Psychophysical properties of midbrain dopamine neurons and implications for the antidepressant effect of deep brain stimulation

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Abstract

Psychophysical properties of midbrain dopamine neurons and implications for the antidepressant effect of deep brain stimulation

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The discovery that animals engage in intracranial self-stimulation (ICSS) provided a direct way to study the neural networks that direct motivation. In ICSS experiments, animals are implanted with electrodes terminating in reward-implicated substrates. The development of optogenetics advanced the study of the brain reward system by confirming a causal role of midbrain dopamine firing in reward seeking. Since then, the correspondence of optical stimulation parameters to the neural signal of dopamine neurons causing operant behavior has been studied. In parallel, attention was paid to the application of deep brain stimulation on refractory mental illness, including depression. This thesis describes two psychophysical experiments that use optogenetic ICSS of midbrain dopamine neurons. The first experiment shows that, for a substantial range of powers (~12.6 mW - 31.6 mW), the trade-off between power and pulse duration undergoes temporal summation, aligning with Bloch's Law. Pulse duration can be used to control the volume of activated opsin-expressing dopamine neurons. The second experiment provides a psychophysical measurement of firing fidelity of midbrain dopamine neurons. This study supports that pulse frequencies higher than 40 Hz are ineffective or counter-productive at improving the vigor of operant behavior. Together these experiments highlight the benefit of using measurable outcomes (e.g., operant response) as the basis for making inferences about the effectiveness of optical stimulation. These experiments contribute to the hypothesis that, similarly to electrical ICSS, the variable determining the intensity of reward seeking is the induced aggregate firing rate. Such insights can aid the understanding of how deep brain stimulation functions to alleviate depression. It is suggested here that the antidepressant effects of deep brain stimulation of the medial forebrain bundle (MFB) may involve activation of non-dopaminergic neural pathways. The reward platform hypothesis is presented, which suggests that MFB stimulation may cause antidepressant effects by facilitating reward seeking. This hypothesis is developed in relation to motivation parameters that promote involvement with response-contingent rewarding activities. Ways to test this hypothesis in both pre-clinical and clinical models are proposed. This thesis provides practical guidelines for optogenetic experiment designs, and it outlines original, theory-driven hypotheses about the structural and functional underpinnings of antidepressant deep brain stimulation.

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Chapter 3. The convergence model of brain reward circuitry: implications for relief of treatment-resistant depression by deep-brain stimulation of the medial forebrain bundle

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Discussion

GENERAL INTRODUCTION

Study of Motivation: The Role of Brain Stimulation Reward

There are several methods to study motivation. The earliest studies relied on natural rewards; most notably, palatable food and water (Thorndike, 1898; Warner, 1928). Later studies integrated a wider range of natural rewards, including social interaction, physical activity, sex, and interaction with the environment (Simpson & Balsam, 2015; Stewart & Hurwitz, 1958). These earlier studies were founded on the theory that reward seeking satisfies physiological states and preserves homeostasis (Hull, 1943). Some of these states, such as the ones dependent on the rewarding effects of drugs of abuse or the aversive effects of substance dependence, can be induced by artificial rewards (Volkow, Michaelides, & Baler, 2019). The study of motivation through means of drugs of abuse continues to be a fundamental paradigm in the field (Volkow, 2010).

That a wide range of stimuli can be rewarding brings into question the very nature of rewards. To provide a sufficiently inclusive definition, one must cast a wide net. In such an attempt, Schultz (2015) states that “any stimulus, object, event, activity, or situation that has the potential to make us approach and consume it is by definition a reward”. This definition emphasizes the orientation of the agent towards a stimulus/situation (i.e., appetitive and consummatory behaviours) and downplays the countless, qualitative differences among the many stimuli and situations that can serve as rewards. All rewards are not equally useful for the experimental study of motivation. Studying reward seeking using stimuli whose salience and importance varies based on

the dynamic interplay of natural or artificial physiological states has certain limitations. Physiological states can influence the interest to pursue a reward as well as the vigor of reward seeking. For example, seeking shelter in a sudden downpour of rain may take precedence over the engagement in other activities, while the drive to seek shelter immediately diminishes once one is found. Similarly, the drive for consuming drugs of abuse will depend on several factors including the physiological effects of the drugs, sensitization and tolerance, and performance impeding effects of higher drug doses (Sanger & Blackman, 1989; Krasnegor, 1978).

A potent alternative paradigm for studying reward seeking that is unaffected by satiety or performance inhibiting effects arose from three independent discoveries in the 1950s. Robert Heath (1977, 1996) investigated the clinical effects of deep brain stimulation of the septum in patients with severe psychotic disorders. Electrical stimulation of the septum produced euphoric states in patients with flat affect and induced social reward seeking in patients with severe asociality (Heath, 1996). His team theorised that stimulation of the reward system could improve anhedonia and restore overall functioning in these patients (Heath, 1977). Delgado, Roberts, and Miller (1954) investigated the motivating effects of aversive brain stimulation. They demonstrated that aversive electrical stimulation of several brain sites of cats was sufficient to motivate trial-and-error learning and to dissuade hungry cats from approaching food that was paired with the aversive brain stimulation.

Perhaps most influential is the discovery by James Olds and Peter Milner (1954) that a rat appeared interested in receiving externally applied intracranial stimulation (Olds & Milner, 1954). To verify whether this rat sought out the stimulation deliberately, the research group allowed the rat to self-stimulate, which it did vigorously. Although Olds and Milner were investigating the effect of brain stimulation on the reticular formation, they discovered that the electrode of the self-stimulating rat had terminated at the septal area. The operant phenomenon was termed intracranial self-stimulation (ICSS), the rewarding stimulation was named brain stimulation reward (BSR), and the seminal study by Olds and Milner substantiated the concept of a brain system that directs motivation. This discovery led to the use of ICSS to study motivation.

As at least 20 areas in the brain support ICSS (Wise, 1996), the reward system is widely distributed, and it may be composed of redundant neural circuits. A few case studies support that humans can also engage in ICSS (Bishop, Elder, & Heath, 1963; Heath, 1963). For two years, a patient who could freely administer stimulation of the right ventral posterolateral nucleus of the thalamus to manage medication-resistant chronic pain lost interest in her family, forwent most social interaction, and neglected basic hygiene to trigger ICSS, until she required hospitalization (Portenoy et al., 1986). This report parallels animal experiments describing the strong drive with which rewarding brain stimulation captivates behaviour. In animals, BSR was shown to induce vigorous and stable behavior that is unaffected by need-state satisfaction. For example, with intense available stimulation, thirsty or hungry animals will forgo water or food respectively to maintain the opportunity to trigger ICSS (Morgan & Mogenson, 1966;

Routtenberg & Lindy, 1965; Spies, 1965). Idle rats under the influence of subanesthetic doses of barbiturates or curare will self-trigger stimulation to the point of neutralizing the quasi-paralytic effects of these drugs (Gallistel, Shizgal, & Yeomans, 1981). An advantage of BSR's over other rewards is its high spatial and temporal resolution, affording researchers higher precision of experimental control of reward delivery and intensity than they can attain otherwise.

Two research questions have been pursued extensively to explore the mechanism underlying ICSS. First, how electrical stimulation is translated into the neural signal that determines the intensity of reward seeking has been studied. This entails documenting how the physical parameters of the electrical stimulation map onto the neural signal that determines operant response. This is analogous to studies on how the quantity of an available reward (e.g., drug dosing, amount of food/water) influences behavioral outcomes. Second, the identity of the neurons responsible for ICSS has been investigated, despite challenges posed by the non-specificity of electrical stimulation.

In the functional front, certain key findings have refined the quantitative methodology and behavioural paradigms used to ascertain the effect of electrical brain stimulation on reward seeking. In the structural front, three successive models describing the reward system architecture have been proposed. Newer methodologies that allow for precise neuromodulation and neuroanatomy can be used to continue refining the mapping of the brain reward system.

Function of the Brain Reward System

The validation of the curve-shift paradigm in BSR experiments provided an adaptable way to evaluate how experimental conditions impact the pursuit for BSR (Campbell, Evans & Gallistel, 1985; Edmonds & Gallistel, 1974). In this paradigm, operant performance is measured, while a physical parameter of the stimulation (e.g., pulse frequency, pulse duration, current) is systematically increased or decreased (in ascending or descending “sweeps” respectively) as the remaining stimulation parameters are held constant. The psychophysical method is used to establish quantitative relations between the dependent variable (i.e., a measure of reward seeking) and the manipulated stimulation parameter.

It has been demonstrated using the curve-shift methodology that reward seeking scales in a sigmoidal fashion (Carlezon & Chartoff, 2007). As the value of a given stimulation parameter increases, measurement of reward seeking complies to a curve that has a lower plateau, whereby the subject rarely performs the operant requirement, and grows initially faster and subsequently slower towards an upper plateau that represents maximal operant performance. Measurement of such operant curves serves as the backdrop for distinguishing how experimental manipulations (e.g., trading off electrical stimulation parameters against one another, evaluating the effects of drugs on ICSS) influence the behavioral effectiveness of the reward from the ability of the subject to perform the operant response (Carlezon & Chartoff, 2007). Practically, manipulations

that effect a horizontal shift in operant curves provide evidence for changes in reward effectiveness; right-ward shifts suggest a reduction in the behavioural effectiveness of the stimulation, while left-ward shifts suggest an increase in its behavioural effectiveness (Trujillo-Pisanty et al., 2020). In contrast, vertical shifts in operant curves reflect changes in the motoric capacity of the subject to perform the operant behavior (Trujillo-Pisanty et al., 2020).

The curve shift method can be combined with trade-off designs, whereby two stimulation parameters are systematically traded off against one another, while operant behavior is measured. Trade-off experiments can establish quantitative properties between the processes that underlie brain stimulation. The counter model of spatiotemporal integration describes how electrical stimulation is translated into the neural signal that determines the intensity of reward seeking. A precondition to outlining the counter model is the notion that different stimulation parameters (e.g., current, pulse frequency, pulse duration) have different effects on the excitation of neurons surrounding the implanted electrode tip. For example, pulse frequency is a temporal variable that scales the induced firing rate of stimulated neurons, whereas current is a spatial variable that determines the number – or volume – of neurons that are fired by the stimulation (Gallistel, 1978; Gallistel et al., 1981). The counter model (Gallistel, 1976) postulates that, at a fixed stimulation train duration, the intensity of the rewarding effect of BSR depends on the cumulative number of action potentials induced in the directly stimulated neurons. Stimulation trains that induce an equivalent aggregate number of action potentials over a given period of time will elicit reward seeking of

equivalent magnitude. This implies that a stimulation train with lower frequency and higher current can cause equivalent operant response with a stimulation train having higher frequency and lower current (Gallistel, 1978; Yeomans, 1975). The key variable determining behavioral output is the aggregate firing rate induced in the neurons fired by the stimulation. The counter model has been used as a quantitative baseline to expand the understanding of the brain reward system (Trujillo-Pisanty et al., 2020).

The interpretation of operant experiments is influenced by the way operant behavior is measured. A common dependent variable in operant experiments is response rate, which provides an ambiguous distinction between learning of the operant criterion, reward valuation, and the ability to perform the operant task. This renders the distinction of operant responding from engagement in all other activities unclear (Carlezon & Chartoff, 2007; Miliaressis & Rompré, 1987; Valenstein & Beer, 1962). Use of response rate limits inferences about the effects of experimental manipulations on reward seeking. A useful alternative is to quantify operant behaviour by its duration (Baum & Rachlin, 1969), a dependent variable referred to in this thesis as time allocation. Time allocation measures behaviour based on the relative values of work (i.e., engaging in actions linked to receiving a reward or avoiding a punishment) and leisure (i.e., engaging in any other activities, including exploring, resting, sleeping, and grooming). Time allocation has been combined with the curve-shift method in ICSS studies (e.g., Trujillo-Pisanty et al., 2020). Using these methodologies, clearer distinctions can be made about the measurement of behaviors directed at pursuing rewards from actions unrelated to reward seeking.

Structure of the Brain Reward System

Early Conceptualizations

Although the mapping of the brain circuit responsible for reward seeking has been studied since the 1950s, the identity of neurons that give rise to ICSS has yet to be determined definitively (Pallikaras & Shizgal, 2022; Trujillo-Pisanty et al., 2020). The understanding of the neural pathways that underlie BSR has evolved substantially with the validation of increasingly refined methods in neuroanatomy, measurement of operant behavior, and neuromodulation (Pallikaras & Shizgal, 2022).

Early conceptualization of the neural circuit underlying ICSS was based on the observation that several sites that support ICSS are located around monoaminergic circuits (Crow, 1971; Dahlström & Fuxe, 1964; Fuxe et al., 2007). Particular attention was paid to the dopamine system because of the juxtaposition of several ICSS sites with dopaminergic projections (Corbett & Wise, 1979; Wise, 1978). It was suggested that ICSS is the result of direct activation of dopamine neurons (Pallikaras & Shizgal, 2022). This aligned with findings that dopamine agonists, such as cocaine and amphetamine, elicit strong operant responding (Pickens & Thompson, 1971). Dopamine agonists were shown to summate with BSR to improve the behavioural effectiveness of BSR (Franklin, 1978; Wise & Rompré, 1989), whereas dopamine antagonists were shown to reduce its operant effectiveness (Wise, 1996). The concurrent administration of a dopamine agonist (amphetamine) and a dopamine antagonist (pimozide) negated

the effects of each other on ICSS performance (Gallistel & Karras, 1984). Electrical stimulation of the MFB was shown to release dopamine in terminals including the nucleus accumbens (Cossette, Conover, & Shizgal, 2016).

Dopamine neurons became a focus of the ICSS literature. The psychophysical method has been used to estimate several biophysical and electrophysiological properties of the neurons activated by electrical brain stimulation (Bielajew & Shizgal, 1982; Bielajew & Shizgal, 1986; Gallistel, Shizgal, & Yeomans, 1981; Shizgal et al., 1980; Yeomans, 1979). The Medial Forebrain Bundle (MFB) neurons that support ICSS were found to have fast-firing, myelinated axons and a short recovery from refractoriness (Trujillo-Pisanty et al., 2020; Pallikaras & Shizgal 2022). These observations are at odds with the known biophysical properties of midbrain dopamine neurons, which have small, unmyelinated axons, a relatively slow tonic and phasic firing rate, and a high threshold to electrical stimulation (Anderson, Fatigati, & Rompre, 1996; Guyenet & Aghajanian, 1978; Yeomans, Maidment, & Bunney, 1988). The initial notion that MFB ICSS was mediated through direct activation of midbrain dopamine axons appeared untenable. After rejecting the original idea that the directly activated neurons were dopaminergic, these MFB cells were termed the “first-stage” neurons.

To reconcile the observations from psychophysical studies with the known involvement of midbrain dopamine activity in reward seeking, the series circuit model was proposed (Shizgal et al., 1980; Wise, 1980). According to this model, the myelinated, fast-spiking axons of the first-stage neurons innervate midbrain dopamine

cell bodies, acting as an intermediary step between the electrical stimulation and the activation of the dopamine system. According to this model, the function of the directly stimulated MFB axons in causing reward seeking is to trans-synaptically activate midbrain dopamine neurons. The brain reward circuit was conceptualized as having the first-stage neurons “in series” with the dopamine neurons. Based on this long-standing model, midbrain dopamine activity is necessary for reward seeking.

Optogenetics and the Convergence Model

The lack of specificity of the cells activated by electrical brain stimulation had to be overcome to advance the conceptualization of BSR neurocircuitry. At a given set of stimulation parameters, the main factors that determine the electrical excitability of cells are their distance from the electrode tip and their biophysical properties that influence their excitability (e.g., axon size and myelination). The non-specificity of electrical stimulation facilitated the initial conceptions that dopamine neurons are activated directly by the stimulation and the reconciliation of data opposing this view into the series-circuit model. Obtaining the means to selectively modulate neuronal activity of specifiable sets of neurons was a long sought after tool for BSR and neuroscience (Deisseroth, 2011).

Advances in genetic and molecular tools facilitated the development of optogenetics, a technique used to modulate the activity of genetically specified sets of neurons (Bi et al., 2006; Deisseroth, 2011). To achieve this, channelrhodopsin-2

(ChR2), a naturally occurring microbial opsin that functions as a light-sensitive cation channel was expressed in specific sets of neurons and trafficked to their extracellular membrane. Illumination of brain tissue containing neurons expressing ChR-2 with blue-shifted light was shown to trigger action potentials selectively in the cells expressing the opsin. Optical stimulation provides precise control over their activity. Since the original development of optogenetics, several opsins with different functional and kinetic properties have been developed, which can either excite or inhibit the activity of selected sets of neurons (Repina, Rosenbloom, Mukherjee, Schaffer, & Kane, 2017).

Optogenetic methods were incorporated rapidly in neuroscience and in BSR experiments. Evidence for hypotheses postulated by the series-circuit model, most prominently that the activation of midbrain dopamine neurons supports ICSS, could now be gathered directly. A main substrate of interest for this field is the Ventral Tegmental Area (VTA), a midbrain area rich in dopamine cell bodies that project widely in the brain (Oades & Halliday, 1987; Morales & Margolis, 2017). Midbrain dopamine neurons have long been involved in the processing and pursuit of natural and artificial rewards, including BSR (Bressan & Crippa, 2005; Wise, 2009; Wise & Rompré, 1989). The dopamine cell bodies housed in the VTA have heterogeneous neuroanatomical, electrophysiological, and functional properties (de Jong, Fraser, & Lammel, 2022; Knowlton et al., 2021; Lammel, Lim, & Malenka, 2014; Morales & Margolis, 2017). Using optogenetics, the properties and the organization of circuits that the midbrain dopamine system takes part in are being investigated with higher resolution.

It was shown in early studies evaluating the rewarding properties of optogenetic activation of VTA dopamine neurons that their activation supported conditioned place preference (Tsai et al., 2009). It was also shown that optogenetic activation of VTA dopamine cells supports ICSS (Adamantidis et al., 2011; Witten et al., 2011, Ilango et al., 2014). This facilitated the direct study of the role of midbrain dopamine neurons in reward seeking and processing. Initially, the observation that optogenetic stimulation of VTA dopamine supports ICSS was taken as evidence supporting the series-circuit model. Optogenetic stimulation of VTA dopamine was seen as a means of direct activation of the same pathway that electrical stimulation activates indirectly to produce reward seeking.

