The Psychedelic Hypothesis for Treatment of Major Depressive Disorder

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Introduction

The word depression is used colloquially as a loosely defined "sad" state of mind, resulting from the lost of a loved one, a bout of bad luck, or other major life event. This sort of depression is typically short lived as the individual reconciles with what happened and learns to move on. When used clinically, however, depression refers to a much more serious and long-term situation. The Diagnostic and Statistic Manual, 5th edition, lists a variety of depressive disorders, including Major Depressive Disorder (MDD).

This paper will elucidate potential neurobiochemical pathways involved in MDD as well as in tryptamine psychedelic drug action and suggest how the two may interact to create a possible neurobiochemical "reset button" that could be used to help treat humans trapped in their own mind's suffering. I hypothesize that psychedelic drugs will greatly aid in the treatment of MDD by:

1. Interrupting the overactive circuit responsible for depressive thoughts.
2. Decreasing cortical activity acting as a neurobiological 'reset button", allowing for increased input from the extraorganismal universe.
3. Creating a state of high susceptibility to neural plasticity in which the brain can make long-term adjustments supplementing curative treatment.

The first two parts of this paper will serve as descriptions of our modern understanding of depression and psychedelics. The final third of the paper will provide evidence and details on how psychedelic drugs might serve as an effective adjunct treatment for MDD.

Depression

In order to be diagnosed with MDD, the symptoms must not be attributed to exogenous substances or other medical conditions, must cause impairment in social or occupational areas of functioning, and must be distinguished from episodes of grief (i.e. depressed thoughts are not centered around the passing of a loved one or other major life event). In order to meet criteria for MDD, five of the following nine symptoms must be met consistently for a period of two weeks – depressed mood, anhedonia, significant weight change, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of guilt and worthlessness, trouble concentrating, and suicidality (American Psychiatric Association). MDD is further characterized by uncontrollable negative thoughts - typically irrelevant information that gets endlessly dwelled upon and mulled over (Foland-Ross, Hamilton, Joormann, Berman, Jonides, & Gotlib, 2013). This aspect of depression, having one's thoughts "stuck in a rut", will be another main focus of this paper.

The neuroscience of depression

If the mind is solely an interpretation of the physical activity of the brain, then it should be possible to describe a disorder by presenting contrasting anatomical, electrical, and biochemical aspects in a brain suffering from MDD to one that is not. While examining these differences, emphasis will be placed upon areas showing promise as a sight for treatment.

Beginning with structural differences, through the use of neuroimaging technologies, we have found consistent reductions in gray matter in the rostral

anterior cingulate cortex, hippocampus, amygdala, and other subregions of the prefrontal cortex (including the dorsal lateral pre frontal cortex and dorsomedial prefrontal cortex) in humans with MDD. The extent of some of these changes is correlated with severity of depressive symptoms, most notably is reduction in hippocampal volume (Singh & Gotlib, 2014). Through the use of diffusion tensor imaging, researchers have recorded consistent decreased levels of white matter in tracts connecting portions of the pre frontal cortex to subcortical structures (Liao, Huang, Wu, Yang, Kuang, Du, Lui, Yue, Chan, Kemp, & Gong, 2013). Many of these abnormalities have been strongly connected in regulation stress and emotion; however, when seeking a treatment method for depression, directly altering anatomical differences is not a practical route.

Developments in neuroimaging studies have allowed us to observe functional differences in the activity of a depressed brain. Increased activity in the dorsal lateral prefrontal cortex, the medial pre frontal cortex, and the anterior cingulate cortex has been observed in subjects experiencing depression (Walter, Wolf, Spitzer, & Vasic, 2007). These regions have been vastly studied as sights of higher level cognitive processing and executive control. This high level of activity in these pre frontal cortical areas has been associated with the repetitive, negative, irrelevant thoughts that haunt a depressed individual (Holtzheimer & Mayberg, 2011). These evolutionarily younger regions of the cortex provide top down control on many subcortical regions; would getting "stuck" in negative cortical activity result in impaired sub-cortical functioning in regions responsible for emotion? Further neuroimaging studies have illustrated the functional differences these sub-cortical

structures, such as increased amygdala activation following exposure to faces expressing fear when instructed to focus on ones own emotion (Oathes, Patenaude, Schatzberg, & Etkin, 2015). This overall activity of the brain may be altered electrically through deep brain stimulation and electroconvulsive therapy. Both of these techniques have showed promise as effective treatments for individuals with MDD, although their mechanism of action is poorly understood (Mayberg, Lozano, Voon, McNeely, Seminowicz, Hamani, Schwalb, & Kennedy, 2005). While it is extremely informative to observe and record changes in electrical activity, glucose metabolism, and oxygenated blood flow to gain an idea of the brains overall activity, much of this activity is heavily regulated by the flow of endogenous chemicals named neurotransmitters.

