychological distress in that moment (Darke 2012; Kauer and Malenka 2007; Milton and Everitt 2012). The research literature that supports how the psychological process of learning (i.e. reinforcement and subsequent conditioning) plays a critical role in the development of as well as relapses to addiction truly emphasizes how addiction is more complicated than simply being a product of biochemical mechanisms which function in a unidirectionally bottom-up fashion to give rise to addiction, as the brain disease model heavily emphasizes (Ashcroft 2004; Milton and Everitt 2012; Volkow and Koob 2015; Volkow, Koob, and McLellan 2016). These examples of critical psychosocial factors therefore underscore limitations of the reductionistic perspective held by the brain disease model, and how such psychosocial elements and other contributors to addiction need to be even more heavily emphasized if we want to more effectively research and treat addiction, rather than overly and primarily focus on 'bottom-up,' unidirectional mechanisms.

In addition to this critical role that psychosocial factors play in addiction, and how the brain disease model is limited by its inadequate emphasis of them due to its dominant

emphasis on unidirectional neurobiological processes, the model similarly oversimplifies and reduces addiction when considering the genetic underpinnings of addiction, emphasizing one of its major causes as being *genetic predispositions* to the 'brain disease' (Ducci and Goldman 2012). Although research has demonstrated genetic underpinnings as being implicated in addiction, the brain disease model does not adequately emphasize how genes do not deterministically give rise to addiction, as gene function and expression can be altered by environmental factors, as has been demonstrated by epigenetic studies (Genetic Science Learning Center n.d.; National Institute on Drug Abuse, e; Nielson et al. 2012). One example of this is how one study found that the rate of substance abuse initiation in those with a genetic predisposition was moderated by environmental factors such as membership in community-building programs and the availability of supportive parenting (Brody et al. 2009; Nielson et al. 2012). Epigenetic studies as such demonstrate that those who assert that addiction is primarily a neurobiological and genetic disease, in which such biological processes give rise to addiction in a unidirectionally causal way, are oversimplifying and overreducing addiction, as the neurobiological and genetic "causes" of addiction need not be deterministic because environment can modulate one's vulnerability to it.

Psychosocial factors and epigenetics evidently play critical roles in the development and reinstatement of addiction, and the examples presented here thus demonstrate how addiction is not a "brain disease" in that it is predominantly neurobiological changes and genetic predispositions which are to blame for its onset and persistence. The brain disease model is therefore greatly limited by this emphasis and its subsequent inadequate acknowledgement of psychosocial factors and epigenetics. Furthermore, such lack of emphasis means that we are heavily approaching addiction research and treatment from a unidirectional angle, rather than trying to wholly understand its multiple integrational causes and applying such knowledge towards treatment efforts, as emphasized by Ashcroft. Indeed, this need to better acknowledge and integrate psychosocial factors has become more addressed in the past two decades, as the *biopsychosocial model* of addiction has gained prominence and become very well-known today (Alonso 2004; Havelka, Lucanin, and Lucanin 2009; Wade and Halligan 2017). However, despite the emergence of this biopsychosocial model and its acceptance, the brain disease model of addiction still dominates the mainstream perspective of addiction, as demonstrated by the discussions of those such as Dr. Volkow (Alonso 2004; Havelka, Lucanin, and Lucanin 2009; Volkow and Koob 2015; Volkow, Koob, and McLellan 2016; Wade and Halligan 2017). Dr. Volkow does acknowledge biopsychosocial factors as playing an important role in addiction; however, reflecting the focus of the brain disease model, she emphasizes

addiction as a *disease of the brain* in which "neuroadaptations," caused by chronic substance use, unidirectionally give rise to addiction and addicts' inability to control their behaviors (Volkow and Koob 2015; Volkow, Koob, and McLellan 2016). Accordingly, Dr. Volkow describes how addiction, being a brain disease, "erodes the neuronal circuits that enable us to exert free-will," further demonstrating the reductionistic and unidirectional emphasis of this model (Volkow and Koob 2015). Thus, despite the growth and acceptance of the biopsychosocial model, we still see today that the brain disease model and its reductionistic emphases hold a dominant position in the mainstream perspective of addiction.

Taken together, I argue that the over-reductionism of the brain disease model leads to many issues in the way we interpret addiction– such as how we inadequately acknowledge the critical role of psychosocial factors as well as epigenetics in the etiology of addiction, as described in this subsection. The brain disease model, instead, emphasizes that addiction is primarily caused by neurobiological changes induced by chronic drug use, which, in turn, unidirectionally gives rise to addicts' compulsive and uncontrollable behavior, or their inability to "exert free will," as has been described (Volkow and Koob 2015). On this note, I turn to the next critical flaw and discrepancy that is exemplified by the brain disease model and its proponents. Proponents of the model emphasize that chronic substance use induces neuroadaptations which cause inevitable 'compulsive' and 'uncontrollable' behaviors in addicts, yet proponents implicitly contradict themselves regarding whether they truly believe that addicts are unable to exert behavioral control, and whether they are truly, fatalistically 'compulsive' due to their 'brain disease.'

Section 2.2: Contradictions Regarding Addict Compulsivity

In addition to the brain disease model being limited by its over-emphasis on neurobiological and genetic factors as being fundamental, unidirectional mechanisms underlying addiction, rather than adequately emphasizing the critical importance of psychosocial factors and epigenetics, the model is also weakened by the contradictions within itself and its proponents regarding whether or not addicts hold some degree of behavioral control. Indeed, despite model and proponent claims that the neuroadaptations implicated in addiction unidirectionally cause inability of addicts to exert behavioral control, we see that proponents implicitly contradict themselves and demonstrate discrepancies regarding this belief.

As mentioned, the brain disease model and its proponents describe the transition to compulsive drug seeking and use in addicts as resulting from neurobiological changes which 'hijack' the brain and subsequently leave addicts unable to control his or her behaviors (Belin et al. 2013; Le Moal and Koob 2007; McKim 2006; Volkow, Koob, and McLellan 2016; Vrecko 2010). NIDA's website describes:

> …addiction changes the brain in fundamental ways, disturbing a person's normal hierarchy of needs and desires and substituting new priorities connected with procuring and using the drug. The resulting compulsive behaviors that override the ability to control impulses despite the consequences are similar to hallmarks of other mental illnesses. (National Institute on Drug Abuse, b)

However, this brain disease model definition of addiction, implicating compulsivity and lack of behavioral control as a key criterion, is often contradicted by the very proponents of the model. An example of such a contradiction is discussed by Henk Ten Have (1985). He explains how although the brain disease model was dominant in Amsterdam in 1985, there was an ambivalence towards the treatment of addicts. On one hand, addicts were viewed as being fundamentally unable to cope with stress and having purely physical root causes of their addictions (Ten Have and Sporken 1985). However, Ten Have points out the contradiction in physicians and treatment teams who touted the brain disease model at this time:

> …it is curious that many intervention projects stipulate that the addicts should be motivated towards the treatment. Conditions are imposed upon the participants of a therapy as well as those who get a free supply of heroin [maintenance treatments]. …If [addicts] want to be helped they have to meet conditions which they are incapable of meeting because of their addiction. (Ten Have and Sporken 1985)

What Henk describes here is that treatment for addicts being provided was contingent on the addicts demonstrating a willingness to put forth effort towards integrity and recovery. However, he points out the contradiction as being that addicts, according to the brain disease model and treatment providers, were not capable of exerting control over their behaviors and substance use; addiction was seen as a fatalistic and organic brain disease.

At the same time, treatment providers expected addicts to demonstrate a degree of control and compliance, such that addicts put forth effort towards ceasing their

substance use as well as recovering. These expectations of addict compliance and self-control therefore contradict a key component of addiction under the brain disease model – compulsivity and persistent drug-seeking and use, despite negative consequences, as stemming from neurobiological alterations induced by chronic substance use (American Psychiatric Association 2013; National Institute on Drug Abuse, c). Here, Ten Have provides an example of how treatment providers who claim to ascribe to the brain disease model contradict themselves and it goes unnoticed, and how the requirements of addiction treatment that is provided by these individuals undermines the very brain disease model definition of addiction.

Another example of how the brain disease model idea of addict compulsivity is often contradicted by proponents is seen in twelve-step addiction recovery groups such as Alcoholics Anonymous (AA). In these groups, alcoholics explicitly admit to being powerless over their addictions and behaviors, yet have expectations from the group as well as themselves to take active, corrective actions, such as making "a list of all persons [they] had harmed, and [to become] willing to make amends to them all" (Alcoholics Anonymous, b; Bower 2014). Through AA, addicts and former-addicts admit that they were at fault as well as responsible for their actions that harmed others, despite his or her state of addiction (Alcoholics Anonymous, a, b). However, to acknowledge and take responsibility for one's actions implies that one has some degree of autonomy and control over his or her behaviors, which again, contradicts the brain disease model definition of addiction, as well as the premise of AA which describes addicts as being powerless and having lost control over their addictions as a function of having this disease (Donovan et al. 2013; Kurtz n.d.; Satel and Lilienfeld 2013; Sussman 2010).

Wilbanks further points out another contradiction from brain disease model proponents: under this model, addicts are viewed as being powerless over their behaviors but they are still seen as holding responsibility in regards to criminal behavior. He discusses how those who adhere to the theory that drug addiction causes crime also believe that addicts need to be held responsible for their criminal acts. Wilbanks points out that "…such a position seems inconsistent with the view of the cause of the behavior. If the addict is truly "not responsible for his addiction," how can he be responsible for the criminality which allegedly inevitably flows from that addiction?" (Wilbanks 1989). Wilbanks' discussion of how addicts are still seen as being responsible for their criminal behavior, despite their state of addiction, again highlights how brain disease model proponents often contradict themselves, as well as weakens the argument that Leshner made regarding the presumed brain disease model benefit of it enabling greater criminal justice for addicts.

From the examples discussed in this section, it is apparent how the brain disease model is a limited model due to the many contradictions and inconsistencies that arise from and within it. The brain disease model overall postulates that addicts are compulsive in their behavior due to their brain disease and related neurobiological alterations which unidirectionally result in them being unable to exert control over their behaviors. Yet, we see many brain disease model proponents, as well as addicts who ascribe to the brain disease model, contradicting themselves. On one hand, they agree that addicts cannot control their behaviors due to this physiological disease, which causes their lack of control and compulsivity. On another hand, they have implicit or explicit expectations of addict compliance and discipline, which contradicts the key criterion of compulsive behavior and lack of behavioral control that the brain disease model asserts. Implications of these contradictions are that they undermine the brain disease model's full legitimacy, as we can see that even proponents of the model as well as addicts themselves do not seem to fully adhere to the idea that addicts are completely powerless over their behaviors.