However similar the optogenetic and electrical ICSS phenomena appear from their behavioral output, a closer look suggests that these phenomena may differ substantially. As with electrical ICSS, understanding the principles determining the excitation of neurons is a way to improve the inferences that can be made from using optogenetics to study the brain reward system. Similarly, to the mapping of electrical stimulation into neuronal firing, a fundamental step in this direction is to understand how the different physical properties of the optical stimulation translate into neural firing. Increases in pulse frequency, pulse duration, and optical power all serve to increase the vigor of operant response and the release of dopamine in terminal regions (Adamantidis et al., 2011; Bass et al., 2010). A lot remains to be known about how each individual parameter affects underlying neural excitation. Many optogenetic studies on the VTA dopamine cells use a fixed set of stimulation parameters or create groups of subjects

based on optical stimulation trains that differ based on a chosen stimulation parameter (e.g., higher vs lower pulse frequency or power). Similarly to electrical ICSS, due to individual differences in implant placement across subjects, the same stimulation parameters can produce different magnitudes of operant behaviour across subjects. In the case of optogenetics, behavioral outcomes are also influenced by the opsin used and the density of its expression. In optogenetic experiments, treating stimulation parameters similarly to drug dosing in pharmacological experiments is inapplicable.

The convergence model, an updated model of the brain reward system architecture, was proposed in a study that combined optogenetic ICSS of midbrain dopamine neurons with psychophysical inference and pharmacological tests (Trujillo-Pisanty et al., 2020). In this study, the reward mountain model was used, which is a behavioral paradigm that measures reward seeking while distinguishing the effects of reward strength and reward cost on operant behavior (Arvanitogiannis & Shizgal, 2008). According to the reward mountain, at a fixed cost (i.e., extent of operant requirement), operant behaviour increases as a function of reward strength. Similarly, for a reward of a given intensity, operant behaviour is inversely related to the cost for obtaining that reward. The reward mountain allows one to disentangle how an experimental manipulation (e.g., administration of a drug) affects reward strength and reward cost. Trujillo-Pisanty and colleagues (2020) combined the reward mountain with the administration of vanoxerine, a potent selective dopamine reuptake inhibitor, to observe the effects of boosting synaptic dopamine availability on optogenetic ICSS. The results of this experiment were compared to prior reward mountain experiments that used

similar designs with electrical brain stimulation of the MFB (Hernandez, Trujillo-Pisanty, Cossette, Conover, & Shizgal, 2012; Hernandez, Breton, Conover, & Shizgal, 2010). This comparison provided a direct test of a tenet of the series-circuit model, which predicts that a systemic boost of dopamine transmission should effect the same behavioral changes in both electrical (MFB) and optogenetic (VTA dopamine) stimulation. This was not the case. Instead, shifts in the reward mountain differed in the electrical and optogenetic experiments. It was inferred that, contrary to predictions of the series-circuit model, reward seeking elicited by electrical MFB stimulation is not fully mediated by the trans-synaptic activation of dopamine neurons.

According to the convergence model, the reward system contains parallel dopaminergic and non-dopaminergic pathways that link up independently onto the downstream neural network responsible for operant behavior. The convergence model postulates that the midbrain dopamine neurons are not in a linear lockstep with MFB axons that support ICSS. Although the electrical activation of MFB axons causes indirect activation of midbrain dopamine neurons, it also leads to reward seeking through a parallel, non-dopaminergic pathway. Despite the unclear identity of these MFB axons, the convergence model hoisted their importance regarding their role in the brain reward system.

The Role of Deep Brain Stimulation in the Treatment of Depression

The dopamine system has not only been featured substantially in the BSR literature. Rather, it is one of the most studied neurotransmitter circuits in neuroscience (Björklund & Dunnett, 2007). Among its several important functions, the dopamine system has been associated with an array of psychological disorders and maladaptive behaviors (Franco, Reyes-Resina, & Navarro, 2021). Establishing a seminal link of the reward system and psychopathology, the pharmacodynamics of agents that were found to have antipsychotic properties in the early 1950s informed the development of the hyperdopaminergic theory of psychosis (Davis, Kahn, & Davidson, 1991). Contemporaneously, two other agents, iproniazid (a monoamine oxidase inhibitor) and imipramine (a tricyclic antidepressant), were found to improve mood regulation (López-Muñoz & Alamo, 2009). These discoveries became the foundation for the serotonergic theory of affective disorders. These developments led to a paradigm shift in the conceptualization and treatment of mental illness from the sociogenic, psychoanalytic tradition towards a biological system akin to the one of internal medicine.

The change in zeitgeist brought by psychoactive drugs led to the decline of then popular mental health interventions, including psychoanalysis and brain stimulation. In the 1950s, pioneers of deep brain stimulation, including Robert Heath and Jose Delgado, explored the therapeutic effects of electrical excitation of the brain in patients with severe psychosis, epilepsy, chronic pain, and other refractory disorders (Delgado, 1969; Heath, 1996). Health experimented on patients with severe psychosis by implanting electrodes in the septum, an area anatomically analogous to the one Olds and Milner (1954) focused on in their seminal BSR experiment (Heath, 1996). Facing

ethical dilemmas, questionable experimental controls, sparse funding, and inconsistent findings, deep brain stimulation failed to become a well-established psychiatric intervention. This changed in the 1990s when the application of deep brain stimulation for Parkinson's Disease and other movement disorders instituted deep brain stimulation as an approved treatment for nervous system disorders (Benabid, 2003; Tronnier et al., 1997).

More recent application of deep brain stimulation has focused on several refractory mental illnesses (Cleary et al., 2015; Holtzheimer, & Mayberg, 2011). Particular attention has been paid to the effects of deep brain stimulation on individuals diagnosed with severe, treatment-resistant depression. Although at least 11 brain sites have served as targets in such clinical trials (Drobisz & Damborská, 2019), findings come mainly from case studies and from experiments with small sample sizes and designs lacking rigorous experimental control. As a result, findings have been inconsistent, ranging from 100 percent response rate to two large randomized controlled trials being discontinued due to unpromising early results (Dougherty et al., 2015; Fenoy, Quevedo, & Soares, 2022). A brain region that stands out in this literature is a part of the MFB, an area that has long been a main focus of the BSR literature. Stimulation of the MFB produces a rapid, safe, and long-lasting antidepressant effect with a high response rate (Döbrössy et al., 2021; Fenoy et al., 2022). That said, the antidepressant efficacy of MFB stimulation is still under study. Three pilot studies with a total of four participants did not detect statistically reliable antidepressant effects after six to 24 months of MFB stimulation (Davidson et al., 2020; Sobstyl & Stapińska-Syniec,

2021). Furthermore, reports support that the antidepressant effect of MFB deep brain stimulation is contingent on continuous stimulation, as discontinuation of the stimulation leads to rapid relapse of depressive symptoms (Fenoy, Quevedo, & Soares, 2023; Kilian et al., 2019).

It has been proposed that activation of the dopamine system plays a critical role in neural systems underlying the antidepressant effect of MFB stimulation (Döbrössy et al., 2021; Fenoy et al., 2022). However, despite being under study for close to a century, pharmacological agents that boost dopaminergic activity do not appear to function as monotherapies to depression (Pallikaras & Shizgal, 2022). This complicates the complete attribution of the clinical phenomenon of MFB stimulation to a boost in dopamine transmission. Similarly to the electrical BSR literature, the non-specificity of electrical stimulation hinders the definitive identification of the neural networks responsible for the antidepressant efficacy of MFB stimulation.

It is suggested, here, that combining a dimensional view of psychopathology with insights from the BSR literature can provide theory-driven hypotheses, which can inform the effort to understand how MFB stimulation attains antidepressant efficacy and what brain circuits underlie it. Specifically, two main hypotheses related to anatomy and function are posed. First, a parallelism with the convergence model of BSR is drawn to ask whether dopamine transmission is necessary or sufficient to produce antidepressant effects by MFB stimulation. Second, whether the clinical effect of MFB stimulation may work by facilitating reward seeking is asked. If this may be the case, the

continuous volley of action potentials induced in the MFB of treated individuals may increase reward seeking by influencing parameters related to motivation, including reward value and subjective effort estimation. These hypotheses are testable both in clinical and animal studies, thus fitting dimensional frameworks such as the Research Domain Criteria (Insel et al., 2010).

Current Thesis

In the first two Chapters of this thesis two experiments are summarized that use psychophysical inference and trade-off designs to expand the understanding of how ChR-2-mediated optogenetic stimulation of midbrain dopamine neurons translates into the neural signal that causes reward seeking. The results support that within-subject designs in optogenetics have the benefit of using measurable and meaningful outcomes as points of reference for making inferences about the effects of the stimulation.

In the first Chapter, the trade-off function between optical power and pulse frequency in producing VTA dopamine-mediated reward seeking is described. It is tested whether there is a reciprocity of time (i.e., pulse duration) and intensity (i.e., power) in determining the behavioural effectiveness of the stimulation. Whether the trade-off between power and intensity in optogenetic stimulation of midbrain dopamine neurons parallels Bloch's Law in human vision is evaluated. It was found that, within a useful range of powers, there is a lawful trade-off between pulse duration and power that breaks down or decelerates at powers over 31.6 mW. This experiment is added to

reports suggesting that, in optogenetic stimulation, pulse duration functions as a spatial variable, similarly to power.

Insights from the first Chapter are applied in the second Chapter to estimate the firing fidelity of midbrain dopamine neurons using psychophysical inference. The frequency following of midbrain dopamine neurons that are transfected with ChR-2 is measured; the behaviorally relevant, effective range of firing fidelity of midbrain dopamine neurons spans 7Hz to 28 Hz - 40 Hz. This experiment supports that the upper pulse frequency value that is useful in improving the behavioural effectiveness of the stimulation lies between 28 Hz and 40 Hz. Higher pulse frequencies (<40 Hz) were either ineffective or reduced the behavioral effectiveness of the stimulation.

The third Chapter consists of a theory article that discusses how insights from the BSR literature can inform studies of MFB deep brain stimulation for depression. Two main ideas are explored. First, it is outlined that, analogously to brain circuitry which supports ICSS, both dopaminergic and non-dopaminergic pathways might underlie the clinical effect of MFB deep brain stimulation. Second, it is suggested that electrical stimulation of the MFB may attain antidepressant efficacy by facilitating appetitive motivation and thus a sustained engagement in reward seeking.

CHAPTER 1:

THE TRADE-OFF BETWEEN PULSE DURATION AND POWER IN OPTICAL EXCITATION OF MIDBRAIN DOPAMINE NEURONS APPROXIMATES BLOCH'S LAW

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Abstract

Optogenetic experiments reveal functional roles of specific neurons. However, functional inferences have been limited by widespread adoption of a restricted set of stimulation parameters. Broader exploration of the parameter space can deepen insight into the mapping between selective neural activity and behavior. In this way, characteristics of the activated neural circuit, such as temporal integration, can be inferred. Our objective was to determine whether an equal-energy principle accounts for the interaction of pulse duration and optical power in optogenetic excitation. Six male TH::Cre rats worked for optogenetic (ChannelRhodopsin-2) stimulation of VTA dopamine neurons. We used a within-subject design to describe the trade-off between pulse duration and optical power in determining reward seeking. Parameters were customized for each subject based on behavioral effectiveness. Within a useful range of powers (~12.6–31.6 mW) the product of optical power and pulse duration required to produce a given level of reward seeking was roughly constant. Such reciprocity is consistent with Bloch's law, which posits an equal-energy principle of temporal summation over short durations in human vision. The trade-off between pulse duration and power broke down at higher powers. Thus, optical power and duration can be adjusted reciprocally for brief durations and lower powers, and power can be substituted for pulse duration to scale the region of excitation in behavioral optogenetic experiments. The findings demonstrate the utility of within-subject and trade-off designs in optogenetics and of parameter adjustment based on functional endpoints instead of physical properties of the stimulation.

1. Significance Statement

To maximize the inferences that can be drawn from optogenetic experiments, we must understand the dependence of behavior on stimulation parameters. Here, we provide the first behaviorally derived intensity-duration curves for ChannelRhodopsin-2. We show that for a useful range of powers, pulse duration trades-off with power almost perfectly. As a result, pulse duration can substitute effectively for power to scale the region of excitation. We also show that higher powers become ineffective or counter-productive at recruiting more neurons. We demonstrate how within-subject trade-off designs yield insights into optogenetic excitation mechanisms. Lastly, we provide practical recommendations on improving optogenetic designs based on our findings.

2. Introduction

Optogenetic excitation establishes causal links between activation of specific neurons and behavior (Boyden et al., 2005; Bi et al., 2006). However, researchers applying optogenetic manipulations face the practical problem of parameter selection. Adopting parameters commonly employed in published studies provides a sub-optimal solution to this problem. Indeed, the widespread adoption of a restricted set of stimulation parameters by the optogenetics community leaves much of the stimulation-parameter space unexplored, the mapping between parameter values and observed behavior partly unexplained, and individual differences in opsin expression and probe placement unaddressed. To realize the full potential of optogenetics, we must map

observable behavior onto stimulation parameters for each subject. We do so here for optical self-stimulation (oICSS; Adamantidis et al., 2007; Witten et al., 2011; Kim et al., 2012; Trujillo-Pisanty et al., 2020). Rats were trained to work for optical stimulation of Channelrhodopsin-2 (ChR2)-expressing dopamine neurons in the VTA. We determined how pulse duration and optical power interact to control reward seeking, and we assessed the correspondence between this interaction and Bloch's law (Bloch 1885; Gorea, 2015), a principle of temporal summation in visual perception.

The irradiance produced by an optical pulse of a given duration, and hence the amplitude of the induced photocurrent, decays as a function of distance from the tip of the implant (Yizhar et al., 2011). Consequently, the greater the distance between an opsin-expressing neuron and the tip of an optical fiber, the longer the required duration of a pulse to trigger an action potential (Foutz et al., 2012). Thus, at a given optical power, the cross-sectional area of the region wherein a pulse activates opsin-expressing neurons scales with pulse duration. In this sense, pulse duration and optical power codetermine the area of excitation and the number of recruited neurons.

Dopamine release in the NAc driven by optical stimulation of midbrain dopamine neurons increases as a function of optical power (Bass et al., 2010). Operant performance for such stimulation increases as a function of both optical power (Ilango et al., 2014; Trujillo-Pisanty et al., 2020) and pulse duration (Ilango et al., 2014). However, the form of the interaction between optical power and pulse duration in determining the behavioral effectiveness of the stimulation has not been described empirically. Such

strength-duration curves have been derived theoretically for ChR2-expressing neurons (Foutz et al., 2012; Williams et al., 2013), but, to our knowledge, no such curves are available either for activation of midbrain dopamine neurons or for oICSS of these neurons. We provide such curves here for the case of oICSS.

In human vision, there is a simple relationship between the intensity and duration of a light flash required to produce a just-detectable stimulus. As flash duration increases, the required illuminance declines initially as a power function of duration and is then roughly constant beyond a critical duration that depends on the spatial frequency (Gorea and Tyler, 1986). This relationship is called Bloch's law (Bloch, 1885; Gorea, 2015). Here, in the case of ChR2-mediated activation of midbrain dopamine neurons, we determine whether pairs of pulse durations and optical powers that cause equivalent reward seeking approximate Bloch's law. This question is germane to the development and use of optogenetic prostheses and to linking specific neural populations to function.

3. Methods

3.1. Subjects

Subjects were 6 male, TH::Cre, Long-Evans rats weighing ~350–475 g at surgery. Rats were singly housed on a reverse 12 h-light cycle and had free access to chow (Envigo #2014). Subjects deemed overweight for their age (Sengupta, 2013) were put on a weight-maintenance feeding schedule. Subject ELOP18 had bilateral implants

and contributed individual datasets for each hemisphere. Procedures for animal care were approved by Concordia University Animal Research Ethics Committee (Protocol #: 30000302) and adhered to standards of the Canadian Council on Animal Care.

3.2. Surgery

Surgical procedures are described in detail elsewhere [6]. Rats were anesthetized (IP ketamine; 87 mg/kg/Xylazine; 13 mg/kg; CDMV) and positioned in a stereotaxic frame for injection of the viral vector (AAV5-DIO-ChR2-EYFP; University of North Carolina) via a micro-infusion pump (Kent Scientific). The injector was aimed at the VTA (AP: -5.5 & -6.2, ML: ± 0.7, DV: -7.4 & -8.4), and 1 µl of virus was infused at each site at a rate of 0.1 µl/min. Optical fiber implants (Thorlabs; 300µm diameter, 0.39 NA) were chronically positioned above the VTA (AP: -5.8, ML: ± 0.7, DV: -7.7).

3.3. Apparatus

We used six operant boxes equipped with a house light and a retractable lever with a cue light above it. The house light flashed once per second during the inter-trial interval (ITI), and the cue light was illuminated while the lever was depressed. The laser head (462 nm; SLOC) was connected via a fiber-optic cable (300 µm diameter, 0.39 NA) to a single-channel rotary joint (FRJ_1 ×1_FC-FC; Doric Lenses) mounted above the box. An optical-fiber cable (Trujillo-Pisanty et al., 2015; 300 µm diameter, 0.39 NA) was connected to the implant via a ceramic sleeve. We set optical power with a power

meter (PM100D; Thorlabs) by measuring the continuous-wave output of the lasers prior to each session.

3.4. Self-Stimulation Training

Four weeks post-surgery, we used successive approximations to train subjects to perform oICSS under an FR-1 schedule. Stimulation trains, 1 s in duration, consisted of 5 ms pulses delivered at 40 Hz. Optical power ranged from 20 to 40 mW.

3.5. Cumulative hold-down schedule of reinforcement

Subjects were trained to hold down an operant lever to trigger stimulation (Breton et al., 2009). A pulse train was delivered each time the cumulative hold-down time reached 2 s. After stimulation was triggered, the lever was retracted for 1.5 s, and the trial timer was paused until the lever re-extended. The dependent variable was time allocation: the proportion of total trial time spent working. Pauses between lever presses shorter than 1 s were classified as work. During such instances, the rat typically holds its paw on or above the lever (Breton et al., 2009).

3.6. Pulse duration sweeps

A sweep was a set of 10 trials over which the pulse duration was decreased systematically (“swept”) while all other parameters were held constant. Trials lasted for

50 s and were preceded by a 10 s ITI. At the 8th second of the ITI, a train of priming stimulation was delivered. This stimulation was identical to the train available on the first trial of the sweep. The pulse duration was fixed within trials. On the first two trials of each sweep, pulse duration was set to the longest value tested and then reduced in eight proportional steps from the 3rd to the 10th trial. The range of pulse durations was customized for each rat and condition. Sessions, roughly 2 h in duration, consisted of 10 pulse-duration sweeps. The first sweep and the first trial of every sweep were considered warm-ups, and their data were discarded. We tested conditions at various optical powers (between 10 mW and 50 mW) at each stimulation site. Five sessions (45 sweeps) were run in every optical-power condition.