Biochemical factors of depression

People have long sought for a chemical explanation for the affliction of depression. During the time of the ancient Greeks, humans believed in the presence of four bodily fluids dubbed *humours*, which included Blood, Phlegm, Yellow Bile, and Black Bile. An excess of black bile was blamed for the disease, thus it was called *melancholia*, translating to "black bile" (Willner, 1985). It was not until 1921, when Otto Loewi discovered the neurotransmitter acetylcholine in a frog's vagus nerve that the search for neurochemical explanations for mental disorders began in full force (Breedlove, Watson, & Rozenweig, 2010 p. 57). In 1952, the chemical reserpine was isolated from the *Rauwolfia serpentia* plant. Reserpine was shown capable of depleting monoamine neurotransmitters (neurotransmitters containing

only one amine group – includes norepinephrine, dopamine, serotonin, and more), and administration of reserpine produced depression-like symptoms (Willner, 1985). This discovery, along with studies showing the efficacy of iproniazid and imipramine in reducing depressive symptoms, led to the development of the monoamine hypothesis of depression. At its most basic, the monoamine hypothesis suggests that depression is a result of decreased levels of monoamine neurotransmitter activity in the brain. Iproniazid is a monoamine oxidase inhibitor (MAOI) used to treat tuberculosis. MAOIs block the activity of the enzymes responsible for breaking down monoamine neurotransmitters, thus causing an increase in the amount of monoamines active in the brain. Imipramine also works to increase the level of available monoamines by blocking reuptake of extracellular serotonin and norepinephrine (Andrews, Bharwani, Lee, Fox, & Thompson, 2015).

As research progressed, the monoamine hypothesis was refined to focus more upon the monoamine 5-hydroxytryptamine (also known as Serotonin or 5-HT). Today, Selective Serotonin Reuptake Inhibitors (SSRIs) are one of the most commonly prescribed medications in the U.S. (Olfson & Marcus, 2009). SSRIs act by blocking the activity of 5-hydroxytryptamine transporter, the protein responsible for transporting extracellular serotonin back into the pre-synaptic cell; thus, SSRIs are capable of increasing the amount of active serotonin available in the synapse, subsequently increasing the amount of serotonergic binding on the post-synaptic cell (Andrews et. al. 2015). While it is common for doctors to explain depression to patients as a deficit in serotonin levels, there is a growing body of research that

contradicts this widely recognized idea (Kirsch, Moore, Scoboria, Nicholls, & Sarah. 2002).

Challenging the serotonin hypothesis

The current serotonin hypothesis suggests that decreased levels of serotonergic activity in the brain cause depressive symptoms. Before analyzing the research that lead to the development of this hypothesis, one must recognize that it is largely untested due to the fact that currently there is no (safe and non intrusive) way to actively measure 5-HT levels in the human brain. Serotonin does not cross the blood brain barrier; therefore we are unable to measure its prevalence in the central nervous system. We are able to measure the levels of serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in urine samples in order to gain an estimate, but this amount may be altered by serotonin activity in any location including the brain. 5-HIAA levels may be measured in the jugular vein responsible for draining blood directly from the brain, therefore is less likely to be contaminated by peripheral 5-HT metabolites, but this method is still unable to show how much 5-HT is active inside and outside of neural membranes. Thus, the low serotonin hypothesis of depression is has not been confirmed by any direct test (Andrews et. al. 2015).

One of the most defining aspects of SSRI treatments is the phenomenon known as "therapeutic delay". SSRIs increase extracellular 5-HT within minutes of the first dose, but it takes multiple weeks before depressive symptoms are reduced. If it was a deficit in serotonergic activity causing depressive symptoms, depressive symptoms should be attenuated at the same rate serotonin is increased.

Furthermore, other drugs capable of blocking serotonin reuptake, such as cocaine and amphetamines, are not effective in treating depression. The inverse of this phenomenon has been observed as well. Serotonin is synthesized from tryptophan, an amino acid the body is incapable of creating, therefore must be obtained through consumption. Reduction of serotonin through dietary tryptophan deletion does not invoke depressive symptoms in non-depressed individuals. Similarly, through a biochemical pathway of amino acid release and uptake, more serotonin may be produced while on a diet high in carbohydrates; yet, high carb diets tend to exacerbate depressive symptoms (Andrews et. al. 2015).

Studies investigating genetic factors at play in depression have helped to shed light on the role of serotonin. While there has not been a significant correlation established between genetic factors and depression, there are significant correlations when environmental factors (i.e. stressful life events) are incorporated in the analysis (Caspi, Sugden, Moffitt, Taylor, Craig, Harrington, McClay, Mill, Martin, Braithwaite, & Poulton, 2003). Caspi *et. al.* have identified a functional polymorphism on the promoter region of the 5-hydroxytryptamine transport gene which causes lower transcriptional efficiency, resulting in lower serotonin reuptake efficiency by their serotonin transport protein (5-HTT) (Caspi et. al. 2003). This deficit in the production of 5-HT transport proteins will yield a similar acute effect to administration of SSRIs – an increased level of extracellular serotonin; however, it is important to keep in mind that developmental effects of this functional polymorphism may have greater ramifications then the acute effects.

As mentioned previously, the presence of the genetic polymorphism does not correlate with the presence of depression until it is paired with an environmental stress. This finding implies that serotonin plays a role in how an individual handles stress (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). In her 1994 book Prozac Nation, Elizabeth Wurtzel largely blames her depression on her inimical childhood until she goes to college and learns that many of her classmates had worse upbringing's then her own. She ponders the reason why so many people experience stress and sadness, but only some move on to develop a depressive disorder (Wurtzel, 2002). Could a deficit in 5-HTT activity, leading to an overall increase in serotonergic activity be responsible for leading so many from stress to depression? This hypothesis is supported by data from jugular venous levels of 5-HIAA, which are significantly elevated in patients with MDD and humans containing the functional polymorphism of the 5-HTT gene. Venous 5-HIAA decreases during chronic anti-depressant treatment in direct relationship with depressive symptoms (Andrews et. al. 2015).