Section 2.3: Empirical Support for Addict Control & Implications of Calling Addicts Compulsive

In addition to these contradictions that exist within the brain disease model as well as from its proponents regarding addict compulsivity, there has been some empirical support for the argument that addicts do actually hold some degree of behavioral control. This support further undermines the brain disease model, in that it clearly points out the inaccuracy (or incompleteness) of its idea that addicts, due to neurobiological changes as a result of chronic drug use, are incapable of controlling their behaviors**.** Furthermore, the brain disease model assertion that addicts are inherently compulsive can have negative implications, such as enabling addicts to take less responsibility for their behaviors, as well as inducing a learned helplessness state in addicts.

Wayne Hall (2003), in support of the argument that addicts do demonstrate some behavioral control, discusses "the Swiss heroin trials." In this study, there were two groups of heroin addicts: one was given immediate access to heroin maintenance treatments, and the other had a delayed entry in receiving treatments, where after a few months, they were given the option of choosing usual treatment, heroin maintenance, or abstinence. The study reported that once the delayed entry group was given the choice of treatment after 6 months of waiting, two-thirds of them decided against the option of

heroin maintenance (Hall 2003). Hall cites this example to argue against the claim that addicts are not fatalistically compulsive in their behavior.

Even Leshner, an adamant proponent of the brain disease model, implicitly points out the contradiction in the brain disease model of addiction regarding addict compulsivity. He cites a study conducted on thousands of US soldiers during the Vietnam War who were addicted to heroin while at war abroad. Surprisingly, it was found that when they returned home, it was relatively easy for these soldiers to be treated for their addictions; Leshner points out how this is because they were no longer in the environmental conditions that had been associated with their drug use (Leshner 1997). Leshner uses this as support for his argument that addiction treatment needs to take into account the social contexts in which addiction is developed, although he still sees addiction as primarily being a brain disease that is caused by neurobiological changes that are induced by persistent substance use (Leshner 1997).

In addition to the empirical evidence that addicts do indeed hold some degree of behavioral control, the assertion that addicts are inherently compulsive in their behaviors has possible negative implications. Namely, such an assertion could enable addicts to not take responsibility for their actions, and it could lead to a state of learned helplessness in which they exert less effort in trying to help their situation (i.e. by seeking various forms of recovery). Accordingly, Hyman (2007) explains how defenders of the moral model often point out how addicts do hold some control over their behaviors, and how the brain disease model can be problematic as it can reinforce the idea that addicts are not responsible for their behavior:

> Those who argue that addiction is best conceptualized as a moral condition are struck by the observation that drug seeking and drug taking involve a series of voluntary acts that often require planning and flexible responses to changing conditions – not simply impulsive or robotic acts. They worry that medicalization [seeing addiction as a physiological, brain disease] will lead addicted people to fatalism about their condition and to excuses for their actions rather than full engagement with treatment and rehabilitation and an effort to conform to basic societal expectations. (Hyman 2007)

Hyman, who validates the neurobiological factors involved in addiction, therefore points out how the brain disease model's use of the word compulsive seems inaccurate to those who advocate for the moral model. Furthermore, he describes how these advocates also argue that the brain disease model can lead addicts to a state where they truly

believe that they have no control over their condition, and therefore they do not have to hold themselves fully accountable for their actions. This makes sense, as telling people that they are a victim of their 'diseased' brains can lead them to truly believe that they cannot do anything to help themselves – so why bother? In that sense, it can become a self-fulfilling prophecy in which the addict fulfills the role of victim. William Wilbanks similarly discusses this argument and how by calling addiction a brain disease, we could induce a learned helplessness state in addicts (Wilbanks 1989).

From these examples, we can see that not only do brain disease model proponents contradict themselves regarding the issue of whether addicts are powerless over their behaviors, but the brain disease model itself is not entirely accurate to assert that addicts are powerless due to neurobiological changes in the brain which fatalistically render addicts compulsive in their behaviors. Furthermore, as Hyman and Wilbanks discuss, the brain disease model assertion that addicts are compulsive in their behavior can have negative implications: addicts may be less inclined to take responsibility for their behaviors, and they may be more likely to fall into a learned helplessness state.

Section 2.4: Substance Use Does Not Fatalistically Lead to Addiction

The final problematic area of the brain disease model that I will address is its claims that the persistent use of substances inevitably and unidirectionally leads to addiction, as proponents like Leshner describe. There is, in fact, good evidence that speaks against this claim. Indeed, relatively small amounts of chronic pain patients who are prescribed opioids for long-term pain relief become addicted to them. Consider, for example, the following:

> In one literature review, Noble et al. 2010 examined 26 studies with chronic opioid pain patients and found signs of opioid addiction in only 0.27% of participants in the studies that reported on such outcomes (Noble et al. 2010). In a different review, Fishbain et al. 2008 examined 24 studies and found that the rate of prescription opioid abuse and addiction for chronic nonmalignant pain patients was 3.27%. Furthermore, within this same group of studies, the percentage of opioid abuse for the chronic pain patients *with no past or current history of abuse or addiction* was 0.19% (Fishbain et al. 2008). In another review, Vowles et al. 2015 included data from 38 studies and found higher rates of opioid addiction in chronic pain patients than

> those that were reported by Noble et al. and Fishbain et al., indicating such rates to be between 8 to 12% (Vowles et al. 2015).[2]

Overall, though, the relatively low rates of opioid addiction that result from persistent prescription opioid use, as demonstrated by such use in chronic pain patients, are in opposition to the brain disease model idea that long-term substance use will inevitably lead to addiction. Furthermore, even the misuse of prescription opioids does not fatalistically lead to heroin addiction, and this is especially important to note because prescription opioid misuse tends to be framed in a way that makes it appear to be a major cause of heroin addiction. For example, the Department of Health and Human Services (HHS) and NIDA report that almost 80% of Americans who use heroin began with the misuse of prescription opioids (National Institute on Drug Abuse, f; US Department of Health and Human Services). Although accurate, this statement is misleading as it makes it seem as if misusing prescription opioids will directly lead to heroin addiction, when in reality, a small amount of people – approximately 4% – who misuse these prescription drugs transition to heroin use (National Institute on Drug Abuse, f; National Institute on Drug Abuse, g; Volkow and McLellan 2016). The idea, however, that prescription opioid misuse "open[s] the door to heroin use" mirrors the brain disease model stance that substances themselves largely cause addiction, and by inducing neurobiological changes in the brain (Leshner 1997; McKim 2006; National Institute on Drug Abuse, f). Prescription opioids by themselves do not cause the addiction to either these painkillers or heroin. This is in opposition to what the brain disease model and proponents like Leshner posit, since they assert that the long-term use of substances will inevitably lead to addiction, when we can see from this example of chronic pain patients that this is not the case.

Overall, the assertion by the brain disease model and its proponents that long-term substance use will fatalistically, and in a unidirectional manner, lead to addiction is clearly inaccurate, as we can see that a relatively small amount of chronic pain patients become addicted to prescription opioids after long-term usage. Furthermore, even the misuse

2. Although the rates of addiction determined by Vowles et al. are relatively higher than those determined by Noble et al. and Fishbain et al., it is important to note that such rates (between 8 to 12%) are still very low when considering the brain disease model assertion that long-term substance use 'hijacks' the brain and leads to addiction. Furthermore, the rates indicated by Vowles et al. did not distinguish patients who had a past or current history of substance use, and such a factor may be very important when trying to determine whether long-term opioid use by itself leads to high rates of opioid addiction, or whether it is peoples' history of substance abuse that makes the overall rates appear higher than they may otherwise be.

of these prescription drugs does not fatalistically lead to heroin addiction, despite how such misuse is often described in a way to make it seem as if it does. This lack of fatality in substances inducing addiction therefore further undermines the brain disease model, in that it indicates that the model does not lay an entirely accurate framework to truly understand addiction and its causes.

Section 3: Towards Greater Integration of Mind-Brain Intermodulation as a Direction Forward

From the discussion in sections 1 and 2, we can see that the brain disease model of addiction has brought forth benefits but also holds many limitations, including inadequate emphasis of psychosocial factors in the etiology of addiction, a discrepancy within the model and its proponents regarding whether addicts hold some degree of behavioral control, and its argument that persistent use of addictive substances fatalistically leads to addiction, which we see, from the example of chronic pain patients, to not be accurate. Although the brain disease model holds such limitations, I argue that most of them stem from its overreliance on neurobiology as a being a *unidirectionally* causal explanation for addiction. Contrary to this over-reductionistic stance, I argue that, based off of empirical evidence, the brain does not unidirectionally give rise to our subjective, experiential mental states and corresponding behaviors, which I will cluster together and thus forth describe via the terminology *mind* and *elements of mind*.[3] Rather, the "mind" and its elements are also able to influence and modulate physiological processes in the brain and body. This latter process is what I will describe in this section as being a "*top-down*" process, and I will also use the term "*bottom-up*" process to describe those of the brain which modulate and induce changes in state of mind and corresponding behavior.[4] I

3. When I refer to the *mind* and its related *elements*, I refer to the self-aware, experiential aspects of humans which we anecdotally consider to be our "selves." I also define them similarly to how Mario Beauregard does; as including consciousness, cognitions, self-awareness, metacognition, expectations, beliefs, volition, emotion and affect, intentions, conscious physiological and behavioral control (both related to intent and volition), as well as behaviors arising from conscious or unconscious "mind" or "mentalistic" processes (Beauregard 2007).

4. The terms "*top-down*" and "*bottom-up*" are adopted from a literature review by Taylor et al. 2010, in which they use the terms to describe a "bidirectional" relationship between the mind and body (Taylor et al. 2010). In this section, I specifically utilize and apply this terminology to my discussion of mind-brain intermodulation as applied to addiction neuroscience, and provide a distinct and novel synthesis of supporting literature.

argue that top-down and bottom-up processes exist simultaneously, interdependently, and interactionally. Overall, I call the ability of these top-down and bottom-up processes to exist in this manner, more broadly, *mind-brain intermodulation*.