3.7. Experimental design and statistical analysis

We used a within-subjects trade-off design to measure time allocation in pulse duration sweeps run at different optical powers. We collected data for 7 stimulation sites across 6 subjects, a sample size typical of within-subjects ICSS designs. Due to noise in the lateral position of curves, plots of averaged time allocation versus pulse duration have a shallower slope than the curves obtained on individual sweeps (Hernandez et al., 2010). Therefore, we fit a sigmoidal function to the time allocation values for each sweep and averaged its parameters (Hernandez et al., 2010). Although time allocation varied systematically with pulse duration on the great majority of sweeps, some aberrant cases were observed. We filtered the data by eliminating sweeps in which the average time allocation on the first four trials did not exceed the average on the last four

trials by at least 20%. Sensitivity to outliers was reduced by a robust fitting method based on Tukey's bisquare estimator (Tukey, J.W., 1960).

The following four-parameter equation was fitted:

$$(TA - TA_{min}) / (TA_{max} - TA_{min}) = 1 / [1 + \exp\{-slp \times (\log_{10}(d) - loc)\}]$$

Where:

d: Pulse duration.

loc: Location parameter. This is the pulse duration at which time allocation falls halfway between its maximal and minimal values. This parameter determines the position of the sigmoidal curve along the pulse-duration axis, thus indexing the effect of changing the optical power.

TA: Time allocation.

TA_{min}: Minimal time allocation.

TA_{max}: Maximal time allocation.

slp: Slope parameter determining the steepness of the rise.

Descriptive statistics (means and 95% confidence intervals) were generated for the fitted parameters (TAmax, TAmin, slp, and loc). Fitted curves were deemed to have shifted between optical-power conditions when the 95% confidence intervals around the location parameters for these conditions did not overlap. All data-analysis and graphing was carried out in Matlab (MathWorks).

3.8. Histology

Rats were anesthetized (sodium pentobarbital; 200 mg/kg IP; CDmv) and perfused transcardially using saline and 4% paraformaldehyde. Brains were post-fiXed for 24 h in 4% paraformaldehyde and subsequently cryoprotected by successive immersion in phosphate-buffered solutions of 15% and 30% sucrose until they sank. Brains were then stored at 80 ◦C. Using a cryostat, 40 µm sections were cut through the VTA and mounted on glass slides. Slices were stained with DAPI (product number: R37605l; ThermoFisher). Sections were imaged on a Nikon Eclipse TiE inverted microscope using NIS-Elements software and processed further using Fiji (National Institutes of Health (USA)) and Matlab (Mathworks). Native fluorescence of eYFP revealed expression of ChR2 in dopamine neurons. Fig. 1 shows implant placements.

4. Results

4.1. Time allocation as a function of pulse duration

Time allocation grew as a sigmoidal function of pulse duration in all subjects. Panel A of Fig. 2 depicts single-session data from an exemplar subject (OP13). The average time-allocation values for this condition are shown in panel B (green diamonds). Also shown in panel B is a curve obtained by averaging the parameters of sigmoidal functions fitted to the data from the individual sweeps for this condition (Hernandez et al., 2010; Fig. 14). The shaded band reflects the 95% confidence interval around the location parameter. TA50, refers to time allocation of 50%, and d50 refers to

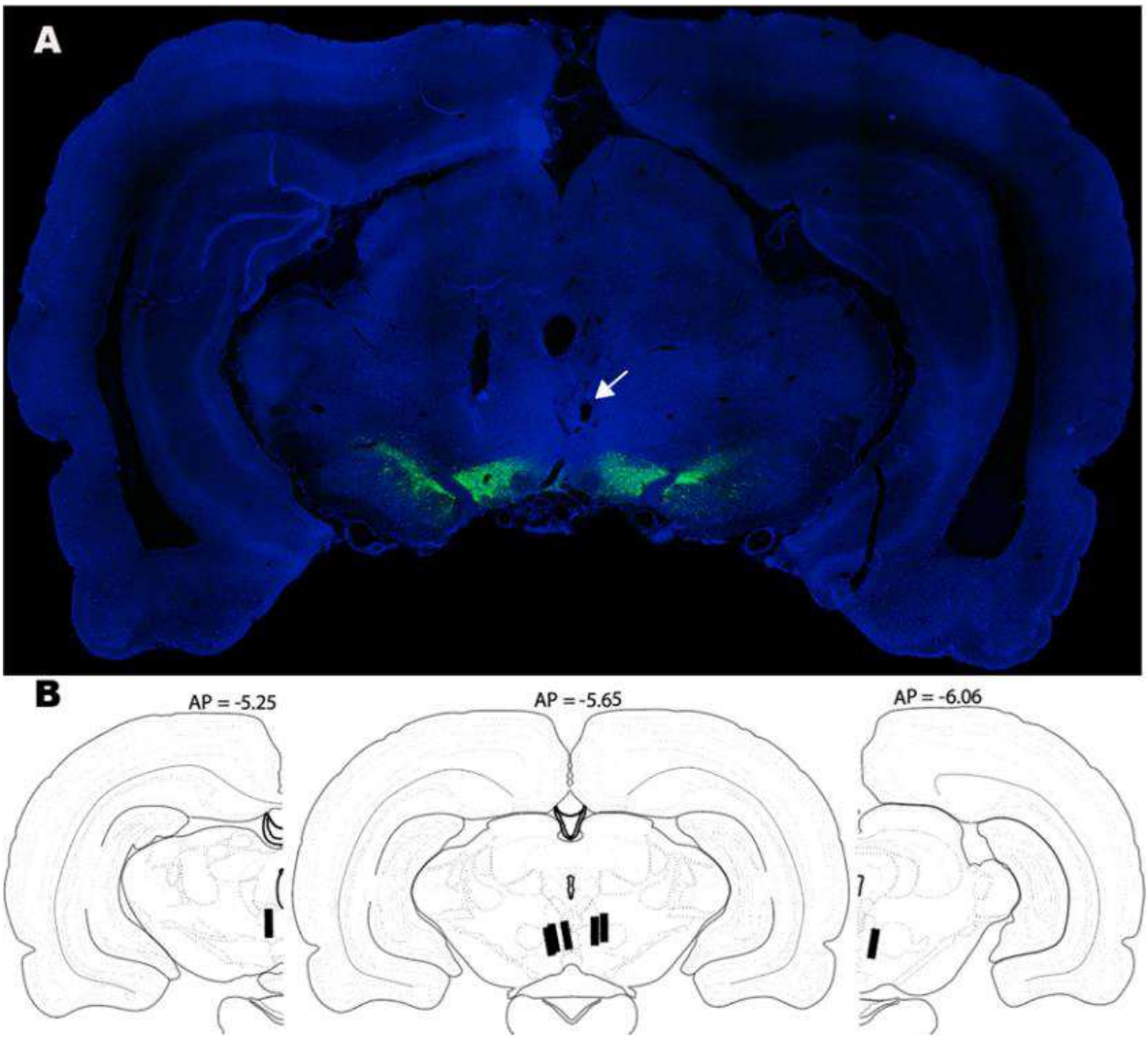


Figure 1. Histology. A: Histological image for subject OP13; eYFP expression (green) shown along with DAPI (blue) for anatomical reference (image enhanced by rescaling the distribution of piXel intensities). Estimated fiber-tip location: white arrow. B: Black lines indicate implant placements. Adapted from Swanson (2018).

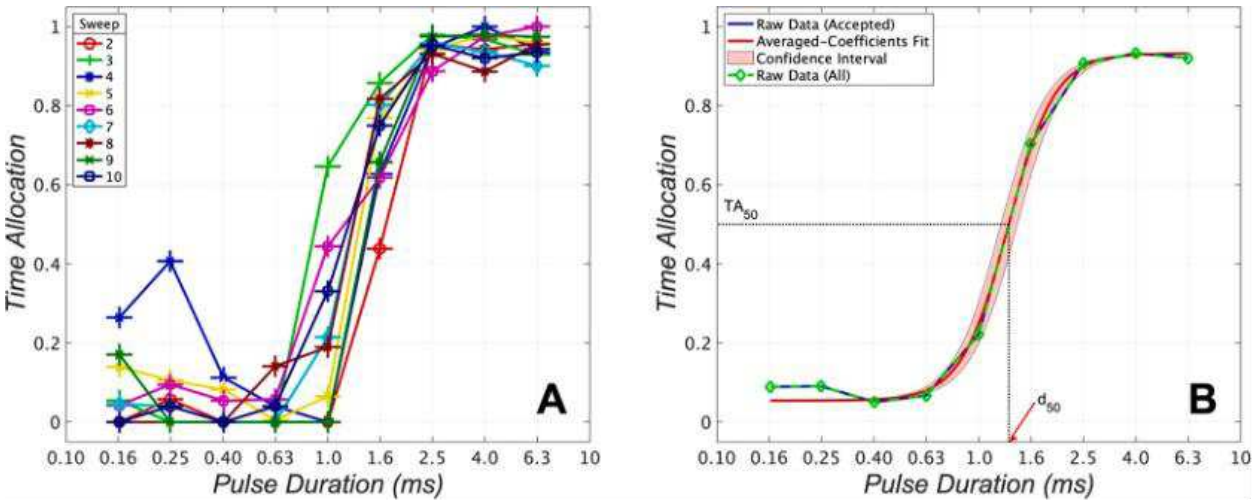


Figure 2. Pulse-duration sweep data for subject OP13 (optical power: 31.6 mW). A: Single-session data depicting individual time-allocation-versus-pulse-duration curves. B: Conventional averaging of time allocation over five test sessions (45 sweeps; green line) and curve produced by averaging the parameters of fitted sigmoidal functions (red line) with 95% confidence interval surrounding the location parameter (pink).

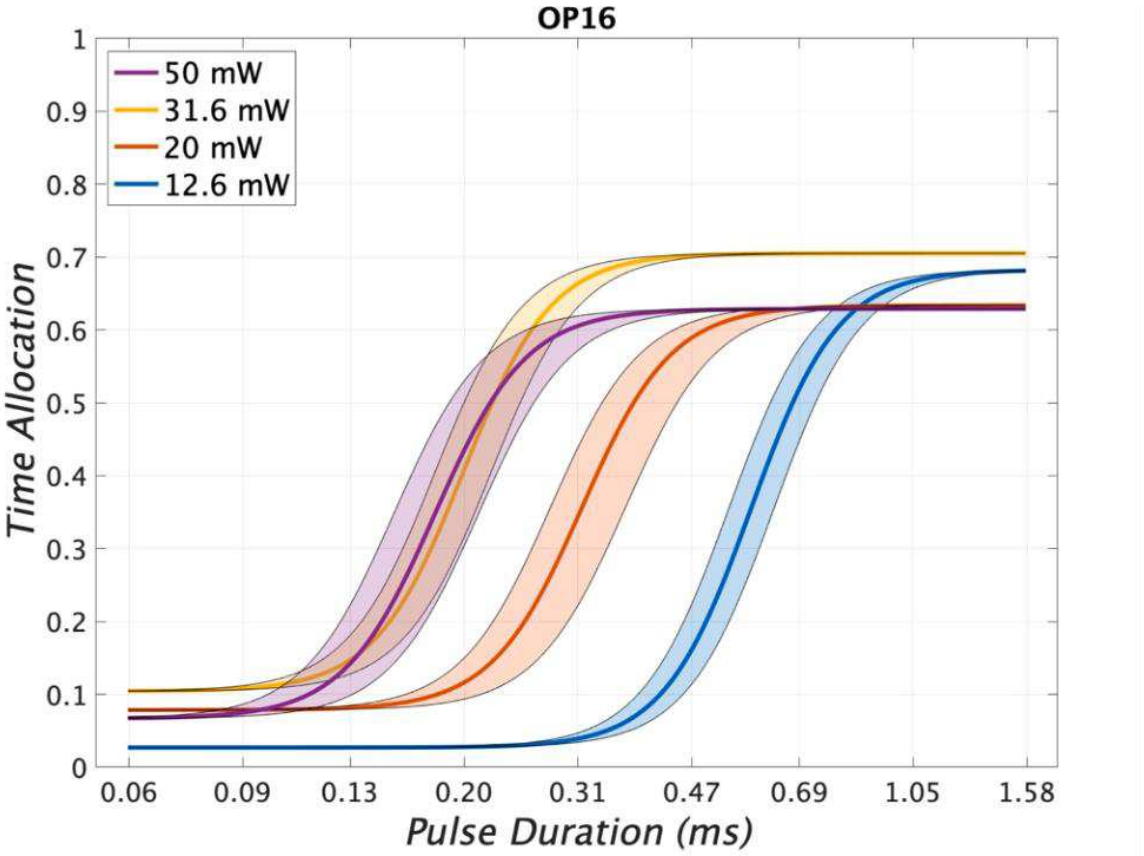
the corresponding pulse duration. The impact of the curve-fitting procedure on noisier data is shown in appendix A (Figure A.1). Appendix B (Tables B.1–5) provides fitted parameter values for the dataset.

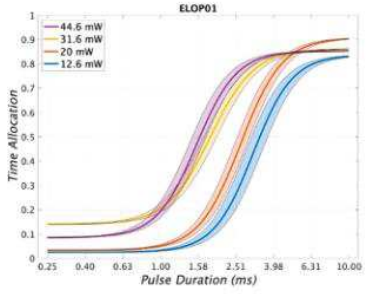
4.2. Pulse duration trades off with optical power

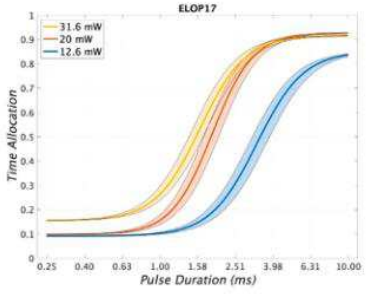
We determined how optical power trades off against pulse duration to hold time allocation constant. Increasing the optical power systematically shifted the time-allocation curves leftwards along the pulse- duration axis (Fig. 3). Thus, the same level of time allocation can be achieved by a stimulation train composed of brief, high-power pulses and a train composed of longer, lower-power pulses. However, at six out of seven stimulation sites that could be tested successfully at the highest optical power (50 mW at 4 sites; 44.6 mW at 1 site; 31.6 mW at 1 site), the final increment failed to produce a leftward shift. Thus, there was an upper limit (generally, beyond 31.6 mW) on the optical power that trades off against pulse duration to hold behavior constant.

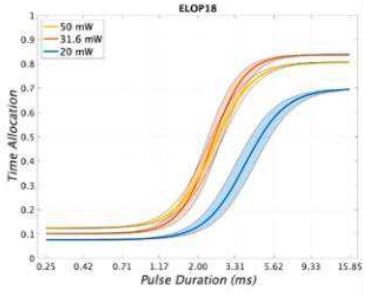
4.3 The trade-off between pulse duration and optical power approximates Bloch's Law

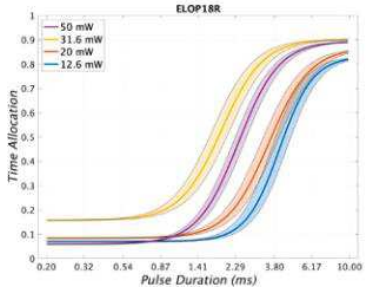
We determined whether the trade-off between the optical power and pulse duration (d50) required to hold time allocation constant at TA50 corresponds to Bloch's Law. If Bloch's law holds, constant optical-energy deposition will produce a constant level of behavior (time allocation) over pulse durations shorter than a critical value. Thus, the product of optical power and d50 will be constant over this range of pulse

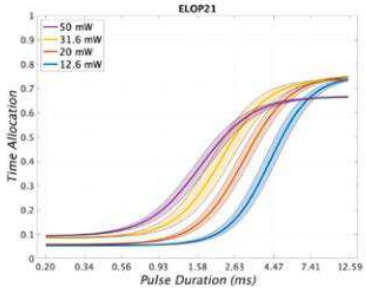

OP16
50 mW
31.6 mW
20 mW
12.6 mW
Time Allocation
Pulse Duration (ms)
0.06
0.09
0.13
0.20
0.31
0.47
0.69
1.05
1.58


ELOP01
44.6 mW
31.6 mW
20 mW
12.6 mW
Time Allocation
Pulse Duration (ms)


ELOP17
31.6 mW
20 mW
12.6 mW
Time Allocation
Pulse Duration (ms)


ELOP18
50 mW
31.6 mW
20 mW
Time Allocation
Pulse Duration (ms)


ELOP18R
50 mW
31.6 mW
20 mW
12.6 mW
Time Allocation
Pulse Duration (ms)


ELOP21
50 mW
31.6 mW
20 mW
12.6 mW
Time Allocation
Pulse Duration (ms)

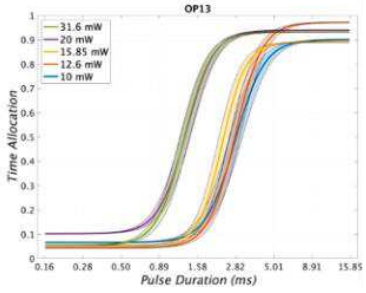

OP13
31.6 mW
20 mW
15.85 mW
12.6 mW
10 mW
Time Allocation
Pulse Duration (ms)

Figure 3. Fitted time-allocation-versus-pulse-duration curves for each optical power at all 7 stimulation sites. Over a range of powers, there is a systematic trade-off between pulse duration and optical power in maintaining half-maximal time allocation. At 6 of 7 sites, the observed trade-off breaks down at the highest power increment (31.6–50 mW at 4 sites; 31.6–44.6 mW at 1 site; 20–31.6 mW at 1 site).

durations. To assess the correspondence of the data to Bloch's law, we mean-centered the common logarithms of the d50 values and plotted them against the common logarithm of the optical power (Fig. 4A) and the product of power and d50 (Fig. 4B). The data from the highest optical powers tested were excluded. Perfect reciprocity between pulse duration and optical power holds if the slope of these lines is 1 (Fig. 4A) and 0 (Fig. 4B), respectively. The 95% confidence intervals surrounding the slopes of the lines of best fit include 1 and 0, respectively: 1.017 ± 0.174 (Fig. 4A), 0.005 ± 0.048 (Fig. 4B). Figure A.2 shows an analogous plot with no data excluded.

5. Discussion

To better understand how stimulation parameters interact in the activation of opsin-expressing neurons and translate into behavior, we measured the trade-off between optical power and pulse duration in optical self-stimulation of ChR2-expressing midbrain dopamine neurons. We show that over a useful range of powers, these two variables trade off reciprocally. The intensity-duration trade-off documented here implies that the pulse duration scales the number of stimulated opsin-expressing neurons and thus provides a convenient means of achieving such scaling in optogenetic setups requiring manual control of optical power. The findings highlight the usefulness of within-subject and behavioral trade-off designs in optogenetic experiments and the utility of testing parameter ranges well beyond the values that have become an informal standard in behavioral optogenetic studies.