Perhaps the most challenging piece of evidence against the serotonin hypothesis is the recent conclusions by researchers and historians that reserpine-induced depression is by and large a myth. Much of the current reverence for this idea may have been induced by research published in 1954 by the renowned physician Dr. Edward Freis, an expert in the study of hypertension. In his 1954 paper, Dr. Freis details the account of five case studies in which patients with bad to severe levels of hypertension are treated with high doses of reserpine coupled with other anti-hypertensive drugs. Each patient experienced crippling depression at some point

during the treatment, only entering remission by ending reserpine administration (Freis, 1954). Due to Freis' stature as a scientist, coupled with a publication in the *New England Journal of Medicine*, one of the most cited journals of general medicine, this case study report gained national attention. As the media and members outside of the scientific community took hold of reserpine-induced depression, many overlooked the fact that these case studies reveal factors constituting to depression included the passing of a husband, a visit to an elderly mother, a past of anxiety and claustrophobia, and the obvious fact that all were struggling with a potentially life-altering condition of extreme hypertension (Freis, 1954). Outside of these and other case studies of individuals developing depression while taking reserpine for hypertension, there is much skepticism as to whether the reserpine was the true cause of these depressive symptoms. Moreover, placebo controlled studies observing the depressive effects of reserpine have demonstrated the potential for the exact opposite – reserpine was able to induce anti-depressant effects (Baumeister, Hawkins, & Uzelac, 2003). While there is hardly any reputable data supporting reserpine induced depression, it has been long accepted as fact in order to support the current monoamine hypothesis. The support it provides for the pharmaceutical industry in its continuous profits from selling monoamine-hypothesis-based antidepressants most likely aids in the continued spread of this idea.

A new role for serotonin

In April, 2015, Andrews *et. al.* published their paper *Is serotonin an upper or a downer? The evolution of the serotonergic system and its role in depression and the antidepressant response.* Within this paper, Andrews and his colleagues propose that the serotonin system is not primarily used to regulate mood, but rather, this system is integral to the allocation and distribution of energy throughout the body.

As mentioned previously, 5-HT is broken down into 5-HIAA. This process is facilitated by monoamine oxidase A, an enzyme that is only found inside the mitochondria, coincidentally the site of energy conversion within the cell. Other enzymes within the mitochondria are capable of converting serotonin to melatonin, a hormone capable of increasing the rate of electron transport during adenosine triphosphate (ATP) production. Reactive oxygen species are produced as a byproduct of electron transport; fortunately, both serotonin and melatonin exhibit strong antioxidant properties. Aside from modulating ATP production within the mitochondria, serotonin has modulatory effects on aerobic glycolysis, a process in which glucose is converted to ATP in the cytosol.

Outside of cellular glucose metabolism, the serotonergic system exerts energetic control throughout a wide realm of biological systems. The serotonergic system includes seven different protein classes (5-HT_1 through 5-HT_7), including proteins capable of producing excitatory (5-$HT_{2,3,4,6,\ \&\ 7}$) and inhibitory (5-$HT_{1\ \&\ 5}$) effects on post-synaptic cells, thus granting the system bi-lateral control of all of the processes under its regulation. These processes include glucagon and insulin secretion from pancreatic cells, leptin-signaling pathways directing lipid metabolism, and vasoconstriction/dilation in both plants and animals. Serotonin receptors are

commonly co-expressed on cholinergic, glutamatergic, GABAergic, dopaminergic, and motor neurons allowing for modulation of whole brain neuronal activity (Andrews et. al. 2015). To quote Andrews *et. al.* (2015), "…the serotonergic system is unique in that it can simultaneously coordinate the production, storage, mobilization, distribution, and utilization of energy. Arguably, no other biochemical system in the body can do this." (pg. 172).

Once accepting the hypothesis that serotonin is primarily for energetic allocation and regulation, it is easy to see the role it would play in depression. When directing more energy towards the cortical regions responsible for getting stuck in depressed thoughts, energy must be pulled away from other brain regions. For example, decreased energy in the mesolimbic pathway from the ventral tegmental area to the nucleus accumbens may result in anhedonia, a common depressive symptom. Furthermore, energy being spent mulling over negative thoughts would be subtracted from the energy needed to get out of bed and attack the day. Once the body has allocated its energy towards depressive symptoms, chronic administration of SSRIs will disrupt the established energy homeostasis in a manner that severely compromises the serotonergic system; thus, the brain must rely on other compensatory mechanisms to re-establish homeostasis, resulting in an effective treatment following a period of therapeutic delay. This pattern is present in the subject effects experienced by patients treated with SSRIs. Typically, as energy homeostasis is initially disrupted there is an increase in depressive symptoms, followed by a reduction as homeostasis is re-established (Andrews et. al. 2015).