Mind-brain intermodulation, as I describe it, may seem overly esoteric and controversial as a concept, as it summons the age-old mind-body problem in which there are a wide array of stances that can be argued regarding the exact relationship and mechanics between mind and brain. Therefore, my intermodulatory model may be subject to debate, as such debate is relevant, but for the purpose of focus, an in-depth discussion of the presupposed theoretical mechanics between the mind and body, in relation to the intermodulatory relationship I posit, will be considered outside the immediate scope of this paper.[5]

Although ultimately there is lack of scientific clarity regarding the exact mechanics between the mind and brain, a huge body of literature has shown that the relationship is not reductionistic in that the brain gives rise to the mind and its elements unidirectionally, with the latter unable to influence the former (as the brain disease model assumes). Rather, the mind and its elements, such as beliefs and intent, are also able to modulate the brain's physiology in a 'top-down' manner. Accordingly, in section 3.1, I begin by providing a review of the extensive neuroscientific literature that provides evidence for such a mind-brain intermodulatory relationship. In section 3.2, I then describe how this intermodulatory relationship can be specifically applied to create novel, combined 'top-down' and 'bottom-up' treatments for addiction, and provide examples of how this is beginning to be examined by researchers, although the area of research is still in infancy and is not the current mainstream perspective in addiction neuroscience. Despite this, I also offer an additional, *theoretical* example of how this intermodulatory relationship could further be explored by researchers, as well as applied to novel treatments. In this section, I overall argue that application of mechanisms involved in the interdependent, intermodulatory relationship between mind and brain holds much potential in allowing us to better understand and develop novel therapeutics for addiction, as well as allowing us move forward from the brain disease model and its limitations.

5. Although this discussion and debate will be considered outside of scope, see Schwartz et al. 2005 for one example of a neurophysical theory and model of how such an intermodulatory, or "bidirectional" relationship, as they describe it, could exist between the mind and brain, as well as how examples and mechanics from quantum physics can be extrapolated to support this model (Schwartz, Stapp, and Beauregard 2005).

Section 3.1: Mind-Brain Intermodulation in Principle

A huge body of neuroscientific literature has shown that the mind and its related elements, such as beliefs and intent, are able to modulate the brain's physiology in a '*top-down*' manner, and I argue that the brain disease model's lack of acknowledgment of this, and overemphasis on how the brain presumably gives rise to addiction and its behaviors in a unidirectional, '*bottom-up'* way, limits it from being an accurate explanatory model for addiction. Indeed, I argue that an interdependent and intermodulatory relationship exists between mind and brain, with mind being able to modulate brain (top-down mechanisms), in *addition* to the brain being able to modulate the mind and corresponding behaviors (bottom-up mechanisms). Here, I thus review the empirical literature which exemplifies the ability of the mind to modulate the brain and body, both on a moment-to-moment basis as well as over time. I argue that this extensive literature provides clear support of the mind-brain intermodulatory relationship, and further showcases the inaccuracy of the brain disease model's assumption that bottom-up mechanisms unidirectionally give rise to addiction and its related behaviors, thus further supporting my overall argument that the model is limited in its explanatory power for addiction.

The Mind as Modulating the Brain on a Moment-to-moment Basis: Studies on Placebo and Conscious Control

Extensive research has shown that the mind and its elements, in a top-down manner, are able to modulate the brain physiologically on a moment-to-moment basis. For example, in an extensive review, Beauregard 2007 discusses some of the literature that demonstrate how one constituent that can be considered part of the mind and its subjective elements, expectations and beliefs, are able to influence and induce changes in the brain physiologically in this moment-to-moment basis. He discusses several studies including one conducted by Kaasinen et al. 2004 (Beauregard 2007; Kaasinen et al. 2004). In this study, the researchers demonstrated that caffeine *expectation* (in a placebo group of participants) induces a release of dopamine in the thalamus, whereas actual caffeine also induces such a dopamine release in this same brain region (Beauregard 2007; Kaasinen et al. 2004). This similarity in the brain's dopaminergic response to caffeine as well as placebo caffeine indicates that the mind and its related "mentalistic variables," as Beauregard describes, such as expectations or beliefs, can induce physiological responses

in the absence of the stimuli (i.e. actual caffeine) that normally produce such responses (Beauregard 2007; Kaasinen et al. 2004).

In addition to this, Beauregard reviews other placebo studies which utilize functional magnetic resonance imaging (fMRI) and show that placebo effects induce changes in physiological brain activation, indicating that the brain undergoes functional changes on a dynamic, moment-by-moment basis when the mind is experiencing an *expectation* of some sort of effect (Beauregard 2007). Other placebo studies, such as those investigating the effects of placebo *analgesia*, have accordingly shown how mere expectation of analgesic properties of treatments can actually induce neurobiological and molecular changes, as well as changes in biochemical processes in the brain, which correspond to an individual subjectively experiencing real, painkilling effects in response to placebo drug (Beauregard 2007; Colloca and Benedetti 2005; Peciña and Zubieta 2015). In this example, it has specifically been shown that this placebo effect is able to induce its painkilling effects due to subjective *expectations* inducing a physiological release of endogenous opioids (as well as endocannabinoids and dopamine) in the brain (Colloca and Benedetti 2005; Peciña and Zubieta 2015). This is noteworthy because, as mentioned, such a physiological response is elicited simply by the *expectation* that one will experience an analgesic effect, and thus this mind-based expectation is able to induce physiological mechanisms which actually lead to tangible analgesic effects. This example, then, clearly underscores how elements of the mind, such as expectations and belief, are able to induce physiological changes in the brain, in a top-down manner.

Another example of how the mind is able to induce brain changes on a moment-by-moment basis, but in a *consciously controlled* "top-down" manner, is demonstrated by magnetic resonance imaging (MRI) and fMRI studies in which participants are asked to mentally visualize an image (or engage in visual recall), and in which subsequent functional brain changes are seen (Ganis, Thompson, and Kosslyn 2004; Le Bihan et al. 1993; Pearson et al. 2015). The variable which is being manipulated in these studies is the visualization or recalling of imagery, which requires the individual's *intent*, *volition*, and subsequent *execution* of action, all via *conscious choice*. This intent and subsequent behavioral execution are examples of the mind and its elements in action, and the results of these studies showed how the mind and its elements thus were able to induce functional changes in the brain as a consequence of participants' mental visualization or recall (Ganis, Thompson, and Kosslyn 2004; Le Bihan et al. 1993; Pearson et al. 2015). Interestingly, also, some of the studies also found that this type of visualization or recall even induced functional changes in brain areas which overlap with those involved in the perception of actual external visual stimuli, which, similarly to the examples of the

placebo studies, shows how such mind-driven, top-down processes are able to induce physiological brain changes in the absence of external stimuli which are also normally able to elicit such changes (Ganis, Thompson, and Kosslyn 2004; Le Bihan et al. 1993; Pearson et al. 2015). Thus, these studies serve as further support for my argument that the mind and its elements are able to physiologically modulate the brain.

These examples of placebo studies as well as those implicating intent and conscious control demonstrate how the mind is indeed able to, in a top-down manner, modulate the brain physiologically, and on a moment-to-moment basis. These studies therefore clearly demonstrate the very real connection that exists between the mind and its elements, such as expectations or beliefs, and the brain on a physiological and functional level, where not only does the brain give rise to the mind and subjective experiences, but the latter also modulates the former, in very concrete ways. This discussion therefore provides support for my overarching argument of a mind-brain intermodulatory relationship, and how the brain disease model of addiction is limited due to its lack of acknowledgment of this relationship.

Physiological Brain Changes Induced by the Mind, Over Time: Support from Studies of Mindfulness Practice, Learning, & Psychotherapy

In addition to elements of the mind, such as expectations, beliefs, and intent being able to modulate the brain on a moment-by-moment basis, the mind and its elements are also able to induce physiological changes in the brain over time. An example of this is illustrated by *mindfulness* and meditative practices which, in addition to inducing moment-to-moment functional changes in the brain when practiced in the moment, they are, over time, able to structurally and functionally alter the brain (Lutz et al. 2014; Yang et al. 2016). Mindfulness, in particular, can be defined as the act of consciously paying attention to the present moment and being aware of both internal and external stimuli, in a nonjudgmental, nonreactive, and accepting way (Keng, Smoski, and Robins 2011). It also allows one to enter a state of mind which has been associated with calmness and cultivation of insight, and which, when practiced over time, has been linked with improvements in psychological health (Keng, Smoski, and Robins 2011; Vago and Zeidan 2018).

Mindfulness and other similar meditative practices implicate the mind and its elements, as they are accomplished through the intent and choice to execute the practice in the moment, as well as repeatedly over time, and through staying mentally engaged

during practice by consciously focusing and re-focusing one's attention (Vago and Zeidan 2018). Therefore, top-down, mind-driven processes are implicated in the practice of mindfulness, and indeed it has been shown by extensive research how, when it is practiced over time, mindfulness is able to induce long-term structural and functional changes in the brain.

For example, studies have shown how long-term mindfulness and meditative practices can cause increases in gray matter density in various parts of the brain, such as the brain stem, right orbito-frontal cortex, and right hippocampus, compared to non-meditating controls (Luders et al. 2009; Vestergaard-Poulsen et al. 2009), which serve as examples of how the top-down process of engaging in these practices induce physiological changes in brain structure over time. Furthermore, changes in brain functionality due to long-term meditative and mindfulness practice have been demonstrated via fMRI studies which show how, after initiation and repeated practice over time, participants' fMRI scans showed changes in functional brain reactivity which corresponded to decreased emotional reactivity to negative, aversive imagery that were presented to them, relative to the scans of non-meditating controls (Desbordes et al. 2012; Guendelman, Medeiros, and Rampes 2017; Yang et al. 2016). These studies show how physiological changes in brain structure, functional reactivity and corresponding emotional reactivity can occur as a function of the top-down, mind-driven practice and execution of mindfulness and meditation over time

In addition to the example of mindfulness and meditative practices, other mind-driven processes are able to induce physiological changes in the brain over time, such as the process of learning. Today, it is well-known by neuroscientists that learning alters the brain physiologically due to mechanisms such as Long-Term Potentiation (LTP), or *synaptic plasticity* (Bliss and Collingridge 1993). There are several known types of LTP; one type, NMDAR-dependent LTP, depends on the activation of N-methyl-D-aspartate receptors (NMDARs) by the presynaptic release of glutamate, which then triggers the process of LTP which enhances signal transmission between neurons (Bliss and Collingridge 1993; Kauer and Malenka 2007). LTP and neuronal plasticity provide support for the argument that the mind and its elements can induce physiological changes in the brain, both immediately as well as over time, and thus that the mind and brain are able to *intermodulate* one another via *interdependent* top-down and bottom-up processes. This is seen by how the process of mind-driven learning induces physiological changes in the brain via LTP, which in turn gives rise to strengthened memories and associations, as well as enhanced ability to subsequently understand a concept or task or to execute it, as an overall consequence of this interdependent and interactional top-down and bottom-

up learning process (Bliss and Collingridge 1993; Kauer and Malenka 2007; Milton and Everitt 2012).