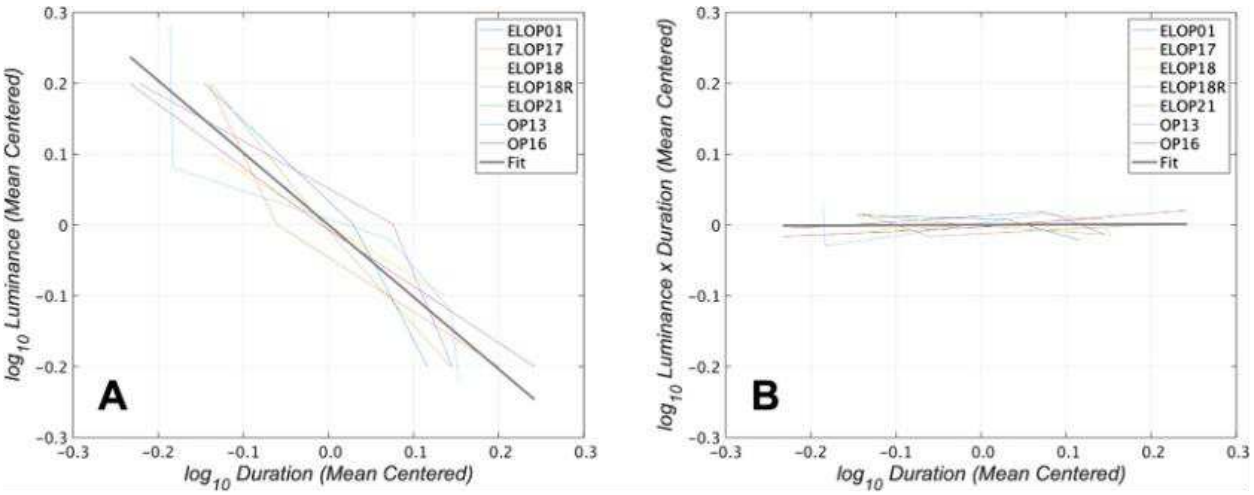


Figure 4. The trade-off between pulse duration and optical power approximates Bloch's law. The data from the highest optical powers tested were excluded. A: Mean- centered optical-power-vs-pulse-duration curves for individual stimulation sites (colored lines) and regression line (thicker black line; slope; —1.017 ± 0.174. B: Mean-centered energy (optical power × pulse duration) versus pulse-duration curves for individual stimulation sites (colored lines) and regression line fitted to the entire dataset (thicker black line; slope 0.005 ± 0.048). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

For simplicity, we assume initially equal expression of ChR2 in dopamine neurons and equal excitability across neurons and pulses. This yields a sharp boundary between the regions in which each pulse either triggers a spike or does not. Relaxing these assumptions creates multiple boundaries that are fuzzy in time and space, but it does not change the fundamental point: pulse duration acts as a spatial variable.

Irradiance is highest at the fiber tip (Yizhar et al., 2011). Thus, the induced photocurrent rises most steeply and surpasses threshold soonest in the nearest opsin-expressing neurons. As distance from the tip increases, irradiance falls off, delaying spike onset. At the sharp boundary defined by the simplified assumptions, the spike is initiated only at the very end of the pulse. Increasing the pulse duration pushes the boundary outwards by providing more time for the photocurrent to achieve suprathreshold depolarization. Thus, pulse duration trades off against the other parameter that acts spatially: the optical power. Bloch's law asserts that this trade-off is reciprocal over an initial range of durations. Fig. 4 shows such reciprocity.

According to the "counter model" of spatiotemporal integration in brain reward circuitry (Gallistel, 1978; Gallistel et al., 1981; Simmons & Gallistel, 1994), the intensity of brain stimulation reward is a function of the aggregate firing rate induced by a pulse train of fixed duration. This model has been tested most extensively in the case of electrical ICSS (Simmons & Gallistel, 1994), but it is also consistent with oICSS data (Ilango et al., 2014; Trujillo-Pisanty et al., 2020). The counter model implies that beyond the outputs of the activated midbrain dopamine neurons, there is a neural signal,

(dubbed “reward intensity”) whose amplitude in response to a pulse train of a given duration is a monotonic function of the aggregate firing rate (Simmons & Gallistel, 1994). According to the single-operant matching law (Trujillo-Pisanty et al., 2020; Herrnstein, 1970, 1974; McDowell, 2005), time allocation is a monotonic function of reward intensity and hence of the aggregate firing rate as well. Thus, during a pulse-duration sweep, time allocation is a monotonic function of pulse duration. If so, every pair of optical powers and d50 values generates the same aggregate firing rate by activating the same dopamine neurons, and the behaviorally derived trade-off function applies to the excitation of these dopamine neurons. This logic is analogous to that underlying the remarkable correspondence between the absorption spectrum of human rhodopsin and the appropriately corrected sensitivity function for scotopic vision (Wald and Brown, 1958).

Both the Bunsen-Roscoe law of photochemistry (Bunsen & Roscoe, 1855; Bonfield et al., 2020) and Bloch’s law (Bloch, 1885; Gorea, 2015; Tauchi & Tanaka, 1987) reflect a constant-energy principle: for sufficiently short durations, the effectiveness of a light pulse is determined by the product of optical power and pulse duration. Within a range of optical powers (12.6–31.6 mW) and pulse durations (0.22–5.00 ms), our results approximate the predicted reciprocity. This implies that at least within the aforementioned limits, the constant-energy principle applies to the optical excitation of ChR2-expressing midbrain dopamine neurons.

The correspondence between the data and Bloch's law broke down or was moderated at the highest optical powers tested. The sigmoidal curve either failed to shift appreciably (OP13, OP16, ELOP01, ELOP18), shifted too little in the leftward direction (ELOP21), or shifted right- wards (ELOP18R). The final increment in optical power should have pushed the excitation boundary outwards by the same amount as the other increments. The failure of the curves to shift sufficiently, at all, or in the predicted direction, implies that neurons were subtracted from the activated population in sufficient numbers to decrease, cancel, or reverse the contribution of the firings added at the periphery of the field. If so, the across-subject variation in the relative position of the curve obtained at the highest optical power would reflect corresponding variation in the ratio of subtracted to excited neurons.

How might the final increment in optical power have subtracted firings? A heating-induced decrease in neural excitability is an unlikely explanation because heating obeys an equal-energy principle analogous to Bloch's law (Stujenske et al., 2015). Moreover, the range of d50 values was roughly an order of magnitude lower in subject OP16 than in the other subjects. The heat deposited by the parameters corresponding to TA_{50} in this rat should have been an order of magnitude lower than in the other subjects, but the equal-energy principle broke down in this rat at the highest optical power tested, as it did in the others.

The highest optical power tested in this study was 50 mW, which generates an optical-power density at the fiber tip of 707 mW/mm2. This value greatly exceeds those

used typically in determining the photocycle of ChR2. For example, the optical-power density of pulses delivered in the ChR2 photocycle study by Kuhne and colleagues (2019) was 1 mW/mm2, and 1–5 mW/mm2 is typically taken as the threshold for opening ChR2 channels (Boyden et al., 2005). We wonder whether the greatly suprathreshold optical-power densities might somehow reduce firing in the region closest to the fiber tip, thereby offsetting firings added at the periphery of the field and violating reciprocity. Is such a reduction seen in response to greatly suprathreshold irradiance in ChR2-expressing dopamine neurons observed by electrophysiological means? These would provide a strong test of the inferences drawn here concerning the application of the constant-energy principle to optogenetic stimulation.

The demonstration that the trade-off between pulse duration and optical power approximates Bloch's law provides a rule of thumb for adjusting one of these parameters when the other has been changed. Moreover, our findings show that pulse duration can substitute effectively for optical power in controlling the size of the recruited population of opsin-expressing neurons. Computer control of pulse duration is readily implemented, whereas only a subset of optogenetic setups offer computer control of optical power or high-power output.

High optical powers have been used to recruit neurons within a large region (Senova et al., 2017). Although this is clearly useful over a limited range, the observed breakdown of reciprocity at the highest power tested suggests that this strategy may ultimately become futile in the case of ChR2. In order to recruit neurons within a large

brain volume, a red-shifted opsin with high sensitivity (Chen et al., 2020) offers a more promising approach.

Our results and methodological approach illustrate how the wide-spread use of a restricted set of stimulation parameters in optogenetic behavioral studies unnecessarily adds across-subject variance and limits the inferences that can be drawn about underlying physical and physiological processes. Note that the pulse durations required to support TA_{50} vary over more than a ten-fold range across stimulation sites at 20 mW and 31.6 mW (Appendix B). Consequently, the 0.5 ms pulse duration drove time allocation to near-maximal values in Rat OP16 at 20 mW but yielded minimal time allocation in Rat OP13 (Fig. 3). This variance obscures the fact that the functional relationship between time allocation and the pulse duration in these two rats is very similar; the same sigmoidal function fits the data very well. Thus, the congruence of the data from these two rats becomes evident when behavioral equivalence is used as the criterion for setting the values of stimulation parameters individually for each stimulation site but not when a fixed, informal standard (e.g., a pulse duration of 5 ms) is imposed. By sweeping the pulse duration over a large range for every rat, the sigmoidal form of the psychometric function is revealed. The fitted functions can then be normalized as was done here to reveal how the pulse duration and the optical power interact. Such normalization compensates for inevitable across-subject variation in the location of the optical fiber tip and the expression of ChR2. Thus, we advocate customization of stimulation parameters for each subject to achieve behavioral or functional equivalence.

The findings of this study illustrate that constant-behavioral-output trade-off functions are typically much more informative of underlying physical and physiological processes than simple input-output relationships between the value of a stimulation parameter and the corresponding vigor of the stimulation-induced behavior (Gallistel et al., 1981). The correspondence between the data reported here and Bloch's law reflects such a trade-off. The underlying logic "sees through" multiple neural stages that translate neural activation into behavior so as to reveal quantitative properties of the processes underlying optogenetic excitation.

Preface to Chapter 2

It was shown in Chapter 1 that, for powers between approximately 12.6 mW and 31.6 mW, there is a lawful trade-off between pulse duration and power in determining the behavioral effectiveness of midbrain dopamine neuron stimulation. Changing either of these two stimulation parameters scales the number, or volume, of neurons that are recruited by the stimulation. It was inferred that pulse duration can be used as a reliable way to control behavioral output by scaling the number of dopamine neurons that are stimulated optogenetically.

In Chapter 2, insights from Chapter 1 are used to provide a psychophysical estimate of frequency following of midbrain dopamine neurons. Methodology used to estimate the firing fidelity of electrically stimulated MFB axons was adapted (Solomon et al., 2015) in this experiment. Pulse duration was used as a spatial parameter that was traded off against pulse frequency, a temporal parameter that determines the rate of induced firing. The aim of this experiment was to provide a psychophysical measurement of frequency following of midbrain dopamine neurons. Together, Chapters 1 and 2 were intended to showcase the utility of within subject designs in optogenetics and the customization of stimulation parameters for each subject.

CHAPTER 2:

ESTIMATION OF FIRING FIDELITY OF MIDBRAIN DOPAMINE NEURONS BY PSYCHOPHYSICAL INFERENCE

Abstract

The midbrain dopamine system is involved in the regulation of learning, motivation, and cognitive functioning. Despite its importance, the firing fidelity of midbrain dopamine neurons is not fully understood. Here, optogenetic intracranial self-stimulation (ICSS) is used to provide a practical, psychophysical measurement of midbrain dopamine neurons' frequency following. The firing rate of stimulated dopamine neurons is traded off across the volume of activated dopamine cells. The firing fidelity of midbrain dopamine neurons scaled up to an upper pulse frequency limit (28 Hz for 1 subject and 40 Hz for 5 subjects). Pulse frequencies beyond this limit either did not improve (2 subjects) or worsened (4 subjects) the behavioral effectiveness of the stimulation. The physiological upper limit of firing in midbrain dopamine neurons and the effective range of their excitability using channelrhodopsin-2 is described. It is shown that the aggregate firing rate induced in optogenetically stimulated dopamine neurons is the key variable determining the behavioral effectiveness of optogenetic stimulation. This is in line with the counter model that describes the spatiotemporal integration of the neural signal induced by rewarding electrical ICSS. Lastly, the variability of behavioral outputs caused by optogenetic stimulation of the same parameters across subjects is exemplified. The importance of within-subject designs or group stratification based on behavioral outcomes (e.g., magnitude of induced operant behavior) in optogenetic experiments is discussed. Practical information for optogenetic parameter selection, experimental design, and computational modeling of the reward system is provided.

1. Introduction

The midbrain dopamine system is involved in several brain disorders and critical functions including motivation, appetitive and aversive learning, motor control, and cognitive functioning (Bissonette & Roesch, 2015; Roeper, 2013). Despite the long-standing interest in these neurons, describing a definitive, mechanistic understanding of their in-vivo firing continues to be challenging (Otomo et al., 2020). Adding to this effort, this paper focuses on firing fidelity, an electrophysiological characteristic that can provide useful guidelines for using neuromodulation and computational modeling to study midbrain dopamine neurons. To this end, we used a free-operant optogenetic paradigm that relies on psychophysical inference to estimate the in-vivo firing fidelity of midbrain dopamine neurons.

It has been supported that midbrain dopamine neurons have fine, unmyelinated axons, slow spontaneous firing rates (~1-8Hz), broad action potentials, large sag currents, and slow recovery from refractoriness (Yim & Mogenson, 1980; Grace & Onn, 1989; German, Dalsass & Kiser, 1980; Feltz & Albe-Fessard, 1972; Anderson, Fatigati & Rompre, 1996). In in-vivo preparations, the slow pacemaking activity of these neurons is thought to be interspersed with occasional, short burst (>15Hz) - pause firing patterns (Grace & Bunney, 1984; Paladini & Roeper, 2014; Mohebi et al., 2019; McCutcheon et al., 2012a; McCutcheon et al., 2012b). Average estimates of the maximal firing rate of midbrain dopamine neurons range approximately from 10 to 41 Hz, while maximal recorded rate in-vivo firing was previously thought to reach up to 50 Hz (Hyland,

Reynolds, Hay, Perk, & Miller, 2002; Tepper, Marting, & Anderson, 1995; Paladini, Iribe, & Tepper, 1999; Otomo et al., 2020; Knowlton et al., 2021). Electrophysiologically district populations of dopamine neurons have been recently described, which separated based on features that include their maximal firing rate into atypical (firing up to approximately 35 Hz) and conventional (firing up to approximately 10 Hz) sub-populations (Knowlton et al., 2021; Otomo et al., 2020). Updating the conception of the maximal firing rate of midbrain dopamine neurons, Otomo and colleagues (2020) conducted in-vivo patch-clamp recordings of 110 dopamine neurons and reported outlier values of short burst firing that peaked over 80 Hz in some of the recorded neurons (Otomo et al., 2020). Seen together, midbrain dopamine neurons appear to be separated in phenomenological groups that differ in electrophysiological characteristics.

There is no clear consensus about the frequency following of midbrain dopamine neurons from studies using optogenetics. Lohani and colleagues (2019) documented weak frequency following for 100 Hz stimulation, suggesting that firing fidelity breaks down at lower pulse frequencies. Two other groups reported high firing fidelity to 50 Hz stimulation (Cohen et al., 2012; Ilango et al., 2014), whereas another two groups found that frequency following declined below 50% at 40-50 Hz stimulation (Tsai et al., 2009; Witten et al., 2011). Complicating the interpretation of these findings, these studies included a set number of stimulation pulses delivered at different pulse frequencies, which created conditions with different stimulation train durations. The rewarding effect of the stimulation depends both on pulse frequency and train duration (Sonnenschein, Conover & Shizgal, 2003). Since train duration and pulse frequency were allowed to

covary in these experiments, the estimate of frequency following in these studies is ambiguous.

In this experiment, we adapted an operant methodology previously used to describe the firing fidelity of medial forebrain bundle (MFB) axons that support self-stimulation (Somolon et al., 2015). By using a fixed stimulation train duration to trade off current (a spatial variable scaling the number of fired neurons) against pulse frequency (a variable scaling number of times the neurons are fired over time) this experiment allowed for a direct psychophysical inference of firing fidelity. This way, a given criterion of operant behaviour was established when the current was reduced (i.e., fewer neurons fired) and the stimulation frequency was increased (i.e., firing a fixed set of neurons faster) proportionately.

Here, we estimated the firing fidelity of ChannelRhodopsin-2 (ChR-2) transfected dopamine neurons. We held the stimulation train duration constant and traded off the number of fired dopamine neurons by varying the pulse duration (Pallikaras et al., 2022) against the number of induced spikes by varying the pulse frequency. We found that the behavioral effectiveness of the stimulation, our measure of firing fidelity, increased lawfully over a useful range of pulse frequencies (starting at 7 Hz) until reaching an upper limit (28 Hz for 1 subject; 40 Hz for 5 subjects). Beyond that limit, firing fidelity broke down as higher pulse frequencies failed to improve the behavioral effectiveness of the stimulation. Notably, in 4/6 subjects higher tested pulse frequencies (>40 Hz; 50 Hz to 79 Hz) reduced the behavioral effectiveness of the stimulation. These findings

provide an estimate of the effective range of frequency following of ChR-2-transfected midbrain dopamine neurons as well as an estimate of their maximal firing rate.

2. Methods

Methodology used is described in more detail previously (Pallikaras et al., 2022).

2.1. Subjects

Subjects were 6 male, TH:Cre, Long-Evans rats weighing ~325-475 g at surgery. Rats were housed singly on a reverse 12 h light cycle, and they had free access to chow (Envigo #2014). Rats were weighed daily. Rats that were deemed overweight for their age (Sengupta, 2013) were put on a weight-maintenance feeding schedule. Procedures for animal care were approved by Concordia University Animal Research Ethics Committee (Protocol #: 30000302) and adhered to standards of the Canadian Council on Animal Care.

2.2. Surgery

Surgical procedures are described in detail elsewhere (Pallikaras et al., 2022). Rats were anesthetized (IP ketamine; 87 mg/kg/xylazine; 13 mg/kg; CDMV) and affixed in a stereotaxic frame for injection of the viral vector (AAV5-DIO-ChR2-EYFP; University of North Carolina) via a microinfusion pump (Kent Scientific). The injector was lowered

in the VTA (AP: -5.5 & -6.2, ML: ± 0.7, DV: -7.4 & -8.4), and 1 µl of viral vector was infused at each site at a rate of 0.1 µl/min. Optical fiber implants (Thorlabs; 300 µm diameter, 0.39 NA) were chronically affixed above the VTA (AP: -5.8, ML: ± 0.7, DV: -7.7) using dental cement.

2.3. Apparatus

Six operant boxes with house lights and retractable levers equipped with a cue light above them were used. The house light flashed once per second during the inter-trial interval (ITI), and the cue light was on while the rats pressed the lever. The laser (462 nm; SLOC) was connected (300 µm diameter fiber cable, 0.39 NA) to a single-channel commutator (FRJ_1x1_FC-FC; Doric Lenses) mounted above the box. An optical-fiber cable (Trujillo-Pisanty et al., 2015; 300 µm diameter, 0.39 NA) was connected to the implant via a ceramic sleeve. Before each session, optical power was set using a power meter (PM100D; Thorlabs).