The role of glutamate in MDD

While serotonin is often the primary focus in the treatment of depression, many other endogenous ligands have been implicated in playing a major role. One neurotransmitter that has been gaining much interest in the study of depression is glutamate. Glutamate is a chemical released by pyramidal cells in cortical regions of the brain, typically invoking an excitatory effect at its post-synaptic receptor (i.e. acts to raise the overall charge of the neuron and increase the likelihood of an action potential). Keeping the excitatory role of glutamate in mind, it is easy to hypothesize a role for glutamate in the overactive regions of the frontal cortex observed in the depressed brain. Further support for this hypothesis is seen in the acute antidepressant effects of drugs such as ketamine and lamotrigine, which act to block the activity and release of glutamate respectively (Popoli, Yan, McEwen, & Sanacora, 2012).

Stress, while playing a large factor in the development of depression, has also been shown to elevate pre frontal glutamate activaty through the production and release of stress hormones called glucocorticoids. These stress hormones are regulated through an important negative feedback loop named the Hypothalamic-Pituitary-Adrenal axis (HPA axis). In its simplest form, when the body is exposed to stress, the hypothalamus releases corticotropin releasing hormones. Next, corticotropin-releasing hormones bind to the pituitary gland, resulting in the release of adrenocorticotropic hormone. The adrenocorticotropic hormone proceeds to bind to the adrenal cortex, resulting in the release of cortisol. Cortisol activity in the brain can instigate a wide variety of neural mechanisms, including the

rapid release of glutamate. This mechanism is certainly very important when viewing glutamate as an excitatory neurotransmitter in the executive functioning portion of our brain; when encountering a stressful situation, it would be advantageous to ramp up our cognitive processes to figure out how to best handle the situation. Once the body has responded accordingly however, the cortisol released by the adrenal cortex will bind to both the hypothalamus and the pituitary gland, subsequently decreasing the activity of each. This negative feedback loop is an important "braking system" in the brain that prevents an over abundance of stressful experiences (Popoli et. al. 2012).

A patient suffering from MDD experiences such an increased levels of stress, both in size and duration, runs the risk of overusing their HPA axis to the point where the negative feedback loop "breaks", resulting in a system that is stuck in a stressed state. The effectiveness of an individuals HPA axis can be measured through the dexamethasone suppression test. Dexamethasone is a synthetic corticosteroid capable of inhibiting the hypothalamic and pituitary portions of the HPA axis negative feedback loop, resulting in inhibition of cortisol release from the adrenal cortex. In an individual with a fully functioning negative feedback loop, a nighttime dose of dexamethasone results in low levels of cortisol the following morning. In a 2001 meta-analysis of dexamethasone suppression tests, it was found that 43% of MDD diagnosed patients would have abnormally high morning cortisol levels following a nighttime dose of dexamethasone. When the dexamethasone suppression test was revamped to include nighttime administration of corticotropin-releasing hormone (DEX/CRH test), the new test was capable of

detecting MDD with up to 90% accuracy (Varghese & Brown, 2001). This data provides further evidence that individuals with MDD are literally stuck in their own negative and stressful thoughts.

Psychedelic Drugs

There are many mind-altering (psychoactive) drugs identified and used by humans daily. These drugs typically fall into three classes based on the effect they exert on the body – stimulants (uppers), depressants (downers), and a final group that is much harder to describe. Psychedelic drugs, also referred to as hallucinogens or entheogens, are a class of substances that have been consumed by humans for thousands of years (Strassman, Wojtowicz, Luna, & Frecska, 2008). There are two categories of psychedelics – tryptamines and phenylalkylamines – that are distinguished by their chemical structures. Tryptamines are recognized by the presence of a hexagonal benzene ring fused to a pentagonal pyrrole ring, a structure referred to as an indole ring (tryptamines are also referred to as indoleamines). This indole ring can be seen in many endogenous chemicals, including the neurotransmitter serotonin and its precursor tryptophan. A phenethylamine core, a structure that also contains a hexagonal benzene ring, along with side chain of two carbons and nitrogen, distinguishes the phenylalkylamine psychedelics (Halberstadt, 2015). This phenethylamine is also seen in stimulants such as methamphetamine, and many phenylalkylamine psychedelics can exhibit stimulant-like qualities, such as MDMA (Strassman *et. al.* 2008). While phenylalkylamine psychedelics are capable of creating similar experiences to tryptamine psychedelics,

this paper has largely focused on the mechanism of action for tryptamine psychedelics.

The neuroscience of tryptamine psychedelics

Indoleamine psychedelics include the drugs psilocybin (4-phosphoryloxy-dimethyltryptamine), the active ingredient in "magic mushrooms"; LSD ((+)-lysergic acid diethylamide), commonly called acid; DMT (N,N-dimethyltryptamine), the active ingredient in ayahuasca; and many others (Strassman *et. al.* 2008). While containing structural differences outside of the core indole ring, all tryptamine psychedelics are capable of developing cross-tolerance (with the exclusion being DMT, a drug has never been shown to produce tolerance[1]); this fact, coupled with the production of extremely similar subjective effects, has led researchers to believe that they all utilize a similar mechanism of action. All tryptamines exhibit a non-selective high affinity binding for the 5-hydroxytryptamine 2A (5-HT_{2A}) receptor. 5-HT_{2a} is a metabotropic receptor coupled to multiple G proteins and second messenger systems. The canonical pathway of 5-HT_{2A} binding in the post-synaptic cell is the activation of the G_q protein, which in turn activates phospholipase Cβ (PLCβ) signaling. PLCβ initiates the hydrolysis of membrane phospholipids into inositol triphosphate and diaglycerol, subsequently mobilizing intracellular calcium^{++}, ultimately leading to an excitatory effect in the neuron. While this is the