In addition to research studies that have demonstrated how the mind and its elements are able to induce physiological changes in the brain, either on a moment-to-moment basis or over time, much research has indicated that undergoing long-term psychotherapy can alter the brain structurally and functionally (Beauregard 2007; Collerton 2013; Gabbard 2000; Joffe, Segal, and Singer 1996; Liden 2006; Liggan and Kay 1999; Lehto et al. 2008; Viinamäki et al. 1998; Zaman 2010). Examples of such findings are studies that have shown that undergoing psychotherapy can induce changes in monoamine transporter densities in the brain, as well as significant changes in brain activation patterns when comparing fMRI scans of individuals before and after undergoing psychotherapy (Collerton 2013; Gabbard 2000; Lehto et al. 2008; Viinamäki et al. 1998). Several researchers have speculated that psychotherapy may induce such brain changes due to learning processes that occur when one undergoes psychotherapy, and accordingly, Beauregard describes psychotherapy as being "a form of controlled learning that takes place in the context of a therapeutic relationship" (Beauregard 2007; Gabbard 2000; Kandel 1998; Liggan and Kay 1999).

As discussed, mindfulness practice is able to alter the brain structurally and functionally, and this further holds true when we consider mindfulness-based psychotherapies, such as Mindfulness-Based Cognitive Therapy (MBCT) and Dialectical Behavior Therapy (DBT). Mindfulness-based psychotherapies such as these have shown to, when one is engaged in the process over time, allow one to become more aware of his or her distressing as well as seemingly compulsive and automatic thoughts (Keng, Smoski, and Robins 2011). In a way, this growth in awareness grants individuals a sort of control, in which they are able to mentally "step back" from their 'automatic' thoughts and simply observe them without judgment and reactivity, and subsequently let them pass without attaching to them and getting 'caught' in a downward spiral via their distressing thoughts and cognitive distortions (Keng, Smoski, and Robins 2011). Indeed, such distressing thinking patterns and cognitive distortions are hallmark symptoms of many mental illnesses, and the alleviation of their distressing effects through mindfulness cultivation, is why mindfulness-based psychotherapies have shown to alleviate symptoms of a variety of mental illnesses as well as addiction (Bowen, Chawla, and Witkiewitz 2014; Dimeff and Linehan 2008; Keng, Smoski, and Robins 2011; Linehan, Camtois, and Murray 2006; Morgan 2010). Engagement in such psychotherapies has also been shown to, similarly to that of mindfulness as a stand-alone practice, as well as other psychotherapies, induce changes in both brain structure and function over time – changes

which also correspond to the decreased emotional reactivity and increased emotional regulation skills one acquires through the process (Desbordes et al. 2012; Goodman et al. 2014; Guendelman, Medeiros, and Rampes 2017; Mancke et al. 2018; Schnell and Herpertz 2007; Yang et al. 2016).

From these examples, we can see that various forms of psychotherapy, including mindfulness-based psychotherapies, can induce both functional and structural changes in the brain over time through their mind-driven, top-down processes. Furthermore, we see that mindfulness as a stand-alone practice as well as the process of learning are also able to induce such physiological brain changes. The examples I provide therefore illustrate how top-down, mind-driven processes not only induce physiological brain changes on a moment-to-moment basis, but are able to induce changes in structure and function over time. These empirical examples thus further support my argument that the mind and brain hold an intermodulatory relationship, and that the brain does not solely give rise to the mind and its subjective experiences and corresponding behaviors in a unidirectional manner, as the brain disease model oversimplifies.

Mind-Body Intermodulation on a Broader Level & as Implicated in Medicine

In addition to the discussion on and examples of how the mind is able to modulate the brain on a moment-to-moment and long-term basis, research has also shown how the mind is able to physiologically modulate the *body* on a broader level. Furthermore, this ability is beginning to be more acknowledged by medicine as a whole, and some have discussed how further acknowledgment and understanding of this intermodulatory relationship may allow more effective treatments for illnesses to be developed, in which either bottom-up or top-down processes may be therapeutically targeted.

An example of how research has indicated that the mind and body hold an intermodulatory relationship is reviewed by Mayer et al. 2014, in which they specifically describe and cite the literature which demonstrate how state of mind and mental stressors are able to affect composition and metabolic activity of gut microbiota, but how these microbiota also, in what Mayer et al. describe to be a "bidirectional manner," can affect state of mind and behavior (Mayer et al. 2014). The significance of these findings is that they further support how both top-down and bottom-up processes exist in intermodulatory and interactional, or in what Mayer et al. call it, "bidirectional," ways in the body. Here we see how not only are these microbiota, in a bottom-up way, able to influence mental state and behavior, but also how the mind is able to

modulate physiological parameters such as composition and metabolic activity of the gut microbiota (Clapp et al. 2017; Cryan and Dinan 2012; Gareau 2014; Mayer et al. 2014). This example further provides empirical evidence for the argument that the mind and body hold an intermodulatory relationship in which both top-down and bottom-up processes function in inderdependent ways.

Taylor et al. 2010 similarly discuss how the mind and body are able to modulate one another in "bidirectional," intermodulatory ways, and accordingly discusses how interdependent "top-down" and "bottom-up" processes are implicated in this relationship. Due to the coexisting and interactional nature of these mind-body processes, Taylor et al. discuss how stressors or illnesses of either the mind or body can therefore be benefitted from therapies that either target the mind directly (top-down therapies such as mindfulness or self-directed relaxation therapies), or the body directly (bottom-up therapies, such as stimulation of the vagus nerve), as targeting either will naturally result in the other being modulated as well (Taylor et al. 2010). In the case of the latter example, stimulation of the vagus nerve, a bottom-up, physiologically-targeted treatment, is known to help treat depression, providing an example of how these types of bottom-up therapies are able to modulate subjective states of mind and provide symptom relief such as in the case of depression (Taylor et al. 2010).

Taylor et al. further go on to explain how "bidirectional" terminology to describe the interdependent relationship between mind and body, as well as how they are mutually affected by either top-down or bottom-up treatments, is an oversimplification, as both constituents interact in a multitude of 'non-linear' ways during various therapies (Taylor et al. 2010). As an example, they discuss progressive muscle relaxation and yoga, which consist of both top-down and bottom-up mechanisms. In particular, the practice of either begins as a top-down process in which *intent* and *conscious choices* are made to practice them (which includes consciously choosing to move the limbs or control the breath, as occurs in yoga), and then physiological alterations, such as reductions in muscle tension and blood pressure, occur in response to to these top-down enactments. These physiological changes then, in a bottom-up way, activate peripheral afferents which relay signals back to the brain, which *leads to further changes in state of mind*, such as greater mental relaxation, all induced by the initial top-down *conscious choice and intention* to practice the activity, and their subsequent execution (Taylor et al. 2010). Through this example, we can see how the effects of top-down and bottom-up therapies can compound and interact, which the authors thus describe as "bidirectionality," but also emphasize this to be oversimplified taxonomy (Taylor et al. 2010). They make their overall point though that due to this interdependent relationship between mind and

body, targeting either during the treatment of mental or physical illnesses subsequently elicits changes in the other which compound in nonlinear, 'bidirectional' ways, and thus targeting either can serve to be an effective treatment.

This concept of targeting either top-down or bottom-up mechanisms, due to the inherently intermodulatory relationship between the mind and body, has also been explored in relation to alleviating symptoms of medical conditions such as irritable bowel syndrome (IBS) and ulcerative colitis (UC). In some studies, researchers found that various top-down, mind-body therapies like hypnosis and meditation, were able to induce therapeutic physiological changes in those with IBS and UC, such as reductions in the release of the pro-inflammatory cytokines interleukins-6 and -13 (IL-6 and IL-13) and tumor necrosis factor-alpha (TNF-α) (Mawdsley et al. 2006; Mawdsley et al. 2008; Smith and Bryant 2002; Taylor et al. 2010). This physiologically therapeutic effect was further seen in studies which showed that such top-down therapies caused decreases in the stress hormone cortisol in oncology patients (Mackenzie, Carlson, and Speca 2005). These studies again support my argument that the mind, in a top-down manner, can modulate and influence not only the brain, but also the body, on a broader level, physiologically. Furthermore, as we see, acknowledgment of this mind-body intermodulatory relationship can be applied to the treatment of those with illnesses, in that we not only target or expect to target illnesses solely via bottom-up ways, but can acknowledge that the application of top-down therapies, through better understanding of this mind-body intermodulatory relation, can also have beneficial, therapeutic effects.

The extensive array of examples that I have provided in this section 3.1 overall highlights how the mind and its elements are able to induce physiological changes in the brain and body in a top-down manner, both on a moment-to-moment basis as well as over time. Taken together, I argue that this extensive literature provides clear support that the relationship between mind and brain, as well as body, is intermodulatory in that they are both deeply integrated and able to mutually influence one another, and that top-down and bottom-up mechanisms exist simultaneously and in a non-linear, interactional manner, as Taylor et al. 2010 emphasize. These examples thus provide extensive support for my argument that the brain disease model of addiction is greatly limited in that it does not take into account this intermodulatory relationship, but rather, describes addiction as occurring due to unidirectional bottom-up processes. I argue that this overreductionism and unidirectionalism of the brain disease model is a core component of its limitations as well as gives rise to the host of other issues discussed in section 2, such as its argument that the chronic use of substances leads to brain changes which thus

result in addiction, when we see, as demonstrated by the case of chronic pain patients, to not necessarily hold true.

Section 3.2: Utilizing Mind-Brain Intermodulation as a Means to Guide Further Research & Develop New Therapeutics for Addiction

Based off of the last subsection, we can see that the brain disease model is limited by its lack of acknowledgment of the intermodulatory relationship between the 'mind' and brain. This relationship is indeed evident, as shown by the abundant literature, and it is being more recognized by medicine on a broader level in recent years although it is still not the mainstream perspective in addiction neuroscience. I thus argue that this area of mind-brain intermodulation remains a research area wide open in regards to addiction, and that, if we aim to better understand the interdependent top-down and bottom-up mechanisms implicated in addiction, we may be able to develop novel treatments which combine both specified top-down and bottom-up treatments simultaneously which I argue may theoretically allow a "summation" effective in which they "potentiate" the therapeutic effects of the other, allowing for more enhanced and effective treatment for addiction.