2.4. Self-Stimulation Training

Four weeks after surgery, we trained subjects to self-stimulate using an FR-1 schedule. Stimulation trains, 1 s in duration, consisted of 5 ms pulses delivered at 40 Hz. Optical power was adjusted between 20-40 mW depending on subject response.

2.5. Cumulative Hold-Down Schedule of Reinforcement

Subsequently, rats were trained to hold down an operant lever to trigger stimulation (Breton et al., 2009). Stimulation was delivered each time the cumulative hold-down time reached 2 s. After each stimulation train was triggered, the lever was retracted for 1.5 s, and the trial timer was paused until it re-extended. The dependent variable was time allocation: the proportion of total trial time spent pressing the lever. Pauses between lever presses that were shorter than 1 s were measured as time allocation. During such instances, rats tend to hold their paws on or around the lever (Breton et al., 2009).

2.6. Pulse Duration Sweeps

A sweep was a set of 10 trials over which the pulse duration was decreased systematically (“swept”) while all other stimulation parameters were constant. Trials lasted for 50 s and were preceded by a 10 s ITI. At the 8th second of the ITI, a priming stimulation train, identical to the stimulation train available on the first trial of the sweep, was delivered. The pulse duration was fixed within trials. On the first two trials of each sweep, pulse duration was set to the longest value tested in that session, and then it was reduced in eight proportional steps from the 3rd to the 10th trial. The range of pulse durations was customized for each subject and condition. Sessions consisted of 10 pulse-duration sweeps and lasted approximately 2 h. The entire first sweep and the first

trial of all subsequent sweeps were considered warm-ups, and their data were not analyzed. We tested conditions at a wide range of pulse frequencies (between 7 Hz - 79 Hz). Five sessions (45 sweeps) were run in every pulse frequency condition.

2.7. Statistical Analysis

On account of random variation in the position of individual operant curves, graphs of averaged curves have a shallower slope than the slopes of curves depicting individual sweeps (Hernandez et al., 2010). To minimize this distortion, we fit a function to the time allocation values for each sweep and averaged its parameters (Hernandez et al., 2010). Although time allocation varied lawfully with pulse duration on the great majority of sweeps, some aberrant sweeps were detected. We filtered the dataset by eliminating sweeps in which the average time allocation on the first four trials was not higher than the average time allocation on the last four trials by at least 20%. Sensitivity to outliers was reduced by a robust fitting method based on Tukey's bisquare estimator (Tukey, J.W., 1960).

The following four-parameter equation was fitted:

$$(TA - TA_{min}) / (TA_{max} - TA_{min}) = 1 / [1 + \exp\{-slp \times (\log_{10}(d) - loc)\}]$$

Where:

d: Pulse duration.

loc: Value of the location parameter.

TA: Time allocation.

TA_{min}: Minimal time allocation.

TA_{max}: Maximal time allocation.

slp: Slope parameter determining the steepness of the rise.

Descriptive statistics (means and 95% confidence intervals) were generated for the fitted parameters (TA_{max}, TA_{min}, slp, and loc). Fitted averaged curves were deemed to have shifted between optical-power conditions when the 95% confidence intervals around their location parameters did not overlap. All data-analysis and graphing was carried out in Matlab (MathWorks).

2.8. Histology

Following data collection, subjects were anesthetized (sodium pentobarbital; 200 mg/kg IP; CDMV) and perfused transcardially using saline and 4% paraformaldehyde. Brains were post-fixed for 24 hours in 4% paraformaldehyde and subsequently immersed in phosphate-buffered solutions of 15% and 30% sucrose until they sank. Brains were stored at -80° C and a cryostat was used to slice 40 µm coronal sections through the VTA. Slices were mounted on glass slides and stained with DAPI (product number: R37605l; ThermoFisher). Native fluorescence of eYFP revealed expression of ChR2 in dopamine neurons. Histology images were captured with a Nikon Eclipse TiE

microscope. Figure 1 depicts an exemplar histology image and implant placements for all subjects.

3. Results

3.1 Time Allocation as a Function of Pulse Duration

As pulse duration increased, time allocation grew in a sigmoidal fashion. Single session data for a sample subject (ELOP18; 40 Hz condition) are displayed in panel A of Figure 2. The average operant curve for this condition is shown in Panel B (green diamonds). The curve constructed by averaging the parameters of the 45 individual fitted sweeps for this condition is shown in red. The shaded red band represents the 95% confidence interval around the location parameter. Tables with the fitted parameter values for the entire dataset are provided in Appendix A.

3.2 Pulse Frequency Trades off with Pulse Duration

The results show that increasing pulse frequency effected a systematic leftward shift on the time-allocation curves along the pulse-duration axis (Figure 3). As a result, a given time allocation may be obtained by a stimulation train composed of brief, high-frequency pulses and a stimulation train composed of longer, lower-frequency pulses. Further, we detected a ceiling on the pulse frequency that traded off with pulse duration to hold time allocation constant; incrementing the pulse frequency beyond 28 Hz (1 subject) or 40 Hz (5 subjects) did not produce leftward shifts in the operant curves.

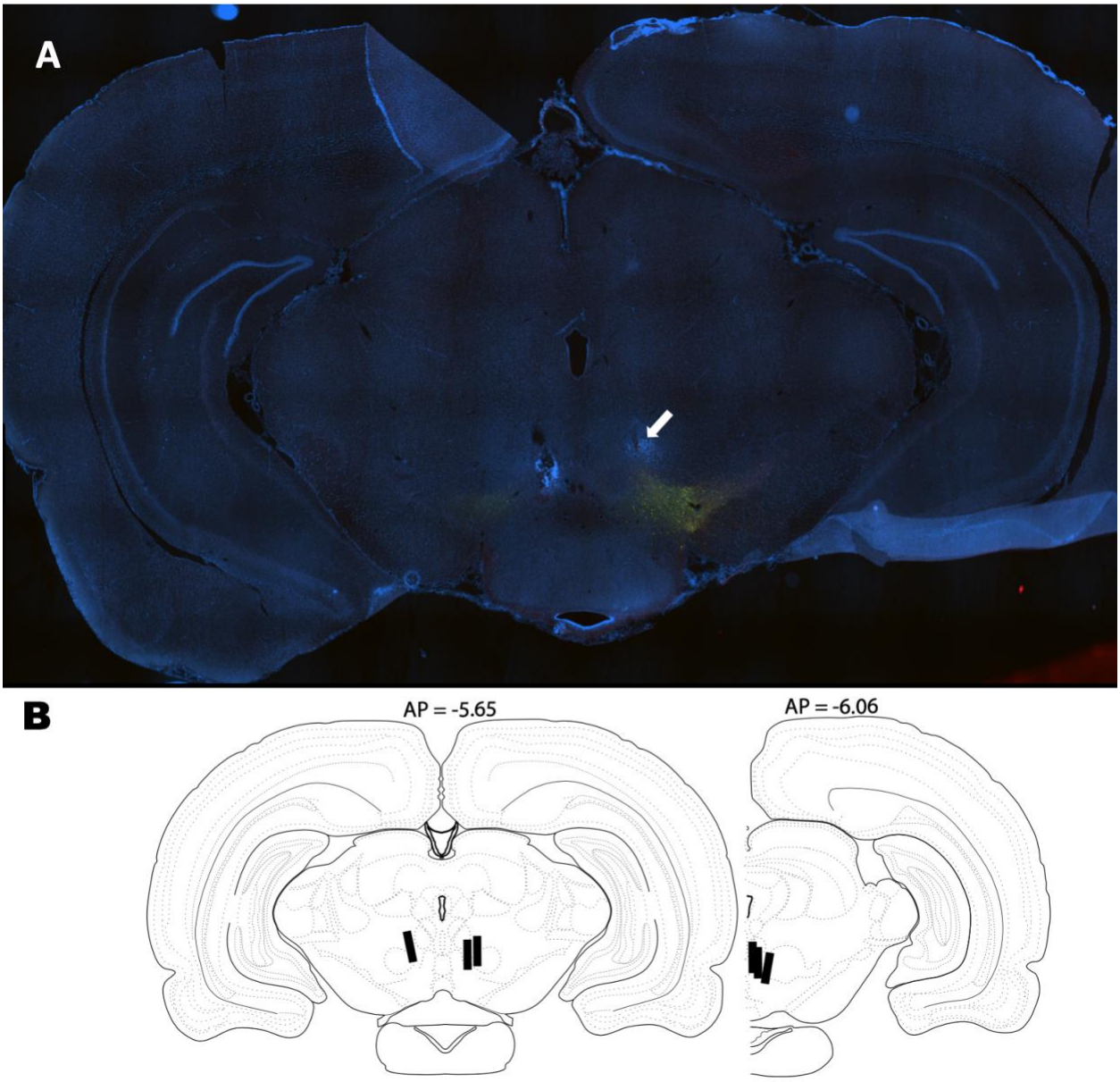


Figure 1. Histology. **A:** Histological image for subject OP18; eYFP expression (green) shown along with DAPI (blue) for anatomical reference. Estimated fiber-tip location: white arrow. **B:** Black lines indicate implant placements for all subjects. Adapted from Swanson (2018).

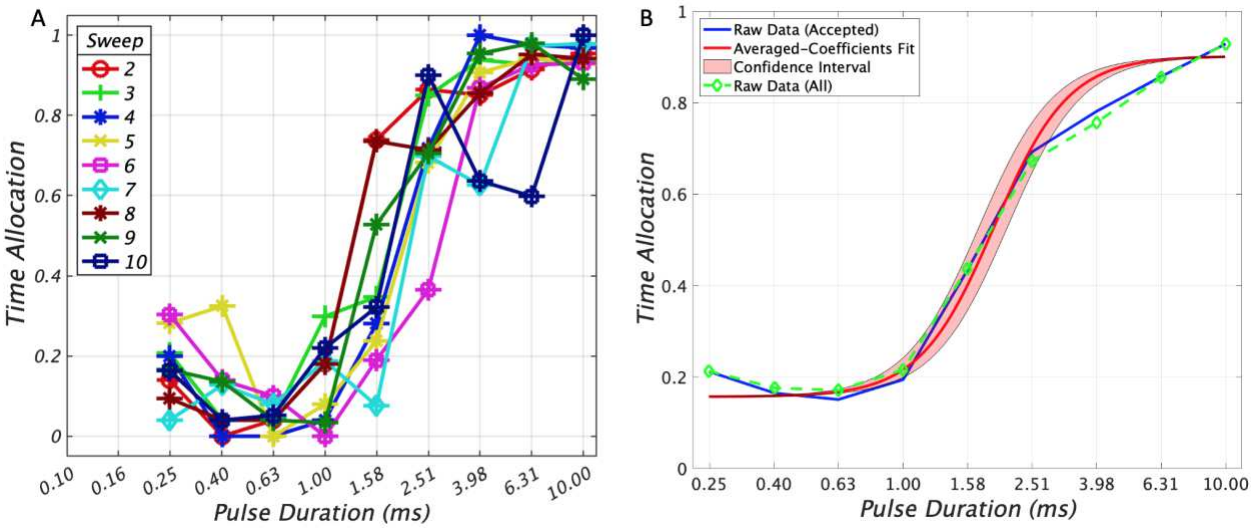
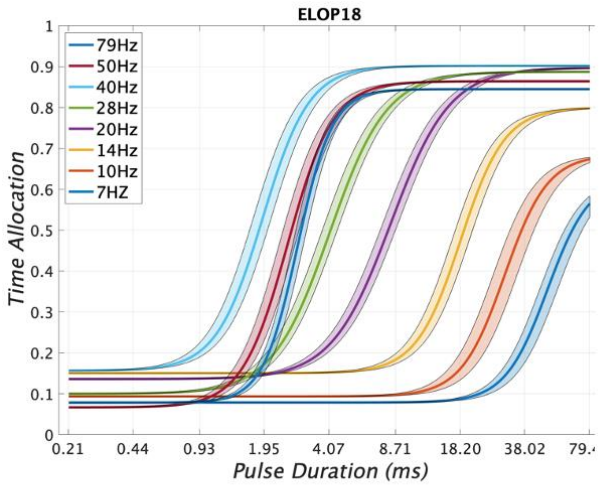
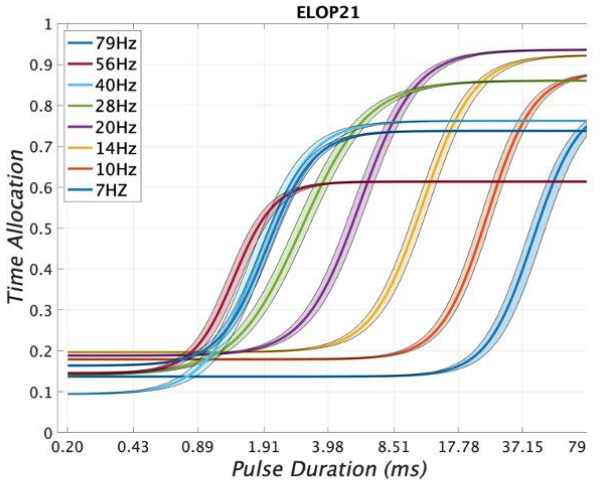
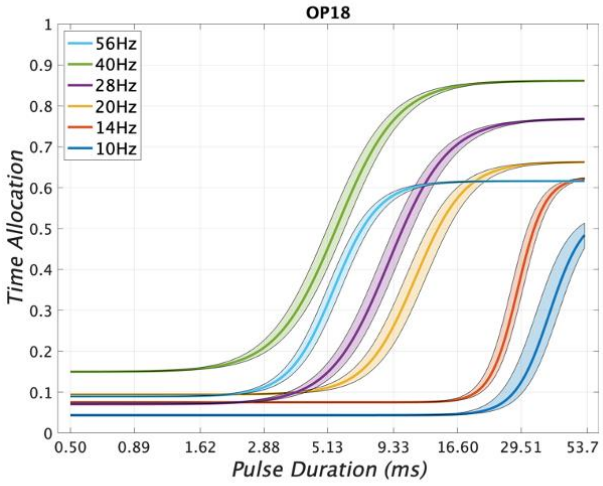
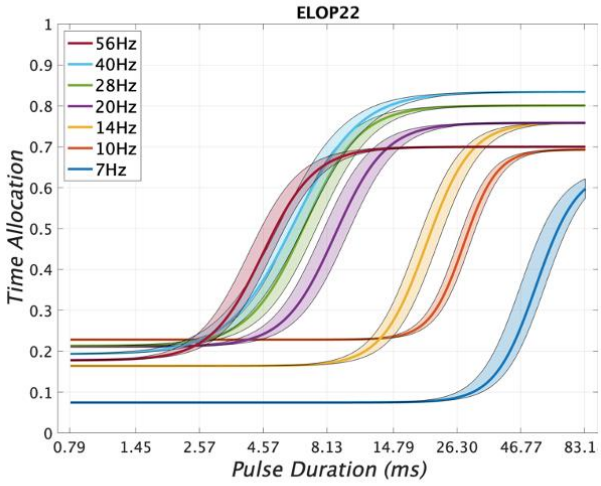


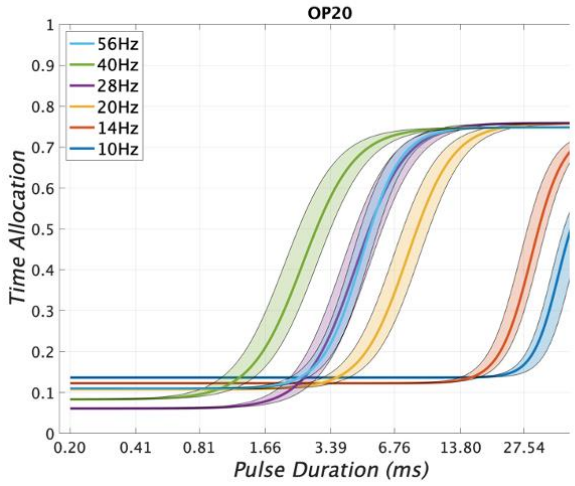
Figure 2. Pulse-duration sweep data for subject ELOP18 (pulse frequency: 40 Hz). **A:** Single-session data depicting individual time-allocation-versus-pulse-duration curves. **B:** Conventional averaging of time allocation over five test sessions (45 sweeps; green line). Curve created by averaging parameters of fitted sigmoidal functions (red line) with 95% confidence interval surrounding the location parameter (shaded band).


ELOP18
79Hz
50Hz
40Hz
28Hz
20Hz
14Hz
10Hz
7HZ
Time Allocation
Pulse Duration (ms)


ELOP21
79Hz
56Hz
40Hz
28Hz
20Hz
14Hz
10Hz
7HZ
Time Allocation
Pulse Duration (ms)


OP18
56Hz
40Hz
28Hz
20Hz
14Hz
10Hz
Time Allocation
Pulse Duration (ms)


ELOP22
56Hz
40Hz
28Hz
20Hz
14Hz
10Hz
7Hz
Time Allocation
Pulse Duration (ms)


OP20
56Hz
40Hz
28Hz
20Hz
14Hz
10Hz
Time Allocation
Pulse Duration (ms)

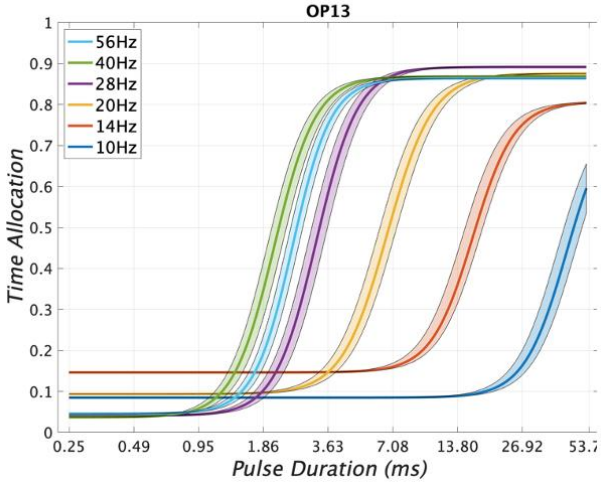

OP13
56Hz
40Hz
28Hz
20Hz
14Hz
10Hz
Time Allocation
Pulse Duration (ms)

***Figure 3*.** Fitted time-allocation-versus-pulse-duration curves for each optical power for all subjects. There is a systematic trade-off between pulse frequency and pulse duration that breaks down at 28 Hz for 1 subject (ELOP22) and at 40 Hz for 5 subjects. Higher frequencies (50 Hz - 79 Hz) were either ineffective at improving operant behavior (for 2 subjects) or they reduced the behavioral effectiveness of the stimulation (for 4 subjects).