[1] Development of tolerance is most likely a result of 5-HT_{2A} down-regulation. Repeated administration of psychedelics results in significantly lowered density of 5-HT_{2A} receptors in specific brain regions. *In vitro* experiments show that LSD exposure desensitizes 5-HT_{2A} receptors, whereas DMT desensitizes 5-HT_{2c} receptors; thus, there is a lack of tolerance to 5-HT_{2A} mediated effects (Halberstadt, 2015).

standard pathway observed following 5-HT_{2A} activation, extensive animal research has suggested that this pathway alone is not sufficient to produce psychedelic behavioral effects (Halberstadt, 2015). Furthermore, other 5-HT_{2A} agonists, such as lisuride and ergotamine, fail to elicit the psychedelic experience in humans (González-Maeso, Weisstaub, Zhou, Chan, Ivic, Ang, Lira, Bradley-Moore, Ge, Zhou, Sealfon & Gingrich, 2007), while 5-HT_{2A} receptor antagonist ketanserin will ameliorate nearly all psychedelic effects (Halberstadt, 2015).

Animal models of psychedelic research

Rodent testing has proved to be extremely valuable to further investigate the neurobiochemical pathways utilized by psychedelic drugs. In order to find a specific behavioral response to psychedelic drugs in a rodent model, González-Maeso *et. al.* (2007) compared tryptamine psychedelics to other non-psychedelic 5-HT_{2A} agonists. Administration of psychedelics resulted in changes in exploratory (neophobia) and grooming behavior, interruption of operant responding, a unique head twitch and ear scratch response, and hypothermia. All of these responses were observed following administration of non-psychedelic 2A agonists, excluding the head twitch response (HTR) and ear scratch response (ESR); however, only the HTR was reliably and robustly seen in response to every psychedelic tested, thus, the HTR has been the selected behavior alluding to a rodent psychedelic experience. HTR was absent in 5-HT_{2A} knockout mice, demonstrating the critical role this receptor plays in psychedelic activity; HTR was only diminished in G_q knockout

mice, implying this secondary pathway is not sufficient in generating the psychedelic experience (González-Maeso *et. al.,* 2007).

Comparing rodent models of psychedelic drugs and non-psychedelic 5-HT_{2A} agonists has revealed specific biochemical, as well as behavioral, markers for psychedelic activity. Following activation of the 2A receptor, there are multiple series of downstream pathways occurring in the cells capable of inducing the activity of dormant genes. Quantitatively observing the genes that are actively expressed at any given time is done by measuring the transcriptome, the total amount of RNA molecules within a group of cells. Unlike a genome, which remains fixed throughout and organism's lifetime, a transcriptome will vary based upon external cues and conditions. Studies done on the rodent somatosensory cortex transcriptome have shown induction *c-fos* genes following 5-HT_{2A} activation, with induction of both *c-fos* and *egr-2* genes only following psychedelic 5-HT_{2A} activation (Gonzalez-Maeso, Yuen, Ebersole, Wurmbach, Lira, Mingming, Weisstaub, Hen, Gingrich, & Sealfon, 2003). The induction of these genes are correlated with the behavioral ESR and HTR – both the ESR and *c-fos* activation is observed following general 5-HT_{2A} activation, whereas the HTR and *egr-2* activation are only seen following administration of psychedelic 5-HT_{2A} agonists, thus allowing scientists to use these responses as reliable markers indicating psychedelic activity in rodents. One must note that although induction of *egr-2* genes is specific to psychedelic activity, this does not imply that it is responsible for psychedelic activity. This is confirmed administering LSD in the presence of tetrodotoxin, a neurotoxin that blocks voltage gated sodium channels and inhibits action potentials. Even in the

absence of neuronal firing, there was still induction of *egr-2* RNA in neurons with 5-HT_{2A} receptor signaling capacity (González-Maeso *et. al*., 2007).

Rodent models have allowed scientists to observe the direct effect of psychedelic drugs on specific individual neurons. Microiontophoresis is the process in which the effect of ionized substances passing through a single nerve cell are recorded by an oscilloscope, providing real time data on the neurons rate of firing. When utilized to measure the firing of neurons located in the dorsal raphe nucleus (DRN), the site of serotonergic origins in the brain, it was found that venous administration of LSD consistently inhibited neuronal firing (Haigler & Aghajanian, 1973). This response implies that the 5-HT_{2A} stimulation of cortical areas allows for top-down control over the DRN, or produces a chemical negative feedback loop for discontinuing DRN activity.

The role of glutamate in psychedelic mechanism of action

While many are quick to point to serotonin as responsible for the subjective psychedelic experience due to the drug's high affinity for the 5-HT_{2A} receptor, the aforementioned research alludes to this not being the only system at play. Recent studies have illuminated a potential mechanism of action for psychedelics that involve both the activity of serotonergic and glutamatergic receptors.

Microdialysis studies have shown a significant late wave increase in extracellular glutamate in the pre frontal cortex succeeding psychedelic administration, resulting in a late and prolonged excitatory post-synaptic current (EPSC). This EPSC can be suppressed by 5-HT_{2a} antagonism, suggesting that the

serotonin protein is involved in origin of this pathway. When introducing the glucan molecule Dextran to the system, thus enhancing the viscosity of rodent cortical extracellular matrix, the EPSC is inhibited while 5-HT_{2A} mediated signaling is left unaffected (Lambe & Aghajanian, 2006). The large impact generated by Dextran has led researchers to postulate whether EPSC is the result of a phenomenon known as glutamate spillover.