In this section, I thus provide examples of recent research endeavors which have been exploring this area of combined top-down and bottom-up treatments, as demonstrated by D-cycloserine (DCS) coupled with extinction therapy and 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy (and ayahuasca and ibogaine as applied similarly). However, acknowledgment of a mind-brain intermodulatory relationship is usually implicit in these endeavors, and despite these recent trends, in general this research area is still in its infancy. Despite this, I argue it does hold much potential, and describe a theoretical example of how further research in this area could be undertaken with the aim of combining top-down and bottom-up treatments in regards to addiction: that of "pharmacologically induced or enhanced mindfulness states" coupled with mindfulness-based psychotherapy**.** I thus exemplify how further research into the mind-brain intermodulatory relationship would allow us to much better understand the addicted mind and brain and to subsequently develop novel and possibly enhanced or "potentiated" treatments, and that acknowledgement and integration of this relationship overall can help us move forward from brain disease model and its limitations.

D-cycloserine

An example of a line of research which has been investigated through implicit acknowledgment of the interdependent, intermodulatory relationship between the mind and brain is demonstrated by D-cycloserine (DCS) as applied to *extinction therapies* for addiction. In regards to this, researchers have recently been targeting *learning* as a growing and more focused on area in research for addiction, and trying to uncover the neurobiological correlates which are implicated in learning which could be manipulated (in a bottom-up way) to help addicts recover and better avoid relapses. This example illustrates how this relationship between processes of the mind (i.e. learning) and the brain (neurobiological changes implicated in learning) can be examined in regards to their interrelated top-down and bottom-up mechanisms, in efforts to apply knowledge regarding them towards creation of therapies which target both processes simultaneously, with the goal of more effectively treating addiction.

In terms of learning being more researched in addiction neuroscience, as mentioned in section 2.1, Milton & Everitt have extensively described the role that various learning processes play in the transition to as well as in the relapse of addiction (Milton and Everitt 2012). In addition to reviewing the literature on the links between learning processes and addiction, they explain how learning processes can also be involved in the recovery from addiction, such as how it occurs in the process of *extinction*. When one becomes addicted, for example, to cigarettes, they may form learned (conditioned) associations between cues such as their ashtray and their cigarette smoking. The conditioned association between the cue and smoking means that when one is not smoking, being presented with the ashtray would very likely give rise to cravings. The process of *extinction* means that when one is presented with this cue (the ashtray) repeatedly over time and in the absence of cigarettes or cigarette smoking, a new learned association is built between the ashtray and the lack of cigarettes, and this subsequently leads to a weakened effect that the cue previously had in inducing cravings (Milton and Everitt 2012; Torregrossa and Taylor 2016). *Extinction Therapy*, a subset of Cognitive-Behavioral Therapy (CBT), and therefore a top-down therapy, is one type of psychotherapy that is used for the treatment of addiction; it uses this principle of extinction learning to help addicts to recover from addiction by weakening the strength that substance-associated cues have in inducing cravings and subsequent relapses (Kaplan, Heinrichs, and Carey 2011; Milton and Everitt 2012).

Extinction therapy involves learning processes which engage the mind in a top-down way, and learning subsequently leads to neurobiological alterations in the brain due to synaptic plasticity, and overall learning is experienced as a function of both of these top-down and bottom-up interdependent mechanisms (as described in section 3.1). Knowing this, one way in which researchers could further investigate as well as apply greater knowledge of these intermodulatory mind-brain mechanisms would be to further investigate the neurobiological correlates of extinction learning in hopes of being able to pharmacologically induce or enhance this learning process to help treat addiction. For example, since glutamate plays a critical role in synaptic plasticity and learning by enhancing signal transmission between neurons, then theoretically, increasing the availability of glutamate in the neural synapses could enhance this process of LTP, and therefore learning (Davis 2011; Kauer and Malenka 2007; Schade and Paulus 2016; Todd, Vurbic, and Bouton 2014). By acknowledging the critical role that glutamate plays in the process of learning, researchers could administer pharmacological agents that are able to increase glutamate levels (a bottom-up therapy) during extinction therapy sessions (a top-down therapy) to strengthen the extinction that occurs during this type of therapy. Research regarding this type of learning enhancement has indeed begun to be undertaken and explored more in recent years, as researchers have demonstrated that D-cycloserine (DCS), an NMDAR partial agonist which has the ability to increase availability of glutamate levels in the synapses, has generally been found to enhance plasticity and learning processes during extinction therapies for addiction, and therefore assist in decreasing the strength that conditioned cues have in inducing cravings (Kaplan, Heinrichs, and Carey 2011; Milton and Everitt 2012; Schade and Paulus 2016; Torregrossa and Taylor 2016). There have been some discrepancies in the findings of the efficacy of DCS when used in conjunction with extinction therapy, but Milton & Everitt posit that this discrepancy is likely due to differences in the extinction paradigms used by researchers, such that the length of the extinction therapy used in the studies seems to play a role in determining whether the DCS administered during this therapy enhances the treatment or not (Milton and Everitt 2012).

This example of DCS as applied to extinction therapies for addiction is therefore an example of how top-down (extinction therapy) and bottom-up (pharmacologically manipulating neural and molecular correlates of learning) therapies can be combined. It demonstrates how we may utilize the framework of the mind and brain as being able to modulate each other as a basis through which we aim to integrate their interdependent mechanisms and apply greater knowledge regarding them towards the creation of such

novel and combinational therapies for addiction, which, as demonstrated through this example, holds much promise in treatment.

MDMA-, Ayahuasca-, and Ibogaine-assisted Psychotherapies

In addition to DCS, another example of mind-brain intermodulation being implicitly acknowledged, as well as where top-down and bottom-up therapies are combined during treatment, is 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy. Here, I describe how MDMA, a bottom-up pharmacological treatment, is coupled with psychotherapy, and how this combination treatment has thus far shown efficacy in treating PTSD in particular. In line with underlying mechanisms of DCS as coupled with extinction therapy, it is speculated that the MDMA combinational treatment approach shows efficacy because MDMA pharmacologically enhances processes which psychotherapy normally targets and modulates (in a top-down manner), such as memory, learning, and extinction. Although there is no current equivalent of MDMA-assisted psychotherapy being seriously investigated for addiction, substances such as ayahuasca and ibogaine, in a similar way when coupled with psychotherapy, have shown promise in effectively treating addiction and preventing relapse. I argue that these examples further illustrate how the area of mind-brain intermodulation is beginning to be more implicitly acknowledged and explored, and how when knowledge of this interrelationship is applied via combined top-down and bottom-up manipulations, it may allow for more enhanced and "potentiated" therapeutic effects.

MDMA, commonly known as 'Ecstasy,' has in the past few years begun being seriously considered as a potential treatment for PTSD when used in conjunction with psychotherapy. Although this has been subject of much controversy, due to the drug often being used recreationally and considered a "club drug," this combination therapy has shown promise in treating PTSD. Due to such promise and demonstrated potential, it is currently undergoing US Food and Drug Administration (FDA) Clinical Trials, soon beginning Phase 3 Trials, and thus moving closer towards becoming a legalized, FDA-approved therapy (Mithoefer et al. 2018; National Institute on Drug Abuse, a). The combination treatment has indeed shown efficacy thus far; for example, the Phase 2 Trials specifically showed that when MDMA was administered at relatively moderate doses and with minimal administrations (2-3 total times, spaced apart by a month) in conjunction with several psychotherapy sessions, participants with PTSD saw significant improvements in their symptoms, and this symptom alleviation was sustained even at a

12-month follow-up (Mithoefer et al. 2018). Furthermore, and very notably, it was found that this combined treatment resulted in therapeutic effects that were significantly larger than when the same psychotherapy protocol was administered, but instead with active or inactive controls for MDMA. The authors, accordingly, describe how MDMA appears to "potentiate" the effects of psychotherapy for PTSD, and therefore is showing to be a useful adjunct to it (Mithoefer et al. 2018).

In regards to the efficacy of this combined therapy, researchers have begun to speculate and investigate the physiological mechanisms by which MDMA is able to enhance psychotherapy. Some studies utilizing preclinical rodent models have shown that MDMA may enhance the psychotherapeutic process due to it pharmacologically targeting molecular processes involved in learning, memory, and fear extinction and through triggering neuroplasticity. Furthermore, they showed that when they combined MDMA administration with fear extinction paradigms in rodents, enhanced fear extinction was observed (Young et al. 2015; Young et al. 2017). Feduccia & Mithoefer further support the speculations that MDMA is able to pharmacologically manipulate processes implicated in memory, reconsolidation, and fear extinction (and possibly introspection and self-reflection), and similarly discuss how, when its administration is coupled with psychotherapies such as fear extinction or socially-supportive types (through a safe, working therapeutic relationship with a trusted psychotherapist), as shown by studies with human subjects, it appears to allow one with PTSD, in an enhanced manner, to undergo recovery (Feduccia and Mithoefer 2018). In particular, such combined treatment appears to allow them to better process their trauma such that they are more easily able to recall related memories with less accompanied distress, reappraise and make better meaning out of their experiences (reconsolidating their memories), and thus experience greater psychological "healing" which lasts (Feduccia and Mithoefer 2018). In line with this, the researchers of the Phase 2 Trials describe how MDMA, by pharmacologically enhancing psychotherapy through such processes, acts as a "catalyst for psychotherapy," and state:

> This model of treatment [MDMA-assisted psychotherapy] is different to most pharmacological interventions, in that its effectiveness appears to be mediated through pharmacological effects augmenting meaningful psychotherapeutic experiences. (Mithoefer et al. 2018)

In this regard, I argue that MDMA-assisted psychotherapy provides further support for my argument that mind-brain intermodulation, when acknowledged even implicitly, and applied to treatment efforts via combination of both top-down, mind-driven,

and bottom-up, pharmacologically-manipulating treatments, an enhancement or "potentiation" effect may occur which allows greater therapeutic efficacy than either of the processes being applied alone.

Although there is currently no equivalent of MDMA-assisted psychotherapy being seriously investigated for the treatment of addiction, some have theorized that different substances, namely the hallucinogenic substances ayahusca and ibogaine, may serve as useful adjuncts to psychotherapies and psychotherapy-like treatments for addiction (Belgers et al. 2016; Brown 2013; Brown and Alper 2016; Inserra 2018; Liester and Prickett 2012; Nunes et al. 2016; Prue and Voss 2015; Ross 2012; Schenberg et al. 2014; Thomas et al. 2013; Winkelman 2014). Although not being considered for the treatment of addiction in the United States,[6] as is the case with MDMA for PTSD, studies on ayahuasca and ibogaine have indeed indicated that when combined with psychotherapy, or used in socially and psychologically supportive and therapeutic contexts, as it often is during "healing" rituals and ceremonies in countries such as Peru and Brazil (where the substances are commonly used for the treatment of addiction), this combination treatment has shown great efficacy in treating addiction as well as preventing relapses (Brown 2013; Brown and Alper 2016; Liester and Prickett 2012; Nunes et al. 2016; Prue and Voss 2015; Ross 2012; Schenberg et al. 2014; Talin and Sanabria 2017; Thomas et al. 2013; Winkelman 2014). Similar to that of MDMA-assisted psychotherapy, it is hypothesized its ability to enhance treatment for addiction when used in this psychotherapeutic context is due to the substances being able to pharmacologically manipulate processes involved in learning, memory, reconsolidation, extinction, introspection and self-reflection, as well as exert its effects through factors such as stimulation of neurogenesis (Brown 2013; Inserra 2018; Liester and Prickett 2012; Ross 2012; Winkelman 2014).