Higher frequencies (>40 Hz; 50 Hz to 79 Hz) produced a rightward shift in the operant curves of 5 out of 6 subjects.

4. Discussion

This experiment estimated the frequency following of ChR-2-transfected VTA dopamine neurons using psychophysical inference. We previously established that varying the optical pulse duration scales reliably the number of dopamine neurons activated by optogenetic stimulation (Pallikaras et al., 2022). Here, we estimated firing fidelity of midbrain dopamine neurons by trading-off the number of stimulated neurons (by varying the pulse duration) against their firing rate (by varying the pulse frequency; between 7 Hz and 79 Hz). We found reliable evidence of frequency following up to an upper limit (28 Hz for 1 subject and 40 Hz for 5 subjects). Beyond this limit, increasing the pulse frequency either did not improve (2 rats) or worsened (4 rats) the behavioral effectiveness of the stimulation. These findings add to our understanding of the physiological upper limit of firing of midbrain dopamine neurons and the effective range of their excitability using ChR-2.

Studies on midbrain dopamine neurons have reported electrophysiological differences between in-vivo and in-vitro preparations. To facilitate the external validity of links between brain and behaviour, researchers have suggested that behavioral measurements should be central in our paradigms (Branchi, 2022; Krakauer et al.,

2017). Here, we add to this effort by estimating the firing fidelity of midbrain dopamine neurons using a free-operant trade-off design that consists of repeated, long testing sessions. Past studies using psychophysical inference have suggested that, for a stimulation of a given duration, the intensity of rewarding brain stimulation is determined by the aggregate firing rate of the targeted substrate (Gallistel, 1976). This theory, called the counter model of spatiotemporal integration, was first developed in experiments studying brain regions that support electrical intracranial self-stimulation. If the rewarding effect of optogenetic stimulation of dopamine neurons also depends on the induced aggregate firing rate of dopamine cells, then, a given level of operant behaviour represents the aggregate rate of action potentials induced by the stimulation. Indeed, increasing the pulse frequency results in greater dopamine release in the nucleus accumbens (Adamantis et al., 2011; Covey & Cheer, 2019), an effect suggestive of greater neuronal activation. In this paper, we add to previous findings (Pallikaras et al., 2022, Trujillo- Pisanty et al., 2020) supporting that a counter-like model extends to principles determining the rewarding effect caused by optogenetic excitation of midbrain dopamine neurons. In this experiment, the trade-off between pulse frequency and pulse duration broke down or decelerated after an upper pulse frequency value (between 28 Hz - 40 Hz). Notably, in four rats, increasing the pulse frequency beyond 40Hz reduced the behavioral effectiveness of the stimulation. According to the counter model, for the effectiveness of the stimulation to stagnate or worsen, a lower aggregate firing rate had to be induced in the stimulated substrate at those higher frequencies.

This upper limit of induced aggregate firing rate may be understood in light of two factors: the physiological upper firing limit of midbrain dopamine neurons and the biophysical limitations of ChR-2. The breakdown of frequency following at frequencies above 28-40 Hz is in line with past electrophysiological findings, placing the upper limit of firing of these cells within this range (Hyland et al., 2002; Tepper et al., 1995; Paladini et al., 1999). In the case of optogenetic stimulation, a subset of opsin-expressing dopamine neurons is activated. As prior studies have shown (Knowlton et al., 2021; Otomo et al., 2020), phenomenological groups of dopamine neurons may have different upper firing frequency limits. As a result, the different frequencies at which we detected a limit in the present study may be a consequence of the noise in implant placements amongst the subjects. That is, due to the spatial distribution of dopamine cells with different maximal firing rate, implant placement may affect the aggregate maximal firing rate of the stimulated neurons that produce operant behavior.

Another contributing factor to the upper limit of frequency following we documented here are the kinetic properties of ChR2. We used ChR2 in this experiment as a means of activating dopamine neurons due to the widespread use of this opsin in neuroscience. The ability of ChR2 to produce more action potentials initially is thought to scale linearly with increases in pulse frequency, and it starts to level off as stimulation frequency continues to increase. For example, with a 5 ms pulse duration, neurons transfected with ChR2 start showing a dip in the percentage of successfully elicited spikes from 20 Hz onwards (Fiorillo, 2011). Extensions of the present study can test opsins with faster kinetic profiles to evaluate whether the upper cut-off for the effective

range of pulse frequencies documented here would be shifted to a higher upper limit. Further, extensions of this study with concurrent neurochemical measurement (e.g., via fiber photometry) in the dopamine terminals can complement the behavioral findings reported here.

In summary, the results of this trade-off experiment support that the intensity of the rewarding effect of optogenetic intracranial self-stimulation depends on the aggregate firing rate of dopamine neurons. The effective range of the trade-off between optical pulse duration and stimulation frequency in this free-operant design extended from 7 Hz to 28 Hz - 40 Hz. These findings can aid the understanding of the physiological upper limit of the firing rate in midbrain dopamine neurons that underlie ChR-2-mediated operant behaviour. In turn, this dataset offers important information for computational modeling of the reward system.

Preface to Chapter 3

In the first two Chapters, operant methods were used to document psychophysical curves describing trade-offs between optical stimulation parameters. It was supported that the key variable determining the behavioral outcome (i.e., reward seeking) of optical stimulation is the induced firing rate in stimulated midbrain dopamine neurons. These experiments are added to other investigations of psychophysical mapping of stimulation parameters across stimulation sites (e.g., VTA, MFB) and techniques (e.g., optogenetics, electrical stimulation). The psychophysical method has also been used to study the biophysical characteristics of stimulated substrates as well as tools used in neuromodulation, such as opsins. Insights from psychophysical experiments, such as the ones summarized in the first two Chapters, can be used to inform stimulation parameter optimization in the clinical application of brain stimulation and to provide hypotheses about its mechanisms of action.

Deep brain stimulation is an experimental treatment that has been applied in refractory depression. Amongst the several brain sites tested for antidepressant effects is the MFB, a region featured extensively in BSR experiments. Although customization of stimulation parameters is an established practice in deep brain stimulation, the psychophysical method is not commonly used and the stimulation is typically constantly on, analogously to stimulation for movement disorders. The non-specificity of electrical stimulation poses the same challenges here as in BSR in regard to mapping the substrates involved in measurable outcomes (e.g., antidepressant efficacy). In Chapter

3, insights from BSR studies are drawn to propose a structural and a functional hypothesis for the antidepressant effect of MFB stimulation. Translational links between BSR experiments and the clinical application of deep brain stimulation are discussed.

CHAPTER 3:

THE CONVERGENCE MODEL OF BRAIN REWARD CIRCUITRY: IMPLICATIONS FOR RELIEF OF TREATMENT-RESISTANT DEPRESSION BY DEEP-BRAIN STIMULATION OF THE MEDIAL FOREBRAIN BUNDLE

Vasilios Pallikaras & Peter Shizgal

Citation: Frontiers in Behavioral Neuroscience (2022)

Abstract

Deep brain stimulation of the medial forebrain bundle (MFB) can provide effective, enduring relief of treatment-resistant depression. Panksepp provided an explanatory framework: the MFB constitutes the core of the neural circuitry subserving the anticipation and pursuit of rewards: the “SEEKING” system. On that view, the SEEKING system is hypoactive in depressed individuals; background electrical stimulation of the MFB alleviates symptoms by normalizing activity. Panksepp attributed intracranial self-stimulation to excitation of the SEEKING system in which the ascending projections of midbrain dopamine neurons are an essential component. In parallel with Panksepp’s qualitative work, intracranial self-stimulation has long been studied quantitatively by psychophysical means. That work argues that the predominant directly stimulated substrate for MFB self-stimulation are myelinated, non-dopaminergic fibers, more readily excited by brief electrical current pulses than the thin, unmyelinated axons of the midbrain dopamine neurons. The series-circuit hypothesis reconciles this view with the evidence implicating dopamine in MFB self-stimulation as follows: direct activation of myelinated MFB fibers is rewarding due to their trans-synaptic activation of midbrain dopamine neurons. A recent study in which rats worked for optogenetic stimulation of midbrain dopamine neurons challenges the series-circuit hypothesis and provides a new model of intracranial self-stimulation in which the myelinated non-dopaminergic neurons and the midbrain dopamine projections access the behavioral final common path for reward seeking via separate, converging routes. We explore the potential implications of this convergence model for the interpretation of the antidepressant effect of MFB stimulation. We also discuss the consistent finding that psychomotor stimulants,

which boost dopaminergic neurotransmission, fail to provide a monotherapy for depression. We propose that non-dopaminergic MFB components may contribute to the therapeutic effect in parallel to, in synergy with, or even instead of, a dopaminergic component.

Keywords: intracranial self-stimulation, dopamine, psychomotor stimulants, affective neuroscience, psychophysical inference

1. Introduction

Major depressive disorder is among the most common mental illnesses, affecting 1 in 20 adults worldwide, and a leading cause of disability and suicide (Mathers, 2016; Friedrich, 2017). Depressive symptomatology is episodic and recurrent with lifetime relapse rates of 50%; some 80% of individuals who have had two major depressive episodes will experience at least a third (Burcusa & Iacono, 2007). Although multiple antidepressant interventions exist, about 3 in 10 individuals with major depressive disorder suffer from chronic symptoms that are unimproved after several rounds of conventional treatment (Gaynes et al., 2020). This condition, which entails serious societal and personal ramifications, is called treatment resistant depression. In comparison to non-resistant depression, treatment-resistant depression is linked to higher hospitalizations and healthcare costs and to lower quality of life (Bergfeld et al., 2018; Gaynes et al., 2020). Importantly, the suicide attempt rate for treatment-resistant depression is at least double the lifetime rate in non-resistant depression and 15 times the rate in the normal population (Bernal et al., 2007).

In an effort to alleviate treatment-resistant depression, experimental interventions are often tried. A class of such interventions focuses on neuromodulation. Among them, deep brain stimulation is a neurosurgical approach that has shown promising clinical efficacy for treatment-resistant depression (Sironi, 2011; Döbrössy et al., 2021). At least 11 brain areas have been studied as candidate targets for relief of treatment-resistant depression by deep-brain stimulation (Drobisz & Damborská, 2019). Particularly effective outcomes have been obtained from electrodes aimed at the medial forebrain bundle (MFB).

In the rat, the MFB is a major, complex, and heterogeneous fiber system that consists of at least 50 components (Nieuwenhuys et al., 1982). Its constituents span a long segment of the neural axis between the basal forebrain and the hindbrain. Debate continues about the structure and appropriate nomenclature of the analogous system in humans and nonhuman primates (Coenen et al., 2009a, 2009b, 2011, 2012, 2021; Haynes & Haber, 2013; Haber et al., 2021, 2022). In this paper, we will refer to the specific MFB stimulation site that has shown antidepressant efficacy in the deep-brain stimulation studies carried out by Coenen et al. (2020) [MNI (Montreal Neurological Institute)/ACPC (anterior commissure – posterior commissure) system x = 6.5 mm, y = –2.5 mm (posterior MCP), z = –5 mm (below ACPC)] as “MFB.”

Several studies and research teams have shown that bilateral deep-brain stimulation of the MFB causes a strong, immediate, and enduring therapeutic effect in a substantial proportion of patients suffering from treatment-resistant depression (Schlaepfer et al., 2013; Fenoy et al., 2016, 2021; Bewernick et al., 2017; Coenen et al., 2019). Case reports document a swift relapse of depressive symptoms following discontinuation of MFB stimulation and swift remission once stimulation was reinstated (Kilian et al., 2019). However, as in studies focusing on other deep brain stimulation brain targets for relief of depression, prolonged randomized controlled trials on MFB deep brain stimulation have not yet shown clear differences between sham stimulation and deep brain stimulation (Dougherty et al., 2015; Coenen et al., 2019). The putative causes of these failures continue to be debated (Coenen et al., 2019) while reports of successful remediation of symptoms in small cohorts continue to appear (Fenoy et al., 2021).

Preclinical laboratory-animal studies can make use of powerful, invasive methods crucial to linking changes in behavior and psychological processes to the underlying neural circuitry, thereby shedding light on the mechanisms underlying successful clinical interventions. A focus in such research on core psychological processes that have been conserved over the course of mammalian evolution can generate new approaches to intervention, such as development of novel pharmacological agents, behavioral therapies, and interventions such as deep brain stimulation (Coenen et al., 2011; Panksepp & Yovell, 2014; Panksepp, 2016).

In his pioneering work in affective neuroscience, Panksepp proposed a set of highly conserved, “primal emotional systems” (Panksepp & Yovell, 2014). He used the label “SEEKING” to refer to the system mediating investigative behaviors, approach, and “appetitive eagerness:” the highly motivating anticipation of hedonically positive events. He strongly emphasized the anticipatory quality of the emotion generated by activation of the SEEKING system and proposed that its neural substrate differs from that of the coveted hedonic experience.

In Panksepp’s portrayal, the MFB constitutes the core of the SEEKING system. The primary evidence for this is the fact that animals willingly and eagerly turn on electrical stimulation delivered via electrodes arrayed all along the MFB (Panksepp & Yovell, 2014), i.e., they engage in intracranial self-stimulation. Panksepp recognized the neuroanatomical and neurochemical heterogeneity of the MFB, but he and his colleagues ascribed indispensable status to the ascending projections of the midbrain dopamine neurons, which they viewed as energizing the SEEKING system. In that way, the dopamine neurons engage the SEEKING system in intracranial self-stimulation

(Ikemoto & Panksepp, 1999), addiction (Alcaro et al., 2007) and relief of depression (Panksepp & Yovell, 2014). Panksepp co-authored several of the early reports documenting the antidepressant effect of MFB stimulation (Coenen et al., 2009b, 2011, 2012), and his portrayal of the SEEKING system provided the initial theoretical foundation for interpreting this effect.

The qualitative approach championed by Panksepp has been paralleled by the development of quantitative methods for measuring reward-seeking behavior, characterizing the underlying neural circuitry, and modeling how the volley of action potentials triggered by MFB stimulation is translated into an enduring record of reward intensity and subsequent pursuit of additional stimulation (Gallistel et al., 1981; Yeomans, 1990; Simmons & Gallistel, 1994; Trujillo-Pisanty et al., 2020). That approach, and the findings and insights it has generated, have yet to be addressed in the literature on the SEEKING system and its role in relief of treatment-resistant depression by deep-brain stimulation. We begin an attempt to fill that lacuna here.

Extension of the quantitative approach to rewarding effects produced by specific optogenetic activation of midbrain dopamine neurons has led to a new view of the circuitry underlying intracranial self-stimulation (Trujillo-Pisanty et al., 2020). On that view, parallel processing channels convey to the behavioral final-common path signals arising in non-dopaminergic MFB fibers and in the ascending projections of midbrain dopamine neurons. We summarize that new view below and explore its potential implications for explaining the relief of treatment-resistant depression by MFB stimulation. Before doing so, we situate the study of intracranial self-stimulation within the context of animal models of depression, we review aspects of depression germane

to the question of how MFB stimulation provides relief, and we discuss how research on the effects of such stimulation in rodents could provide insight into the mechanism underlying the antidepressant effect in humans.

1.2. Animal Models of Depression

Behavioral models of depression in laboratory animals often entail exposure to stress followed by measures of consummatory behavior, exploration, disruption of sleep or comfort, and resistance to survival threats (Yan et al., 2010). These measures have been proposed as indices of the putative effectiveness of antidepressant manipulations. Although animal models of depression are widely used, the external and construct validity of such modeling of psychopathology in laboratory animals has been questioned (Molendijk & de Kloet, 2015; Pound & Ritskes-Hoitinga, 2018).

In our view, animals working relentlessly for rewarding stimulation of the MFB and choosing to pursue such stimulation in lieu of competing natural rewards manifest the antithesis of the blunted motivation characterizing depression. Thus, we argue that much may be learned about the core psychological processes underlying depression, their neural substrates, and the therapeutic effect of deep-brain stimulation from research on reward-seeking in laboratory animals in general, and on intracranial self-stimulation in particular. On that view, intracranial self-stimulation provides an animal model amenable to powerful, invasive research methods for investigating psychological processes at the core of depressive symptomatology and for linking these processes to

their neural substrates. The processes at the core of the current account are motivational and decisional anhedonia (Zald & Treadway, 2017).

2. Depression: Symptoms, Proposed Mechanisms, And Interventions

2.1. Anhedonia in Depression

The most widely used psychiatric diagnostic manual lists anhedonia as one the two cardinal depressive symptoms (American Psychiatric Association, 2013). Originally coined as the complete loss of pleasure (Ribot, 1897), the concept of anhedonia has broadened and differentiated (Treadway et al., 2012; Zald & Treadway, 2017). In contemporary research anhedonia is now operationalized using multiple sub-constructs. Among them are consummatory anhedonia: a reduction in hedonic perception, or enjoyment of rewards (the original definition); motivational anhedonia: a reduced capacity to expend effort in reward pursuit; and decisional anhedonia: an impairment in reward learning and goal selection (Zald & Treadway, 2017).

In studies of anhedonic sub-constructs, deficits in pleasure perception have been distinguished from deficits in motivation and expectation. For example, hedonic ratings of palatable sucrose solutions are not reliably lower in depressed patients than in never-depressed controls (Amsterdam et al., 1987; Berlin et al., 1998). This suggests that systems related to pleasure perception, at least those pertaining to taste and smell, may be unaltered in depression and that the primary deficits do not include consummatory anhedonia. In contrast, motivational and decisional anhedonia are well documented in

patients with depression (Cooper et al., 2018). They are less willing to expend effort to acquire rewards of increasing value, and they are less efficient in integrating reward-related information to guide decision making (Treadway et al., 2012; Kumar et al., 2018). Below, we illustrate how intracranial self-stimulation can be used to study motivational and decisional anhedonia. We also emphasize the difficulty of distinguishing anhedonia from other determinants of reward pursuit.

In a Bayesian, decision-theoretic account, depression entails pessimistic expectations about the value of future rewards and possible actions (Huys et al., 2015), an observation well supported by evidence (Cooper et al., 2021). As noted above, Panksepp emphasized the role of the SEEKING system in anticipation of positive outcomes rather than in ongoing hedonic experience, and he viewed hypoactivity of the system as a determinant of depression (Panksepp & Yovell, 2014). That view seems well aligned with the notions of pessimistic expectations and decisional anhedonia. Huys et al. (2015) argue that alterations in model-based, rather than model-free, learning are the most likely route to pessimistic expectations. Definitive isolation of model-based learning in rodents from other forms of learning is not easy to achieve, but it has been demonstrated convincingly (van der Meer et al., 2012; Redish, 2016; Miller et al., 2017). The experimental paradigms in question should be amenable to assessing the effect of MFB stimulation on reward expectations.