Essentially, glutamate spillover occurs when extracellular glutamate drifts out of the synapse and binds to high affinity NMDA receptors located in the synapses of neighboring dentritic spines (Diamond, 2002). A neuron communicates information through electrical signaling based upon its charge at the axon hillock. This charge is affected by alterations in the cells overall chemical density of ions in relation to the extracellular matrix. Alterations in neural charge are largely the result of ionic passageway through the membrane, capable of prescribing both directional and ionic specificity. NMDA receptors - when properly activated by depolarization of the post-synaptic neuron[2] and binding of glutamate plus glycine or d-serine - are ionotropic channels that allow the displacement of intracellular potassium cations by non-selective extracellular cations; these extracellular ions can have twice the positive charge of potassium, causing a rapid raise in neural charge and likelihood of depolarization. Because the NMDA receptor requires a post-synaptic action potential in order to activate, this event only happens when sufficient glutamate is already stimulating excitatory post-synaptic AMPA receptors

[2] When at rest, there is a magnesium cation bound to the NMDA receptor, preventing glutamate from opening the channel. The channel can only open if an action potential raises the membrane charge positive enough to displace the magnesium cation coupled with simultaneous bonding of glutamate (Breedlove *et. al.* 2010).

(Breedlove *et. al.* 2010, 536-538). An influx of glutamate large enough to cause depolarization via AMPA receptor activation is more likely to overflow towards neighboring synapses where high affinity NMDA receptors will be ready to activate. This compounding effect results in a summation of action potentials, proliferating the size and speed an important signal.

The significance and impact of this mechanism is further highlighted by the ubiquity of the NMDA receptor, particularly on dendritic spines with reduced glial cover (Diamond, 2002). By increasing the viscosity of the extracellular matrix, glutamate's ability to drift away to neighboring synapses is greatly reduced; therefore, the evidence that Dextran can attenuate the psychedelic EPSC implies the role of glutamate spillover.

Aside from increasing extracellular glutamate, psychedelic drugs appear to rely on metabotropic glutamate receptor 2 (mGlu2) for their mechanism of action. This was demonstrated in a 2011 experiment in which José Moreno and colleagues administered psychedelic drugs (LSD and the phenylalkylamine 2,5-Dimethoxy-4-iodoamphetamine (DOI)) to wildtype and mGlu2-knock out mice. The HTR was used as a dependent measure. Typical psychedelic induced HTR was observed in wildtype mice, but not in the mGlu2-knock out variety. Ketanserin binding displacement curves confirmed the presence of a fully functioning 5-HT_{2A} receptor; thus, this change in behavior must have been mediated by the mGlu2 receptor (Moreno, Hollowaya, Albizub, Sealfon, & González-Maeso, 2011).

The modulatory relationship between mGlu2 and 5-HT_{2A} receptors has been documented in a number of other experiments. Administering LY379268, mGlu2

receptor agonist, will induce specific locomotor and vertical activities in wildtype mice, a response that is not observed in 5-HT_{2A}-knock out mice. With focus placed upon psychedelic specific response, co-administration of an mGlu2 receptor agonist and psychedelic drugs has been shown to modulate the induction of *egr-1*, whereas mGlu2 agonism has no effect on induction of *c-fos*. MGlu2 receptor agonists are capable of suppressing the HTR generated by administration of LSD and DOI; conversely, administration of DOI will decrease the affinity for three mGlu2 receptor agonists (González-Maeso, Ang, Yuen, Chan, Weisstaub, López-Giménez, Zhou, Okawa, Callado, Milligan, Gingrich, Filizola, Meana, Sealfon, 2008).

Instead of a linear or temporal pathway of synaptic transmission from 5-HT_{2A} activation to the alteration of glutamate function, it is likely that these metabotropic receptors combine to form a heterocomplex receptor. By using fluorescent in situ hybridization, scientists have been able to document heavily overlapping distribution of 5-HT_{2A} and mGlu2 mRNA, with co-localization observed in cortical primary tissues. Studies on the molecular chimaera of mGlu2 demonstrated that the segment containing transmembrane protein helices 4 and 5 are both necessary and sufficient for the formation of a complex with 5-HT_{2A}, providing the structural bridge for transmembrane communication between proteins (González-Maeso *et. al*, 2008). The presence of 5-HT_{2A}- mGlu2 receptor complex provides explanation for DOI activity at the 5-HT_{2A} binding site yielding allosteric inhibition at the mGlu2 binding site.

Drugs with an affinity for 5-HT_{2A} receptors may bind to the receptor complex with functional selectivity, creating a wide-breadth of outcomes dependent upon

various second messenger systems mediated by 5-HT_{2A} and mGlu2. A 5-HT_{2A}-mGlu2 receptor complex could act as possible site of action for psychedelic drugs, with activity stemming from the glutamatergic portion of the complex responsible for distinguishing psychedelic 5-HT_{2A} agonists from non-psychedelic 5-HT_{2A} agonists.

Neuroimaging studies on psychedelic activity

Stepping away from the microscopic lens that views biochemical action of psychedelics, brain-imaging studies can be used to show how these drugs act on a macro level and effect whole-brain activity.