I argue that these examples of MDMA as well as ayahausca and ibogaine exhibiting efficacy in treating addiction and PTSD[7] (as well as the earlier example of DCS), when

6. Both substances are currently illegal in the United States, both being classified as Schedule I substances with no currently accepted medicinal use (US Drug Enforcement Agency).

7. Although here I emphasize that MDMA (as well as ayahuasca and ibogaine), when coupled with psychotherapy, have shown efficacy at exerting therapeutic effects for PTSD and addiction, I wish to clarify that I do not necessarily argue that these treatments are foolproof and without risks. Currently, many of the immediate and long-term effects of these substances at a range of doses are unknown, but there has been evidence regarding the ability of MDMA and ibogaine to induce adverse health effects such as neurotoxicity and cardiac arrhythmia, for MDMA and ibogaine, respectively (Curran 2000; Gouzoulis-Mayfrank and Daumann 2006; Koenig and Hilber 2015; Litjens and Brunt 2016; Rubi et al. 2017; Sarkar

coupled with psychotherapy, thus support my argument of how greater knowledge of mind-brain intermodulatory mechanisms and subsequent application of them through combinational top-down and bottom-up therapies may allow for a more "potentiated" treatment of addiction. Thus, these examples show how there is a very real possibility of being able to develop novel therapies which may allow for such enhanced treatment of addiction, if we further research mind-brain dynamics and seek to tease apart the specific mechanisms of interdependent top-down and bottom-up processes implicated in addiction.

Theoretical Example of "Pharmacologically-induced or –enhanced Mindfulness"

Although this area of mind-brain intermodulation has been starting to be somewhat more acknowledged, albeit implicitly, as demonstrated by the examples of DCS and MDMA-assisted psychotherapy, this research area remains wide open and still in infancy, and therefore I argue holds much promise and potential if it is further explored in hopes of applying new knowledge on this intermodulatory relationship towards the creation of novel treatments for addiction. On this end, I illustrate how this area of research is wide open but holds great potential, as well as how it could further be explored with the aim of combining top-down and bottom-up therapies, through my theoretical example of "pharmacologically inducing or enhancing mindfulness states," coupled with the undergoing of mindfulness-based psychotherapy. Let's take a further look at the logic behind this theoretical proposal:

Research on mindfulness meditation and mindfulness-based psychotherapies, as mentioned earlier, have indicated how they have wide therapeutic benefits in terms of improving clinical symptoms for mental illnesses and in helping to treat addiction (Bowen, Chawla and Witkiewitz 2014; Dimeff and Linehan 2008; Keng, Smoski, and Robins 2011; Linehan, Camtois, and Murray 2006; Morgan 2010). Part of the efficacy of mindfulness-based psychotherapies is due to its emphasis on and training of becoming more aware of one's own emotional states and behavioral and cognitive patterns, and subsequently being better able to, over time, self-regulate distressing emotions, cognitions, and

and Schmued 2010; Schep et al. 2016). Therefore, I do not necessarily advocate the use of these particular substances per se, but use them as examples to illustrate how pharmacological manipulations, when coupled with top-down therapies, as illustrated, are able to exert "potentiated-like" therapeutic effects due to their abilities to manipulate, in this interactional way, processes such as memory, learning, and introspection, which I argue is highly notable.

seemingly-compulsive and impulsive behaviors (Bowen, Chawla and Witkiewitz 2014; Keng, Smoski, and Robins 2011; Linehan, Camtois, and Murray 2006; Morgan 2010). Furthermore, mindfulness and mindfulness-based psychotherapy simultaneously, in both a *moment-to-moment basis* as well as over time, induce structural and functional brain changes (American Psychiatric Association 2013; Desbordes et al. 2012; Goodman et al. 2014; Guendelman, Medeiros, and Rampes 2017; Lutz et al. 2014; Mancke et al. 2018; Schnell and Herpertz 2007; Yang et al. 2016). In regards to mindfulness inducing moment-to-moment functional brain alterations, these changes specifically correspond to and reflect being present in the actual 'mindful state,' in that particular moment (Guendelman, Medeiros, and Rampes 2017; Lutz et al. 2014; Vago and Zeidan 2018; Yang et al. 2016). The long-term structural and functional brain changes, on the other hand, correspond to later outcomes such as the enhanced self-regulation as well as ease at which one is subsequently able to self-regulate and practice further mindfulness over time, due to posited neuroplasticity 'rewiring' the brain and subsequently enabling such behaviors to feel more habitual and easily achievable on a consistent basis (Huffzinger and Kuehner 2009; Lee, Cadman, and Philo 2014; Shaffer 2016; Tang, Hölzel, and Posner 2015; Tang and Leve 2016; Tang, Tang, and Posner 2013; Teasdale et al. 2000).

In light of these understandings, I propose that by further understanding the mechanisms of how mindfulness, in a top-down way, corresponds to physiological brain changes, such as when one is engaging in mindfulness practice at a particular moment, we could develop novel pharmacotherapies that target and manipulate these neural correlates implicated, subsequently being able to, theoretically, pharmacologically induce such physiological changes and the corresponding states of mind – or, more simply put, pharmacologically "induce" or "enhance" mindfulness states. I argue that since we know that interdependent changes in brain and mind occur during mindfulness practice, being able to pharmacologically induce (or enhance) both via bottom-up manipulations appears feasible in theory (especially when based off of the logic for the treatments such as DCS). Furthermore, when coupling such pharmacological manipulations with a corresponding top-down therapy, such as mindfulness-based psychotherapy, in theory it could further allow one to more easily achieve or maintain a mindfulness state, thus being able to more easily practice mindfulness over time, leading to enhanced ability to attain the clinical benefits accompanying mindfulness practice, such as greater emotional self-regulation.

Therefore, a potentiation of the therapeutic effects of mindfulness-based psychotherapy could occur, due to one being more easily able to achieve or simply practice this mindfulness state in the psychotherapeutic context, being further facilitated by the neuroplastic changes that one would develop over time due to being able to consistently

engage in mindfulness. Such neuroplastic changes would thus theoretically make the mindful awareness more easy to "maintain" (by one's self, without the pharmacotherapy and outside of the context of psychotherapy) and the mindfulness-based skills, such as emotional regulation, easier to practice and implement on a day to day basis. This combination therapy therefore would allow mindfulness and its benefits to be more easily achieved versus mindfulness-based psychotherapies undergone alone. Furthermore, its long term engagement would induce such neuroplastic changes which may allow the more easily gained skills (as well as state of mindfulness as a whole) to feel more habitual in nature and easier to integrate into day to day life. Taken together, I argue that through this theoretical example, this combinational therapy would allow addicts to more easily learn to be aware of their cravings, urges, emotions, and maladaptive cognitive and behavioral patterns, and to subsequently be more easily able to self-regulate over time and on a day to day basis, and possibly to more effectively avoid relapse.

For example, through being able to engage in and hold a mindfully aware state on a consistent basis, one could become more aware of his or her cravings and their related triggers, and subsequently be better able to take preventative measures ("coping ahead," as the skill is described by DBT)**,** such as by avoiding certain people or cues associated with the drug use, or consciously choosing to engage in self-soothing replacement activities such as cooking a meal or taking a relaxing bath when experiencing emotional distress which may trigger cravings (Bowen, Chawla, and Witkiewitz 2014; Dimeff and Linehan 2008). I argue that such a theoretical bottom-up treatment coupled with mindfulness-based psychotherapy would therefore allow for an enhanced therapeutic effect, and would ultimately *help addicts better help themselves*, due to, as mentioned, this combination treatment enabling them to more efficiently gain the skills and a mindful disposition which would help them manage their cravings and to be better able to avoid relapses.

This idea of *helping addicts to better help themselves*, interestingly, is also similar in nature to that which appears to occur through the use of ibogaine coupled with psychotherapy for the treatment of addiction, and accordingly, one person who underwent such treatment described:

> …you could safely say that iboga will give an opiate addict several months to a half a year of freedom from cravings and an expanded awareness. This gives the user a period of time in which to get his/her life together and learn to face things straightforwardly, directly and

> honestly. Iboga will not do the work for you. However, it will help you do your own work. (Brown and Alper 2016)

Therefore, my theoretical example has a similar underlying theme to that of the combination ibogaine treatment in that both consist of bottom-up and top-down therapies being coupled for the treatment of addiction, in a way which enables addicts to be learn how to better self-regulate and which enhances their ability to put a sustained, conscious effort towards recovery. Such an outcome is, in both cases, facilitated through the bottom-up, pharmacological manipulations, which, when coupled with psychotherapies, may allow for an enhanced therapeutic effect through which addicts may be given the opportunity to more easily recover as well as avoid relapses in a more enhanced, self-driven way.

My theoretical example of such a combinational top-down and bottom-up therapy, in reality if to be further investigated, would take much more teasing apart of the various mind-driven (top-down) and neurobiological (bottom-up) processes which are implicated in this obviously highly complicated process, but of which are clearly interdependent in terms of being able to modulate one another, as demonstrated by the other examples in this section. This theoretical example of "pharmacologically induced or enhanced mindfulness" is overall a more novel example of how this area of research in mind-brain intermodulation and interdependence can continued to be pursued, in the hopes of more inclusively and holistically understanding and treating addiction. This area indeed holds promise, as the recent examples of DCS and MDMA-assisted psychotherapy indicate. Overall, this area of research currently remains wide open, and I believe this interactional model can allow us, if it is more integrated into our perspective of addiction, to develop novel and effective treatments for addiction that may be heavily grounded in neurobiology but which also take into account how it works interdependently with the mind. Development of such novel treatments could be accomplished, as demonstrated by the discussed examples as well as my theoretical one, through the application of new knowledge on top-down and bottom-up processes towards the development of combinational therapies, which may allow for the more enhanced or potentiated treatment of addiction.