It would clearly be of great interest to determine which anhedonia constructs are impacted by MFB stimulation in patients with treatment-resistant depression. Might this be done by comparing appropriate behavioral measures acquired prior to and after the onset of stimulation or a patient-initiated pause (Kilian et al., 2019)?

2.2. Behavioral Activation

The antidepressant efficacy of behavioral activation (Dimidjian et al., 2011) appears to fit well with notions of motivational anhedonia and pessimistic reward expectations. Behavioral activation is a parsimonious psychotherapy that focuses on increasing engagement of depressed patients in reward seeking activities and decreasing engagement with punishing events. This therapy originated from the hypothesis that systematically increasing engagement in rewarding activities will alleviate depressive symptomatology (Lewinsohn, 1975). Indeed, meta-analyses of research on youth, adult, and elder populations attest to the effectiveness of behavioral activation as a monotherapy for depression (Ekers et al., 2014; Orgeta et al., 2017; Tindall et al., 2017). Moreover, a landmark component analysis study of Cognitive Behavioral Therapy for depression demonstrated that the behavioral activation component of Cognitive Behavioral Therapy is equally as effective at reducing depression symptoms as complete Cognitive Behavioral Therapy (Jacobson et al., 1996).

Although many factors have been proposed as mediators for the antidepressant effect of behavioral activation, a recent systematic review of 21 potential mediators was inconclusive (Dimidjian et al., 2011; Janssen et al., 2021). Consequently, to understand how behavioral activation works, the authors proposed that researchers should turn to the basic behavioral neuroscience of reward seeking (Janssen et al., 2021).

Here, we endorse the idea (Panksepp & Yovell, 2014) that research on intracranial self-stimulation can shed light on the motivational and decisional processes involved in the relief of depression and can contribute to identifying their neural substrates. In particular we consider whether deep-brain stimulation of the MFB achieves antidepressant efficacy by driving one or more of the multiple processes that determine the proclivity of laboratory animals to seek rewarding brain stimulation. Could MFB stimulation and behavioral activation share a common mechanism of action? Recall the evidence that hedonic responses are broadly normal in depressed patients (Amsterdam et al., 1987; Berlin et al., 1998). If so, one would expect that convincing depressed patients to perform activities that re-expose them to pleasurable experiences would correct pessimistic expectations. Could MFB stimulation provide a raised pedestal for expectations, and could this be assessed in an experimental paradigm that isolates model-based learning in rodents (e.g., van der Meer et al., 2012; Redish, 2016; Miller et al., 2017)?

2.3. Psychomotor Stimulants Appear Ineffective as a Monotherapy for Depression

The midbrain dopamine system and its direct afferents have received particular attention in the literature on the antidepressant effect of MFB deep-brain stimulation. Although the authors have been careful to acknowledge the potential contributions of non-dopaminergic neurons, the role of midbrain dopamine neurons occupies center stage in preclinical work inspired by the therapeutic effect of MFB stimulation in humans (Furlanetti et al., 2016; Dobrossy et al., 2019; Döbrössy et al., 2021). On that view, the

antidepressant effect of MFB stimulation arises, at least in part, from the *trans*-synaptic activation of midbrain dopamine neurons (Schlaepfer et al., 2013; Döbrössy et al., 2021; Fenoy et al., 2021). This proposal predicts that psychomotor stimulants will have antidepressant effects.

Psychostimulants increase the postsynaptic impact of dopamine by blocking reuptake and/or stimulating release (Kopnisky & Hyman, 2002). The effect of psychostimulants on mood and depression has been under study since the 1930s, predating the discovery of the first and second generation of antidepressants (Hegerl & Hensch, 2017). Early on, researchers concluded that stimulants do not induce reliable antidepressant effects (Hegerl & Hensch, 2017). Those early findings have since received considerable corroboration (Hegerl & Hensch, 2017). Naturalistic studies, randomized controlled trials, reviews, and meta-analyses alike have recorded mixed to negative findings for the effectiveness of several psychostimulants on depression (Candy et al., 2008; Corp et al., 2014; Rohde et al., 2020). Moreover, a pharmaceutical company has scrapped plans to seek regulatory approvals for Lisdexamfetamine (Vyvanse) as adjunct treatment for depression after two large, multi-center, stage three randomized controlled trials failed to demonstrate a clinical effect (Hegerl & Hensch, 2017).

It has been proposed that interest in the antidepressant efficacy of psychostimulants persists due to the induction of a fast-acting, but short-lived, mood elevation (Candy et al., 2008; Malhi et al., 2016). This suggests that stimulants influence mood differently than established antidepressants, which have a delayed clinical onset of days or weeks (Malhi et al., 2016; Harmer et al., 2017). Given that the mood

elevation produced by psychostimulants is typically short lived, one may wonder whether such drugs can induce a lasting mood improvement when their bioavailability is increased. An initial answer is provided by a randomized controlled trial carried out to assess the effectiveness of an extended-release formulation of methylphenidate as an adjunct medication for treatment-resistant depression (Patkar et al., 2006). No clinical efficacy was found. Further research is needed to evaluate whether the rapid-onset mood elevation inducted by psychostimulants can become sustained by drug formulation or dose regimen. In addition, it would be of interest to assess the efficacy of drugs that target the dopamine transporter more specifically than conventional psychomotor stimulants. At present, the prescription of stimulants for depression remains controversial: Clinicians are advised to use stimulants sparingly and only as additions to other antidepressant drugs for the purpose of improving arousal and tiredness (Malhi et al., 2016).

The lack of robust evidence that psychomotor stimulants are effective in relief of depression raises concerns about the attribution of the strong antidepressant effect of MFB stimulation to the indirect activation of midbrain dopamine neurons. Further research on the possible effect of dopamine agonists on depression could focus on whether these drugs exert influence on motivational and decision-making anhedonia in depressed individuals. Optogenetic methods (Yizhar et al., 2011) provide a powerful way to assess the influence of enhanced dopamine tone on reward pursuit and reward expectations in rodents. We touch on that issue in the following section, in which we discuss the rewarding effect of MFB stimulation in laboratory animals. We highlight evolving views of the role played by midbrain dopamine neurons, and we entertain the

possibility that the antidepressant effect of MFB stimulation in humans may involve non-dopaminergic components of brain reward circuitry.

3. Intracranial Self-Stimulation of The Medial Forebrain Bundle

3.1. Overview

The study of brain reward circuitry was launched by Olds and Milner's (1954) discovery of electrical, intracranial self-stimulation. Olds noticed that a rat returned repeatedly to a location in an open field where it had previously received deep-brain stimulation (Olds, 1973). An apparatus was quickly constructed to allow the rat to trigger the stimulation (Milner, 1989). The experimenters then observed a gripping spectacle: the rat worked energetically and persistently for the electrical reward. The location of the electrode tip was not verified definitively, but x-ray imaging suggested that the tip was located in or near the septal area (Milner, 1989), an important source of MFB fiber (Nieuwenhuys et al., 1982).

A flood of research findings emerged during the first decade following the seminal discovery of Olds and Milner. Among these were the results of mapping studies that documented particularly vigorous lever-pressing behavior for stimulation of the MFB (Olds and Olds, 1963). That decade also saw the introduction of pharmacological approaches (Olds, 1958b; Stein and Ray, 1960; Stein and Seifter, 1961). Refinement of behavioral methods for drawing neurochemical inferences about the reward substrate

and development of increasingly specific pharmacological agents helped build a consensus that dopamine neurons play a crucial role in the phenomenon (Franklin, 1978; Wise, 1978, 1980). In parallel, psychophysical inference of anatomical and physiological properties of the directly activated neurons underlying the rewarding effect implicated non-dopaminergic neurons with highly excitable (Yeomans, 1975, 1979), myelinated (Shizgal et al., 1980; Gallistel et al., 1981; Bielajew & Shizgal, 1982, 1986) axons that course through the MFB. The properties of these neurons contrast sharply with those of dopaminergic MFB axons, which have high thresholds to activation by extracellular electrical currents (Guyenet & Aghajanian, 1978; Yeomans et al., 1988; Anderson et al., 1996). To resolve these discrepancies, the “series-circuit” hypothesis portrays the myelinated MFB axons as a source of direct or indirect synaptic input to midbrain dopamine neurons whose excitation is responsible for the rewarding effect (Shizgal et al., 1980; Wise, 1980; Bielajew & Shizgal, 1986). The discovery that rodents also work vigorously for specific, optical excitation of opsin-expressing midbrain dopamine neurons (Adamantidis et al., 2011; Witten et al., 2011; Kim et al., 2012) appeared to fit the series-circuit hypothesis neatly: On that view, the optical input achieves directly what the electrical stimulation achieves indirectly by driving mono- or multi-synaptic inputs to midbrain dopamine neurons.

Despite its face validity, the series-circuit hypothesis has been challenged by recent findings (Trujillo-Pisanty et al., 2020) obtained by measurement of operant performance as a function of both the strength and cost of the reward. Blockade of the dopamine transporter enhanced the reward seeking behavior, but it did so differently in the cases of electrical and optical self-stimulation, thus violating predictions of the

series-circuit hypothesis. To account for both datasets, a new architecture for brain reward circuitry was proposed. In this new model, the myelinated MFB axons and the axons of the midbrain dopamine neurons give rise to reward signals that converge, via separate routes, on the behavioral final-common path for the evaluation and pursuit of rewards.

In the following subsections we summarize evidence that gave rise to the series-circuit hypothesis as well as evidence that challenges this longstanding account of brain-reward circuitry. We then discuss the implications of the convergence model for interpretation of the effect of MFB stimulation on relief of treatment-resistant depression.

3.2. Intracranial Self-Stimulation of the Medial Forebrain Bundle: Phenomenology

Rats and other laboratory animals manifest exceptionally strong motivation to earn rewarding MFB stimulation. To gain access to a lever that administers strong MFB stimulation, rats will run uphill leaping over hurdles (Edmonds & Gallistel, 1974) or endure foot-shocks administered by an electrified grid (Olds, 1958b). Provided with continuous access to rewarding MFB stimulation, rats may lever press for 24 h or more until they drop from exhaustion (Olds, 1958a). In an unpublished account (Gardner, Eliot, *personal communication*), macaques refused to surrender a manipulandum that triggered rewarding electrical stimulation of the MFB. At the conclusion of the test session, the experimenter was unable to muster sufficient strength to pry the device from the monkey's grip and had to wait patiently for the animal to relent. The problem

was solved by a mechanic on the air-force base where the experiment was conducted. He rigged a powerful motor normally used to retract the landing gear of an airplane to pull the manipulandum away from the monkey.

The extraordinary zeal, vigor, and persistence shown by laboratory animals working for rewarding MFB stimulation provides a diametrically opposed image of the weakened motivation and goal seeking shown by patients with depression. In the throes of a depressive episode, even goals that normally loom as urgent can lose their incentive power. Could hypoactivity of conserved neural circuitry subserving electrical self-stimulation in laboratory animals account for the motivational deficit burdening depressed humans? If so, it seems plausible that chronic electrical stimulation of such pathways could provide relief and that a deep understanding of the neural mechanisms underlying electrical self-stimulation could contribute further to the development of novel, effective treatments.

3.3. Contingency

In intracranial self-stimulation experiments, delivery of stimulation is contingent upon the behavior of the subject. In contrast, deep-brain stimulation of the MFB for relief of treatment-resistant depression is delivered non-contingently and typically, continuously (but see Scangos et al., 2021). Does this pose an insurmountable problem for efforts to relate these two applications of MFB stimulation? We address the issue of contingency below within the framework of the convergence model. Here, we point out

that an effect of non-contingent MFB stimulation has long been prominent in the literature on intracranial self-stimulation.

Non-contingent delivery of free stimulation trains prior to a trial increases the vigor of subsequent stimulation-seeking behavior, a phenomenon called the “priming effect (Gallistel, 1966; Edmonds & Gallistel, 1974).” Such non-contingent pretrial stimulation also exerts a powerful influence on reward selection. When a long delay intervened between delivery of non-contingent. pretrial stimulation, thirsty rats chose an arm of a T-maze that led to water, whereas after zero or short delays, they chose an alternate arm that led to a goal box in which rewarding stimulation was delivered (Deutsch et al., 1964). Such energizing and directing effects are the two defining characteristics of motivation. That they can arise following noncontingent delivery of stimulation provides a conceptual link between the intracranial self-stimulation phenomenon and the hypothesis that deep-brain stimulation of the MFB may offset motivational anhedonia. That said, the priming effect of MFB stimulation can be construed as a rapidly decaying aftereffect of exposure to strong, episodic rewards (Sax & Gallistel, 1991). If the priming effect is to be linked convincingly to the antidepressant action of MFB stimulation in humans, it must be demonstrated that continuous non-contingent stimulation can exert a motivational influence on self-stimulation performance. Below, we discuss how such an experiment could be done.

3.4. Measurement of Electrical Intracranial Self-Stimulation

Before we can explore more deeply how research on intracranial self-stimulation can inform our understanding of the mechanism by which deep brain stimulation of the MFB relieves treatment-resistant depression, we need to delve into how ICSS is measured and how conclusions about mechanisms are drawn from the behavioral observations. What do changes in the observed performance of the animal reveal about the internal variables that control goal-directed behavior and its neural underpinnings?

Experimenters adopted a simplistic “more is better” approach to the measurement of ICSS in early studies: manipulations that increased response rates were deemed, implicitly or explicitly, to have boosted the rewarding effect of the stimulation (Olds et al., 1956; Crow, 1970). Among the obstacles on which this approach founders is the sigmoidal form of the curves that relate response rates to stimulation strength. There is a ceiling on response rate, and responding will cease when stimulation strength falls too low. Thus, the magnitude of any change in response rate will depend on the level observed in the control condition, which will vary due to the scatter of stimulation sites. Moreover, response rates are subject to multiple influences in addition to the strength of the rewarding effect (Hodos & Valenstein, 1962). For example, how can overall suppression or enhancement of response rates for fixed stimulation parameters be distinguished from changes in reward?

Measurement of response rates for a fixed set of stimulation parameters has been largely replaced by the “curve-shift” method (Barry et al., 1974; Yeomans, 1975; Edmonds & Gallistel, 1977; Miliaressis et al., 1986). A measure of response vigor, such as response rate, is obtained at each of a set of stimulation strengths that drive the response variable through its full range. This traces the full psychometric curve. The

effect of a manipulation, such as the administration of a drug, is assessed by whether and how it displaces the sigmoidal psychometric curve along the axis representing stimulation strength, typically the pulse frequency. The “more is better” approach represented by the measurement of changes in the rate of responding for a fixed set of stimulation parameters is thus replaced by a “bang for the buck” approach: Manipulations that boost the effectiveness of the rewarding stimulation reduce the pulse frequency required to produce responding of a particular vigor (the response criterion), whereas manipulations that reduce rewarding effectiveness produce the opposite effect, necessitating a compensatory increase in pulse frequency in order to restore responding to its initial level. The sigmoidal curves are roughly parallel when plotted against the logarithm of the stimulation strength. Thus, the magnitude of the observed shift is independent of the response criterion.

Proponents of the curve-shift method have argued that it removes the ambiguity inherent in interpretation of changes in response-rate measures (Carlezon & Chartoff, 2007). On that view, lateral displacements of the psychometric curve reflect changes in reward effectiveness, whereas changes in the vertical scaling of the curve reflect changes in motoric capacity. Alas, that hopeful formulation is not well supported by evidence: adding weight to the lever produces both vertical rescaling and lateral shifts (Frank & Williams, 1985; Fouriezos et al., 1990). The reason for this is intuitive: the vigor of performance depends both on the *cost* of the reward as well as on its strength. To address this, Shizgal and colleagues measured performance while varying both strength and cost (Arvanitogiannis & Shizgal, 2008; Hernandez et al., 2010; Breton et al., 2013).

Time weighs heavily in accounts of foraging behavior and conditioning (Gallistel and Gibbon, 2000). A reward that can be secured rapidly outweighs one that is delivered only following a prolonged behavioral investment (Solomon et al., 2017). The former is said to have a lower “opportunity cost” than the later. Shizgal and his team manipulate opportunity costs in ICSS experiments by requiring rats to put time on a clock: the rats do so by holding down a lever until the accumulated time meets the experimenter-imposed criterion for earning a stimulation train (Breton et al., 2009). They quantify the rat’s behavior by measuring the partitioning of the rat’s time between “work” (holding down the lever) and “leisure,” anything else the rat chooses to do, such as resting, grooming or exploring. Not surprisingly, the proportion of the rat’s time devoted to working for a reward of a given strength (“time allocation”) declines as the required opportunity cost grows. Conversely, time allocation grows as a function of stimulation strength (e.g., pulse frequency) when opportunity cost is held constant. By measuring time allocation over a large set of opportunity costs and pulse frequencies, a fitted surface is obtained that looks like the corner of a plateau: the “reward mountain” (Arvanitogiannis & Shizgal, 2008; Figure 1).

The reward-mountain method removes a key source of ambiguity inherent in curve-shift measurements. Response-rate-versus-pulse-frequency curves are displaced laterally either by altering reward strength or the effort required to press the lever. In contrast, the reward mountain is displaced in orthogonal directions by manipulation of the strength and cost variables. This disambiguation is crucial for interpreting displacement of the reward mountain by experimental variables. As we will describe shortly, application of the reward-mountain method has falsified the long-standing

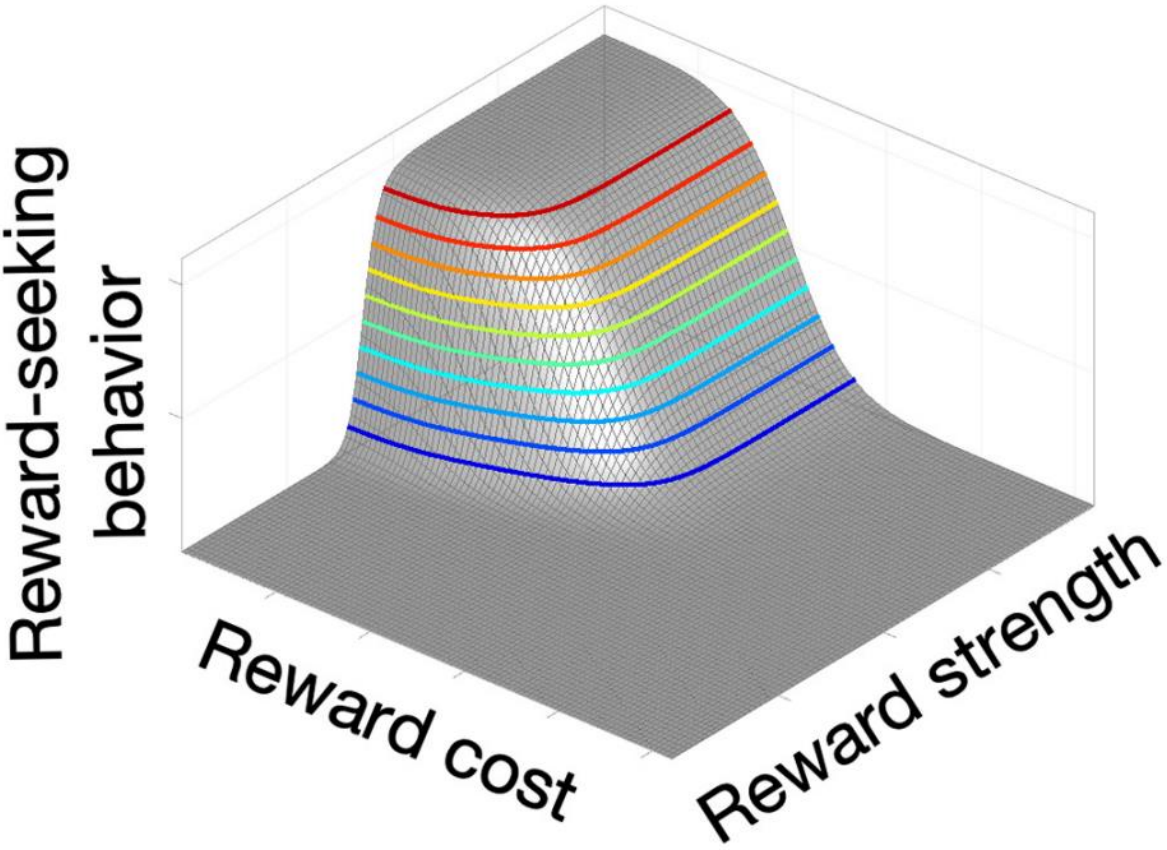


Figure 1. Schematic of the reward mountain, a method used to measure reward seeking while varying both reward strength and cost.