In 1997, Franz Vollenweider and colleagues used the radioactive isotope [F-18]-fluorodeoxyglucose, a sugar molecule that has a half-life of around 110 minutes, to measure psychedelic drug activity via positron emission tomography. Due to the duration of this molecules half-life, along with the time necessary for the sugar to build-up in the brain, this study did not provide insight into the instant activity of psilocybin, but rather, a time-delayed response to the drug. The results from this experiment showed a significant increase of activity in the frontomedial cortex, frontal lateral cortex, anterior cingulate cortex, and tempormedial cortex. By using of a radioactive sugar molecule, the researchers were able to conclude the presence of a global increase in cerebral metabolic rate of glucose during psilocybin exposure (Vollenweider, Leenders, Scharfetter, Maguire, Stadelmann, & Angst, 1997).

Contradictory to PET scan studies of psilocybin, functional magnetic resonance imaging (fMRI) studies performed in 2012 by Robin Carhart-Harris and

colleagues found decrease in cortical activity, particularly in the medial pre frontal and posterior cingulate cortices. Unlike PET scans, fMRIs are capable of actively measuring the flow of oxygenated blood throughout the brain, thus, fMRI is capable of providing real time information on neural activity during psilocybin exposure (Carhart-Harris, Erritzoe, Williams, Stone, Reed, Colasanti, Tyacke, Leech, Malizia, Murphy, Hobden, Evans, Feilding, Wise, & Nutt, 2012). When taken together, these two studies may describe a time-dependent pathway for psychedelic action in which cortical activity is initially decreased and later increased. This pattern is reflected in allosteric inhibition of mGlu2 by psychedelic drugs, followed by the late wave increase of glutamate and EPSCs.

The psychedelic hypothesis for treatment of major depressive disorder

Interrupting the overactive circuit responsible for depressive thoughts

As outlined in the depression portion of the paper, MDD can be characterized by the experience of being trapped in one's own negative thoughts, an experience reflected by increased activity in cortical regions of the brain. While largely mediated by the energy-allocation properties of the serotonergic system, much of this increased activity is facilitated by the excitatory role of glutamate. SSRIs provide effective treatment by disrupting the energy homeostasis established by the serotonergic system through tonic adjustment of extracellular 5-HT. Following a period of therapeutic delay, the brain can use compensatory mechanisms to reestablish serotonergic homeostasis, resulting in a reduction of cortical activity and subsequent attenuation of depressive symptoms.

Rather then taking this indirect path to free a human from the grip of MDD, psychedelics are capable of disrupting the negative thought loop in a phasic and immediate manner. As demonstrated by fMRI studies, immediate administration significantly decreases activity of brain regions that are typically overactive in patients with MDD. This most likely occurs through secondary pathways mediated by both portions of the 5-HT_{2A} – mGlu2 receptor complex. Activation of the serotonin pathway allows for the re-allocation of energy, aiding in the re-distribution of energy from cortical regions to other parts of the body. The mGlu2 mediated pathway, whether stimulated directly or through functional selectivity at the 5-HT_{2A}, reduces glutamatergic binding and successive excitatory post-synaptic potentials throughout the cortex.

A neurobiological 'reset button' and the extraorganismal universe

The interruption of depressed thoughts shares the same first step of the neurobiological reset button. By invigorating the serotonergic system and downregulating the glutamatergic system, psychedelic drugs effectively turn down the areas of the brain responsible for higher order cognition in mammals. While these regions of the frontal cortex are functioning less, the human is able to escape their inner thoughts. It is possible that the serotonergic system works to place the energy previously used to dwell inside one's head, to instead increase connectivity to the rest of the world, or the 'extraorganismal universe'. This phenomenon has been famously described by English writer Aldous Huxley in his 1956 essay, *The Doors of Perceptions*, in which Huxley documents his experience with the

phenylalkylamine psychedelic, mescaline. Huxley wrote of a mechanism he termed "the reducing valve", the belief that the frontal cortex and surrounding regions are largely responsible for filtering out irrelevant outside information, thereby reducing the intake of stimulus from the extraorganismal universe. By ingesting mescaline, Huxley believed he turned off the reducing valve, thus allowing him to perceive much more, exposing him to thoughts and ideas that were previously over-ridden by the frontal cortex (Huxley, 1956). This lack of a connection to the extraorganismal universe can be seen in MDD patients experiencing anhedonia, as well as patients who are to preoccupied with their own thoughts to focus on anything. Using the psychedelics as a reset button, an individual is able to escape from their own negative loop, and re-connect with the universe around them.

A state of high susceptibility to neural plasticity

The final step of the psychedelic treatment is the latter portion of the mechanism. After the initial shut down of activity observed at the start of the neurobiochemical reset button, through a pathway that is not well understood, psychedelics then cause an increase of glutamate release, glutamate spillover, and NMDA receptor activity in cortical areas. It is the activation of NMDA receptors, proteins that have been extensively studied for their role in learning and memory encoding, that induces brains shift to a state of high susceptibility towards neural plasticity.