Mind-Brain Intermodulation as a Means to Balance Dichotomy Between the Brain Disease & Moral Models of Addiction: Implications & Conclusion

Overall, the brain disease model has indeed provided us with a neurobiological basis for understanding addiction more accurately than the moral model had described it to be, and has been deeply beneficial in some ways, such as by providing greater financial support for addiction treatment and research, and an advanced and growing understanding of how neurobiology is implicated in the development and reinstatement of addiction. However, there are many problematic aspects of the brain disease model and these limitations heavily lie in the model's emphasis on reductionistic posited mechanisms in which changes in the brain, due to chronic substance use, lead to addiction in a unidirectional manner. The perspective of the brain disease model, however, does not take into account the *interdependent* and *intermodulatory* relationship that exists between the mind and brain, in which the mind and its elements are able to top-down, physiologically modulate the brain and body, as demonstrated by the abundant literature. Despite this literature, the brain disease model still dominates and is the mainstream perspective (Volkow and Koob 2005; Volkow, Koob, and McLellan 2016).[8]

Despite this, this intermodulatory relationship is indeed beginning to be more acknowledged as well as investigated, in an implicit way, as demonstrated by the examples of DCS and MDMA-assisted psychotherapy. I argue that this research area remains wide open, and thus holds much potential, if to be further explored, in allowing us to develop novel treatments for addiction which treat addiction in combinational top-down and bottom-up-directed ways. I argue that such combinational treatment approaches may allow for enhanced or potentiated treatment, and I further demonstrate such a combinational approach through my theoretical example of pharmacologically-induced mindfulness coupled with mindfulness-based psychotherapies. By better acknowledging and aiming to understand the interdependent mind-brain relationship

8. Despite the current dominance of the brain disease model of addiction and its emphasis on reductionism and a unidirectional relationship between brain and mind, researchers such as Mayer et al. and Pecina & Zubieta discuss a "paradigm shift" in neuroscience which is beginning to occur, where what they call the "bidirectional relationship" between brain/body, and mind dynamics are becoming more acknowledged and integrated into medicine, and beginning to in neuroscience as well, although this perspective is still not the mainstream in addiction neuroscience (Mayer at al. 2014; Peciña and Zubieta 2015).

and integrating it via research, we can move forward to a more accurate and all-inclusive model that can help us create such novel treatments for addiction.

Overall, I argue that the move towards more of an integrational model of the mind holding an intermodulatory relationship with the brain, and acknowledging addiction as being more of a 'gray area' rather than being 'black-or-white,' would allow us to "*balance the dichotomy*" between the moral and brain disease models of addiction, and that this has many positive implications. In particular, when addiction is not seen as being a predominantly physiological disease, and the ability of brain-driven and mind-driven processes in modulating each other is acknowledged, addicts are likely to feel more empowered due to their understanding that the brain is highly malleable and that struggling with addiction is not a fatalistic life-sentence. This enhanced understanding can also help combat any learned helplessness that addicts may succumb to when they are told that they have a brain disease. Furthermore, this could lead to addicts taking more responsibility for their actions, which echoes sentiments of the moral model, as research has indeed demonstrated that they are not completely compulsive in their behavior, such that they demonstrate zero behavioral control.

At the same time, the acknowledgment of how addiction is a consequence of this complex relationship between elements of the mind and the brain on a physiological level allows us to move farther away from the moral model idea that addiction is caused by moral flaws, active choices, and weak self-discipline and willpower; rather, the neurobiological processes involved demonstrate how addiction literally becomes "wired" into the brain, and how addicts simply cannot "get over it" and recover as if it were an easy and straightforward process. However, this move forward would contrast from the brain disease model in that it would also validate how the mind and its elements and processes, such as learning, as well as mindfulness practice and mindfulness-derived skills, can alter neurobiology, and how this can lead to more effective recovery from addiction. In addition, this mind-brain intermodulatory model would further integrate the biopsychosocial model and continue its efforts forward, but take it a different step further and extend it into greater reflection and understanding of addiction in a way which it currently does fully account for. Namely, rather than the biopsychosocial model's acknowledging of biological, psychological, and social factors as all contributing to addiction in various degrees and combinations, in addition to this, a new understanding of mind-brain dynamics would explicitly explain how the brain and elements of mind are able to *intermodulate* one another through their interdependent relationship of top-down and bottom-up mechanisms, and that such knowledge can be applied to novel

treatments for addiction which specifically target this intermodulatory relationship (Alonso 2004; Wade and Halligan 2017).

Overall, as mentioned, such a move forward through acknowledgement and integration of mind-brain intermodulation would help to create a balance between the dichotomy of the moral and disease models of addiction, as mind and brain would be seen as interdependent and able to intermodulate one another (a complex 'gray' area) versus addiction being seeing according to overreductionism as seen by the brain disease model (demonstrating one end of the 'black-and-white' spectrum; the 'white' end, so to speak), or according to the moral model idea that addicts who are unable to recover are "choosing" to stay addicts and are thus morally flawed (representing the other end of the polarity; the 'black' end, for example). Therefore, adoption of this model leads to greater balance of dichotomy between the two models, and may pave an avenue for us to better understand and treat addicts, while taking the benefits that the brain disease model has provided us with while moving forward to be able to better benefit addicts and describe addiction more holistically and in a compassionate and understanding way. It would allow us to move further away from judgment and character-blaming of addicts as shown through the moral model of addiction, while also not reducing addiction to be a fatalistic disease of the brain, helping addicts understand that it is not a deterministic life-sentence, thus empowering addicts and reminding them continuously that healing and recovery is very possible, as the brain is highly dynamic in complex ways which we are only beginning to truly understand.

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The Ethical Defensibility of Memory Dampening Pharmaceuticals Hinges on Context and Regulation

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Biography

Matthew Goss is a medical student at McGovern Medical School in Houston, TX. Having obtained a master's degree in bioethics from Columbia University prior to medical school, Goss strives to strengthen the alliance between bioethics and medicine, particularly in the realms of policy implementation and patient interaction. His current research interests include the ethics surrounding donor organ procurement and allocation, donor pool expansion, and off-label prescription drug utilization.

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The Ethical Defensibility of Memory Dampening Pharmaceuticals Hinges on Context and Regulation

Matthew B. Goss

Abstract

An estimated 8% of Americans suffer from post-traumatic stress disorder (PTSD). With most treatment options falling under the umbrella of cognitive behavioral therapy (CBT), effective pharmaceuticals are lacking. While the physiological underpinning for PTSD symptomology is ambiguous, the disorder's universal root cause is not. If pharmaceuticals could sever emotional connectedness to traumatic memories, PTSD may be avoided. An emerging field of research, memory dampening refers to the use of pharmaceuticals to diminish the deleterious emotional component of unpleasant or traumatic memories. While unregulated memory dampening poses pressing ethical issues, so does the discontinuation of research with promising potential in allowing the suffering to reclaim their lives. Memory dampening research is ethically justified when focused on this therapeutic intention with appropriate regulation.

Keywords

Memory Dampening, Post-Traumatic Stress Disorder, Neuromodulation, Autonomy

Abbreviations

CBT: cognitive behavioral therapy, EM: emergency medicine, PTSD: post-traumatic stress disorder, SSRI: selective serotonin inhibitor, USA: United States

Introduction

Once doubted as legitimate by much of the general public and even many mental health professionals, post-traumatic stress disorder (PTSD) is now recognized for its physiological basis and shocking prevalence, affecting millions of Americans yearly. Fortunately, the suffering are now acknowledged and research efforts into prospective treatments have snowballed. Emanating from said research, cognitive behavioral therapy (CBT), a common type of talk therapy (psychotherapy), has demonstrated efficacy as a safe intervention for both acute and chronic PTSD. Focused on altering the thought patterns disturbing one's life, CBT may actually influence the underlying biology of PTSD (Levy-Gigi et al. 2013). While life-changing for many individuals, nonresponse to various

subsects of CBT, such as prolonged exposure therapy and stress inoculation training, can be as high as 50% (Kar 2011). To supplement psychotherapy, brain chemistry-modifying medications are routinely prescribed, primarily aiming to mitigate the easily triggered fight-or-flight responses characteristic of PTSD. Despite the two selective serotonin inhibitors (SSRIs) paroxetine and sertraline being the only FDA-approved drugs for PTSD treatment (Alexander 2012), 'off label' prescriptions are typical in PTSD recovery processes considering person-dependent symptoms and bodily responses to medications. While the current pharmaceuticals are generally successful in decreasing hyperarousal and negative mood manifestations, symptoms of re-experiencing, emotional numbing, and behavioral avoidance often remain (Ipser and Stein 2012).

In an unrelentless pursuit to aid the millions stuck under the grave cloud of PTSD, researchers are beginning to develop memory dampening pharmaceuticals. Intended to erode the negative emotional impact of emotionally-laden memories, memory dampening has already found a foothold by happenchance. An FDA-approved beta blocker designed to treat tremors, hypertension, and other heart or circulatory conditions, propranolol appears to disrupt memory reconsolidation, thereby dampening fear responses (Brunet et al. 2014; Lonergan et al. 2013; Schwabe et al. 2012). Seemingly an effective drug to block noradrenergic receptors in the amygdala during the reconsolidation process of traumatic memories (a postreactivation blockade of noradrenergic receptors is known to impair reconsolidation of fear memories (Dębiec, Bush, and LeDoux 2011)), propranolol can diminish the lingering effects of trauma and consequentially presents as a potentially efficacious PTSD treatment (Schwabe, Nader, and Pruessner 2013). Nonetheless, research is far from sufficient for FDA approval of propranolol's newfound use. Numerous studies contend memories do not necessarily undergo reconsolidation upon reactivation, unless new information is encoded (Sevenster, Beckers, and Kindt 2012; Parsons and Ressler 2013). Therefore, propranolol's targeting of reconsolidation may lack benefit for the older memories plaguing those with PTSD. A second issue warranting further investigation, strongly encoded fear memories undergo frequent reactivation, possibly resulting in overconsolidation (Pitman and Delahanty 2005). Could such overconsolidation limit propranolol's functionality?

To touch on the most topical memory dampening research, an activity-blocking mutant of the naturally-occurring protein kinase M zeta, or PKMzeta, has been discovered to suppress memory (LeBlancq, McKinney, and Dickson 2016). While trials to date have been exclusively performed in rats, researchers are optimistic for future translation to humans. Due to the debilitating nature of PTSD, research focused on alleviating symptoms, or better yet preventing the disorder's initial development, ought

to continue to ultimately determine pharmaceuticals' capacity to bring about long-lasting symptomatic relief. Foreseeable ethical dilemmas must inform the direction and application of research rather than prevent its continuance.

Discussion

In looking at the ethical implications of memory dampening research and the potential widespread accessibility to these pharmaceuticals, arguments on both sides of the aisle arise. Starting with the negative outlook, perhaps the greatest concern is compromising personal identity. After all, memories constitute our sense of personhood and dictate life perspective. Memory dampening may create an altered humanity with the chance for abuse and reckless use if left unregulated. If we are discouraged from authentically coping with trauma, is the traditional sense of 'growing from experience' lost? In turn, are we demeaning the genuineness of human experience while denying individuals the lives they would have lived without access to memory dampening (Kolber 2011)?

The next argument in opposition to the drugs, some have posited that there is a responsibility to remember, i.e. it is not ours to decide what memories we have/keep. While ethicists contend a distinctive duty to remember mass violence/injustice can reasonably fall upon societies (Walker 2017), the moral imperative is being forced upon individuals in this shoddy case against memory dampening. Such rationale is perplexing for a few reasons. If we ought not interfere with personal memories, then should psychotherapy and hypnotism also be disallowed? If so, what treatment is left for those suffering from PTSD? Must this so-called 'responsibility' to remember carry more weight in our deliberation than life-saving therapeutic interventions facilitating memory alteration?

Third, memory dampening challengers describe the potential for abuse, including the use for illicit purposes. For instance, memory dampening drugs could be dispensed to witnesses of crimes. However, the premise of this argument is flawed. While memory dampening may work in reducing the impact of traumatic memories by preventing overconsolidation, it does not erase memories. While forced administration of these drugs to people having witnessed nefarious activities is a scary concept, memory dampening does not fit into the predicament as the counterargument would wish.

Contrary to the above arguments, well-founded concerns must indeed direct research/dispensary guidelines. Blanket access to memory dampening pharmaceuticals

may aid criminals in their mischievous enterprises by inuring them to the pain of their victims. If numbed to others' agony, the moral compass is profoundly undermined, facilitating greater peace of mind amidst committing crime. On the other end of the spectrum, victims of horrendous acts may feel less obliged to fight back against injustice when emotional connection to memories is lost. That being said, the inherent propensity to help others must run parallel in our discussion. If memory dampening pharmaceuticals were regulated, those with the power to prescribe hold an obligation to recognize its complete ramifications, including the possibility that an individual seeking medication may be less willing to act against the experienced trauma/perpetrator later on. At the core of regulation is the need for documentation. Therefore, the documented need for memory dampening may stand in for the lack of emotional association with a particular memory subsequently. If a crime victim persistently shrugs off the opportunity to hold the aggressor(s) accountable, a medical professional may potentially report the offense on behalf of the victim. Regardless, we must ask ourselves the following question: is it ethically justified to prevent memory dampening for the purpose of ensuring all injustice is dealt with? The answer is a simple no; we must value the victim's long-term health above a potential conviction.

An obvious counterargument to this position would reference a patient's autonomy to decide whether or not to move forward with legal action. If the situation were to arise that a victim of a traumatic crime availed himself/herself of memory dampening drugs but refused to press charges at a later date, should another individual be allowed to circumvent this decision and take matters into his/her own hands? This is certainly a tricky ethical quandary to traverse, as is the potential for courts to delegitimize victim testimony. If a victim proceeded to press charges against a perpetrator following memory dampening, courts may consider his/her testimony null and void. From the legislative standpoint, how can a jury be persuaded by a victim's recall when memory has been purposely dampened? Again, this rationale represents valid apprehensiveness to the developing practice of memory dampening. Be that as it may, nuanced contexts must be evaluated in light of the advantages bestowed.

Before delving into the many benefits of memory dampening, a couple of other rightfully-concerning ethical considerations warrant discussion. Upon memory dampening availability, there is understandable uneasiness with the possibility of forced drug consumption. The tragedy that comes with PTSD is now widely circulated and family members or medical professionals may press someone having experienced an adverse event to utilize memory dampening. However, what if the individual wants to come to grips with the tragedy on his/her own? Perhaps he/she greatly values the

complete emotional ramifications of all memories regardless of prospective disorder development. Bearing in mind this foreseeable predicament, memory dampening must never be obligatory, nor should it be overly advocated. In fact, this defeats the treatment's purpose to honor autonomy and empower individuals to live their lives as they deem fit. Another ethically-contentious incentive to push memory dampening is the tremendous economic burden accompanying PTSD. In 2012, the government spent $3 billion on PTSD treatment for veterans (Zarembo 2014). For a typical patient, the average cost for the first year's treatment alone is $8,300 (Cushman 2012). What if physicians broadcasted this sometimes-crippling economic burden and inadvertently compromised autonomous choice? Once more, such subtleties must be considered and strict regulation/safeguards are mandatory before memory dampening may be ethically justified.

While the muddling ethics of physicians' prescribing practices have been alluded to, what about physician usage of memory dampening? Underrecognized, PTSD is more prevalent in physicians than the general population in the USA (Lazarus 2014). Particularly common amongst emergency medicine (EM) personnel, PTSD is a primary driver of their shortened average career length (4-7 years). To motivate EM physicians to stay in the field despite mentally-onerous trauma, salaries have increased 31% and clinical hours worked have dropped 12% in the past decade (Katz 2017). While more money and time away from work is helpful, the greatest incentive would be PTSD prevention, potentially accomplishable via propranolol administration prior to or immediately following traumatic situations. Sounding great in theory, it is important to delve into implications for patient care. If taken as a preventative measure, it is possible moral judgment may be impaired given reduced emotional connectivity. But what really is the greater danger to quality of care, the potential for PTSD development or an obstruction to moral judgement? How does the ethical landscape change when memory dampening is used prophylactically instead of reactively, particularly in the medical field?

Moving on to the analysis in favor of memory dampening, let's predictably start with autonomy. As our healthcare system progresses towards an autonomy-focused model, we ought to thoroughly question inverse action plans. If effective memory dampening pharmaceuticals were to become available, how can anyone decide for someone else whether or not a traumatic memory is allowed to plague him/her? PTSD can derail and even end lives, as evidenced by the well-established link between PTSD and increased risk of suicidal ideation (Lutwak and Dill 2017). With that in mind, how could an individual not be allowed to write the script of their own destiny, unencumbered by mental anguish? While memory dampening protestors often cite a threat to identity, traumatic

memories and PTSD demonstrably endanger individuality and personality (Burnos and Bargiel-Matusiewicz 2018). If both memory dampening and PTSD can alter identity, the input of autonomy must be the deciding factor in our moral calculus.

While memory alteration stirs up a hornet's nest of controversy in the context of memory dampening, where are the critics of psychotherapy? Often aiming to alter memory and proven to affect brain chemistry (Levy-Gigi et al. 2013), psychotherapy is an almost ubiquitously-accepted practice. We seem to commend memory modulation until pharmaceuticals become involved. In an attempt to justify this perspective, memory dampening opponents might state, "But there are ethically-relevant differences between talking with a patient and administering medicine." Well there are at least 2 distinctions, but they both bolster continued memory dampening research. First, CBT for PTSD usually lasts 8-12 weeks and is often cost prohibitive (many insurance plans neither cover psychotherapy nor behavioral medicine) (Hofmann et al. 2012). Memory dampening drugs would provide an expedited intervention process while being more affordable. Second, memory dampening can address the root cause of PTSD and potentially prevent the disorder's formation while CBT's use is restricted to a reactive fashion. While it may appear an oversight to play down the pertinence of drug side effects, there is simply not much to discuss. Even when compared to the relatively benign side effects of paroxetine and sertraline (Otto et al. 2011), propranolol presents minimal risk. In 1-10% of individuals taking the drug, the mild side effects of sleeping disturbances, transient fatigue, and cold extremities manifest (Steenen et al. 2016).

Not only is talk therapy almost incontestably permissible but FDA-approved drugs for treating PTSD have more serious side effects than propranolol. Barring newfound side effects of propranolol or other drugs to be developed, psychotherapy and memory dampening ought to be on an even playing field in terms of ethical deliberation. However, just as CBT has adapted in recent years (Blease 2015), memory dampening would require a rigorous informed consent process. While this might sound obvious, informed consent merely connotes signing a piece of paper for the average patient. A proper informed consent process ought to ensure with that signature comes a thorough understanding of the full breadth of risks/benefits. Practically-speaking, the informed consent process in psychotherapy is less challenging as an individual may continue to learn about the intervention throughout multiple sessions and can opt-out at any time. The fact that memory dampening pharmaceuticals may work with a single dose adds pressure to the process. Further, there is a potential time-sensitive facet, e.g. initial studies with propranolol demonstrated the need for administration within hours of a trauma (though more recent research points to an ability to exploit the fragility of recalled

memories without a steadfast time constraint - that propranolol could weaken emotional memories if PTSD patients took the drug after conjuring up the details of a painful experience (Brunet et al. 2011)). The gravity of a sufficient informed consent process for memory dampening must not be understated in the argument that it be included as an ethically-justified vehicle of memory modulation.

At the hub of arguments both for and against memory dampening is regulation. Without provisions, memory dampening cannot be permitted. If individuals took the drugs without a comprehension of their effects, which informed consent should counteract, a person's personality may be unknowingly at risk. But what if regulation ensured only those wanting to diminish the emotional strain of memories for medical reasons were candidates? Doesn't this transform the ethical debate? I argue it does. If an individual is seeking to reclaim his/her identity following a traumatic event, the pharmaceuticals must only be seen in a positive light. However, an individual requesting memory dampening in an attempt to alter his/her identity without therapeutic intent must not have access to the drugs. But isn't that contradictory to my sentiment that personal identity is up to the person? Superficially yes, but in the correct context no. Brain chemistry-modifying agents are typically prescription-only. We do not offer these drugs to individuals without a clinical reason. This is not because we are keen on distributive injustice but rather physicians hold an obligation to 'do no harm.' The same goes for memory dampening; it ought to be available to those needing it for its intended function and not those with drug abuse in mind.

While all potential reverberations necessitate rumination if memory dampening were to be determined safe/effective, ethical concerns must not preclude continued research efforts. As millions suffer from PTSD without successful therapies, advancements in our understanding of prospective treatments is critical. Given memory dampening's demonstrated promise to date, we owe it to our military veterans and all those suffering to soldier on. The key caveat for memory dampening's ethical defensibility is regulation. But can't we regulate just like any other drug while encouraging safe application? Put simply, we must not deny individuals the lives they were meant to have before being afflicted by horrible experiences. We must press forward with memory dampening research while acting in accord with the multitude of ethical considerations.

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