The NMDA receptor, named after the synthetic agonist N-methyl-D-aspartate, plays a very important role in modulating the strength of a synapse[3]. A key element of the NMDA receptor is its ligand/voltage-gated activation, requiring both the binding of chemical ligands and a depolarization sufficient for removal of the allosteric magnesium. When activated, it may open an ion channel allowing for the flow of non-selective cations, subsequently altering the overall charge of the neuron and affecting the probability of depolarization. Calcium is a cation that commonly transports into the cell through NMDA receptors; once inside, calcium can activate an array of protein kinases including calcium/calmodulin-dependent protein kinase II, in turn producing more AMPA receptors in the post-synaptic membrane. Influx of calcium also works in the cell by modifying membrane bound AMPA receptors, raising their affinity for binding (Breedlove *et. al.* 2010). When totaled, this amendment to the post-synaptic membrane results in long-term modifications to the synaptic strength of the neuron. If manifesting the mind as the physical brain, one would expect to make physical long-term alterations to the brain as part of an effective long-term treatment for depression.

Aside from NMDA receptor mediated synaptic plasticity, psychedelics appear to induce an increased level of plasticity through up-regulating the rate of neurogenesis, particularly in the dentate gyrus of the hippocampus (Catlow, Song, Paredes, Kirstein, & Sanchez-Ramos, 2013). It is suspected that activation of NMDA and AMPA receptors on pyramidal neurons stimulates the expression of Brain

[3] Strength of a synapse can be described through the equation:
Synaptic Strength = Pre-synaptic release probability • post-synaptic response to release of a single neurotransmitter • number of release sites.

Derived Neurotrophic Factor (BDNF) (Vollenweider & Kometer, 2010), a substance used as nourishment for neurons, aiding in the genesis, differentiation, and preventing apoptosis (Breedlove *et. al.*, 2010). A similar increase in BDNF is closely correlated with the efficacy of classic antidepressant treatment, alluding to the role neuronal reproduction, development, and health has in treating MDD (Malberg, Eisch, Nestle, & Duman, 2000). There is a direct relationship between psilocybin-modulated neurogenesis in the rodent dentate gyrus, ability to remember previously conditioned rules, and the speed to learn a new set of conditioned rules (Catlow, *et. al.*, 2013). Translated to a human paradigm, this data could imply the increased ability to remember traumatizing events in order to accept and reconcile, as well as the increased ability to reconcile with and re-learn a new attitude for reflecting upon these events.

Anthropological observation of psychedelic therapy

Humans have been ingesting psychedelic drugs for thousands of years for therapeutic reasons. It is becoming increasingly important to recognize the power of these substances as mankind drives themselves further away from their evolutionary roots through technology, medication, and processed food. The ability to use psychedelic drugs as a reset button has already been recognized by the modern media. Former CNN correspondent Amber Lyon developed post-traumatic stress and subsequent depression from her journalistic investigations into some of the more dangerous cultures in our world. It was not until comedian Joe Rogan introduced Lyon to the power of psychedelic drugs that Lyon was finally able to heal

her mental state. The impact psychedelics left upon her life inspired Lyon to develop the website reset.me. This online community states their objectives as…

> "1. To produce and aggregate journalism covering the positive and negative attributes of psychedelics and natural therapies.
>
> 2. To create a community that fosters open and honest discussion of psychedelics and natural medicines.
>
> 3. To provide ample safety news and expert advice in order to promote harm reduction." (Reset.me: About, 2015).

Users all over the world use reset.me to share their stories of psychological healing facilitated by psychedelic drugs.

The subjective experience of the psychedelic reset button has been measured scientifically as well. In a 2006 experiment at John Hopkins University, Roland Griffiths and colleagues provided psilocybin for thirty-six volunteers, recording the details of the experience and the effect upon mood immediately after through a period of 14 month. Volunteers consistently rated the experience as highly mystical and the majority described the psychedelic experience among the top five personally meaningful experience of a lifetime (Griffiths, Richards, McCann, & Jesse, 2006). The mystical part of the experience is most likely attributable to the down regulation of glutamate and cortical activity at the start of the psychedelic experience. The less energy being spent thinking inside one's head, the more energy available to absorb more of the extraorganismal universe, including the signals that lead so many to devoutly following religion. The latter portion of the psychedelic experience, when glutamatergic activity ramps back up, is responsible for the long

lasting impact caused by psychedelics. In the aforementioned study at John Hopkins, the vast majority of subjects who ingested psilocybin gained a positive behavior change for at least fourteen months following the experiment. Another important takeaway from Dr. Griffith's study is that not a single subject had a negative change following psychedelic treatment (Griffiths, *et. al.,* 2006).

Conclusion and future direction

Psychedelic drugs have played an important role in history since the dawn of human existence. As some of the least physiologically harmful substances in the pharmacologists tool-belt, it is surprising to see them listed as Schedule-1 substances by the U.S. government (thereby stating a high potential for a abuse and zero medical value). Modern techniques for studying the neuroscience of psychedelics has revealed potential pathways in which these drugs may serve as excellent forms of medication for patients suffering from an illness of the mind. By acting on the 5-HT_{2A} – mGlu2 receptor complex, psychedelics may serve as a neurobiochemical reset button for the human mind, aiding in the curative treatment of depression. Psychedelic medicine should only be consumed at specially designed clinics where doctors and psychiatrists are available as guides through the experience. Talk therapy is essential to an effective psychedelic treatment; the drugs are only to serve as catalyst for change, not as the full treatment. While the specific pathways involved in the psychedelic mechanism of action, and the true efficacy of treating depression still require large amounts of research before they can be understood, the available literature shows a lot of promise for the future.

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