“series-circuit” model of brain reward circuitry and has inspired its replacement with a new candidate germane to interpreting the effects of deep-brain stimulation in humans: the convergence model.

3.5. Mapping the Reward-Mountain Model onto Stages of Neural Processing

The interpretation of shifts in the position of the reward mountain is based on a quantitative model of how the volley of action potentials triggered by the stimulation is translated into observable operant performance (summarized qualitatively in Figure 2). The formal derivation is provided in the supporting information for Trujillo-Pisanty et al. (2020). An alternative formulation, derived from reinforcement-learning principles, has been developed by Niyogi et al. (2013, 2014).

The top row of Figure 2 depicts the translation of the physical parameters of a stimulation train into a reward-intensity value stored in memory (nicknamed “benefit”). The “reward growth” function that does the heavy lifting in this regard has been measured by Mark and Gallistel (1993); Simmons and Gallistel (1994), and Leon and Gallistel (1998) using operant matching on concurrent variable-interval schedules. The reward mountain method can distinguish between effects of drugs and other manipulations that operate on the input to the reward growth function (the green box labeled “benefit” in Figure 2) and those arising from all subsequent stages. Modulation of the input to the reward-growth function shifts the reward mountain along the pulse-frequency axis. This is intuitive given the longstanding view that the input is the

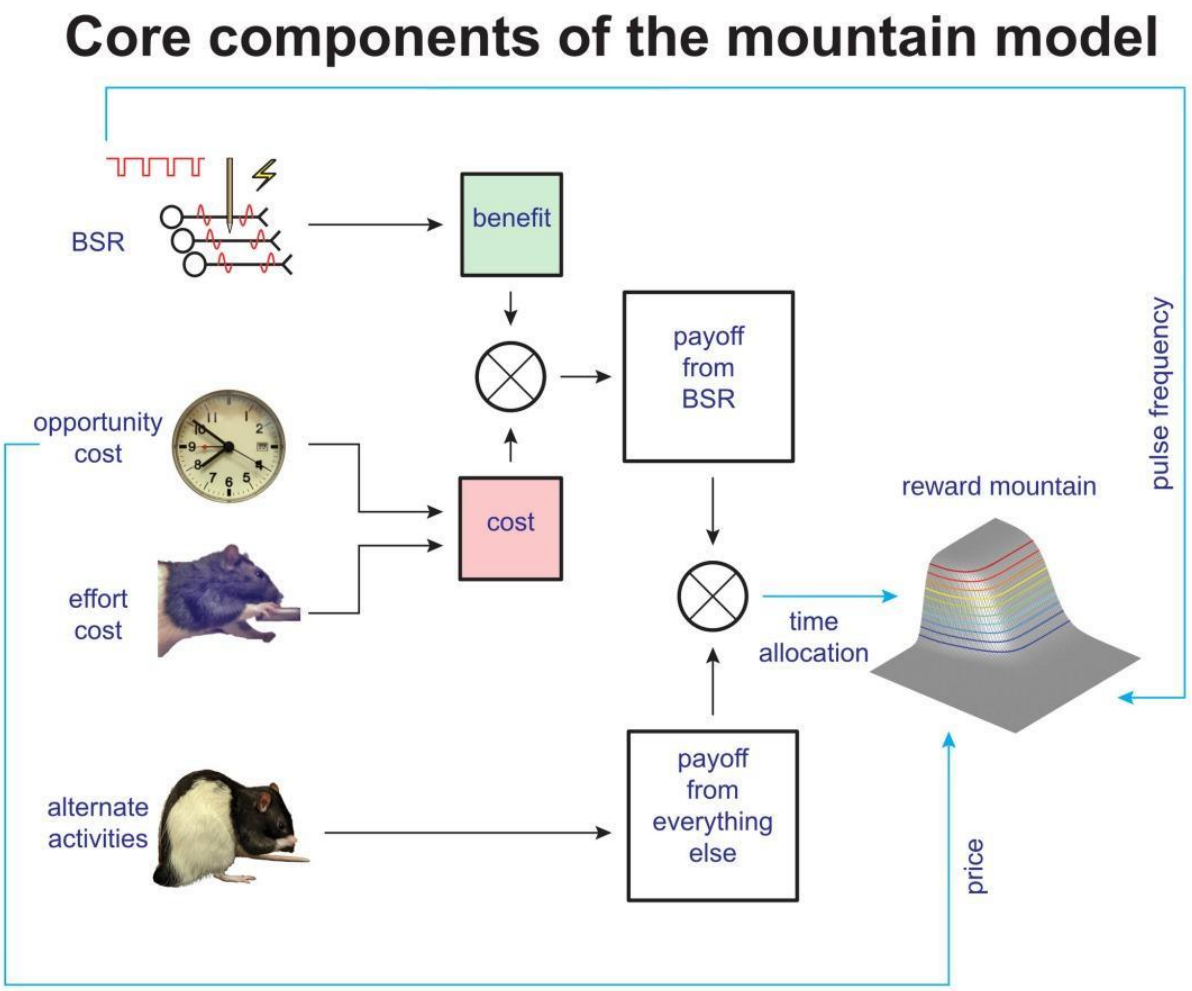


Figure 2. Simplified schematic of core components of the reward-mountain model (from Trujillo-Pisanty et al., 2020).

aggregate rate of firing in the neurons subserving the rewarding effect (the total action potential count elicited by a pulse train of a given duration) (Gallistel, 1978; Gallistel et al., 1981; Simmons & Gallistel, 1994). If the number of stimulated neurons is increased by boosting the stimulation current, a compensatory decrease in pulse frequency will be required to hold the aggregate firing rate constant, thus shifting the reward mountain along the pulse-frequency axis. This has been confirmed experimentally (Arvanitogiannis & Shizgal, 2008).

The neural signals responsible for the rewarding effect of electrical or optical stimulation arise initially as a volley of action potentials in neurons adjacent to the tip of an electrode or fiber-optic probe. Identifying these neurons and tracing their outputs must lead to the circuitry that translates the stimulation induced volley into an enduring record of reward intensity. The reward-mountain model and the associated measurement method tell us whether a manipulation such as administration of a drug or delivery of constant background stimulation alters reward processing prior to or beyond the reward-computing and encoding circuitry.

Figure 2 shows that multiple variables intervene between the output of the reward-growth function (the green box labeled “benefit”) and the observable behavior of the rat. These variables, which all shift the mountain along the cost axis (Breton et al., 2013, 2014; Trujillo-Pisanty et al., 2020), include the subjective effort entailed in holding down the lever, the value of alternate activities, and a scale factor applied to the output of the reward-growth function (not shown). Thus, although the reward mountain method reduces an important source of ambiguity in the interpretation of curve-shift data, we must put some water in our wine. Other sources of ambiguity persist in the interpretation

of data obtained by means of the reward-mountain method, and they are likely to do so until the conceptual entities in the model are replaced by measurable neural signals in identified neurons.

To our knowledge, only two studies have evaluated the effect of continuous background stimulation of the MFB on intracranial self-stimulation (Walker and Fouriezos, 1995; Rea et al., 2014). Neither employed the reward-mountain method, and in the study by Rea et al. (2014) background stimulation was not delivered while the rats were working for the reward. Given the effectiveness of continuous MFB stimulation in relieving treatment-resistant depression, it would be highly worthwhile to use the reward-mountain method to revisit the question of whether and how continuous background stimulation of the MFB alters pursuit of additional stimulation. If there is an effect of such background stimulation, is it brought to bear on the input or output side of the reward-growth function (or both)? An effect on the output side (i.e., a rightwards shift of the reward mountain along the cost axis) would be compatible with the concepts of motivational and decisional anhedonia. For example, such an effect could arise from summation between the tonic effect of the continuous stimulation (see the full, updated convergence model in Supplementary Figure 1) with reward intensity values retrieved from memory. Such summation would offset pessimistic reward expectations in depressed individuals (Sherdell et al., 2012; Huys et al., 2015), thus increasing the proclivity to invest effort in reward pursuit. That proclivity would also be boosted by a reduction in subjective effort costs, another of the perturbations that can shift the reward mountain rightwards along the cost axis.

Let us now consider how the reward-mountain model recasts the role of midbrain dopamine neurons in intracranial stimulation, and, potentially, in the relief of treatment-resistant depression by MFB stimulation.

3.6. Dependence of Intracranial Self-Stimulation of the Medial Forebrain Bundle on Dopaminergic Neurotransmission

Drugs that alter dopaminergic neurotransmission produce systematic changes in rate-frequency curves obtained from self-stimulating rats (Franklin, 1978; Wise and Rompré, 1989; Wise, 1996). A particularly elegant demonstration was provided by Gallistel and Karras (1984) in rats working for electrical stimulation of the MFB. The curves were driven leftwards by 2 mg/kg of amphetamine (which increases dopamine release) and rightwards by 0.3 mg/kg of pimozide (which blocks the dopamine D2 and 5HT-7 receptors); the effects of the two drugs canceled when administered together.

We have shown (Hernandez et al., 2010; Trujillo-Pisanty et al., 2020) that drug-induced shifts in rate-frequency curves could arise either from drug-induced modulation of the input to the reward-growth function or from modulation of its output. This ambiguity in the interpretation of curve shifts induced by changes in dopaminergic neurotransmission is resolved by application of the reward-mountain method. In 7/10 rats treated with the specific dopamine transporter blocker, GBR12909, the reward mountain measured in rats working for electrical MFB stimulation was shifted reliably along the opportunity-cost (“price”) axis, whereas no rat demonstrated a reliable shift

along the pulse-frequency axis (Hernandez et al., 2012). The dopamine D2/5HT-7 receptor blocker, pimozide, shifted the reward mountain reliably along the price axis in 5/6 rats, whereas no rat demonstrated a reliable shift along the pulse-frequency axis (Trujillo-Pisanty et al., 2014). Thus, these studies show that the drug-induced modulation of dopaminergic neurotransmission altered reward seeking by means of actions at or beyond the output of the reward-growth function.

3.7. Convergent Causation: Multiple Determinants of Reward Seeking

The results obtained in pharmacological studies employing the reward-mountain method send an important message beyond the role of neurotransmitter systems in reward seeking. These results remind us that we ignore convergent causation ("equifinality") at our peril. It is obvious that a given measurement, such as a change in response vigor, may arise from multiple causes, but the ease with which convergent causation can be obscured and ignored in the interpretation of curve shifts is often unappreciated.

In conventional curve-shift studies of the effects of drugs on intracranial self-stimulation, the data are typically plotted in two dimensions, with the stimulation-strength variable (usually pulse frequency) on the *x*-axis and a response-strength measure (usually response rate) on the *y*-axis, as shown in the top-right panel of Figure 3a. Implicitly, the independent variable, plotted on the *x*-axis, is taken as the *cause* of the variation observed in the dependent variable, plotted on the y-axis. We assume,

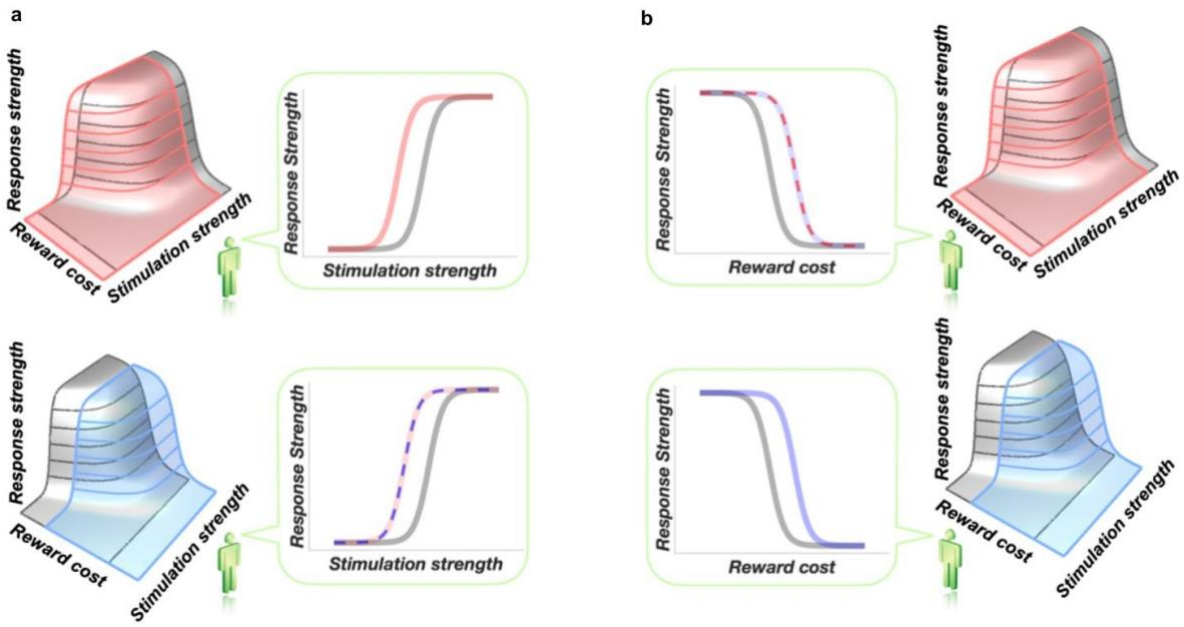


Figure 3. The inherent ambiguity of two-dimensional scaling of operant-conditioning data, such as rate-frequency and progressive-ratio curves. Redrawn from Hernandez et al. (2010). The two-dimensional graphs in panel (a) are drawn from the perspective of the little green figure, who views the three-dimensional structure from the stimulation-strength axis. The two-dimensional graphs in panel (b) are also drawn from the perspective of the little green figure, but here, this observer views the three-dimensional structure from the reward-cost axis. For a video illustrating this issue in more detail, see: https://spectrum.library.concordia.ca/978205/. The little green figure is from Shutterstock Images LLC.

quite reasonably, that boosting the strength of the stimulation (by raising the frequency or current) will increase the intensity of the resulting rewarding effect. In the baseline condition (gray), this attribution is fine: we are confident that it is only the stimulation strength that varies from trial to trial. A problem arises when we introduce a second independent variable: administration of a drug. The effect of stimulation strength on reward intensity is salient on our minds when we view the graph. Thus, when we then observe a drug-induced curve-shift (top-right panel of Figure 3a), we are prone to assuming that this is due to a drug induced change in sensitivity to stimulation strength: the variable represented on the *x*-axis. Such a shift would displace the reward mountain leftwards along the pulse-frequency axis (top-left panel of Figure 3a). In such a case, the two-dimensional graph correctly captures the shift, and the observer viewing that graph intuits the correct conclusion.

The lower-right panel of Figure 3a shows that the convert assumption of a leftward shift of the reward-growth function is premature. The very same shift in the rate-frequency curve could arise from a shift of the mountain along the cost axis (lower-left panel of Figure 3a; thin, blue, dashed curve in the lower-right panel). In such a case, the intuitive conclusion (thick, solid, pink curve in the lower-right panel) drawn by an observer focused on the *x*-axis label is incorrect. This is indeed the case in intracranial self-stimulation experiments entailing manipulation of dopaminergic (Hernandez et al., 2012; Trujillo-Pisanty et al., 2014) or cannabinoid (Trujillo-Pisanty et al., 2011) signaling. In those experiments, the reward mountain shifts along the cost axis (e.g., bottom-left panel of Figure 3a), which does not appear in the two-dimensional graph, and not along the stimulation strength axis that is so salient in the mind of the observer. The

intracranial self-stimulation data are consistent with the thin, dashed, blue curve in the lower-right panel, and not with the thick, solid, pink curve representing the intuitive conclusions drawn by experimenters who used the curve-shift method. The trap that causes intuitive interpretation of rate-frequency curves to go awry is illustrated in more detail in a video available here: https://spectrum.library.concordia.ca/978205/.

Analogous ambiguity is inherent in interpretation of progressive-ratio data. In progressive-ratio experiments (Hodos, 1961), response strength is plotted against the effort cost of the reward, as determined by the required number of lever presses. That scenario is depicted in Figure 3b. In the baseline condition (gray curve in top-left panel), there is a clear and systematic relationship between response strength and the reward cost. The observer viewing the two-dimensional data (left column) thus tends to jump to the premature conclusion that a drug-induced shift in a response-rate-versus-fixed-ratio curve is due to a change in sensitivity to reward cost: the variable plotted on the *x*-axis. That interpretation (thick, solid blue curve in the top-left panel of Figure 3b) would be correct if the reward mountain indeed moved in the direction shown in the lower-right panel, but it would be incorrect if the shift were in the orthogonal direction (thin, dashed, pink curve in the upper-left panel). When plotted in two-dimensions (left column), changes in sensitivity to either reward strength or reward cost can produce indistinguishable results (superimposed curves in the upper-left graph), but only sensitivity to reward cost is salient in the mind of the viewer. The three-dimensional representation (right column) made possible by the reward-mountain methods resolves the ambiguity and makes both the strength and cost axes salient.

Like the reward-mountain method, the effort-expenditure-for-rewards-task developed for use in experiments with human participants measures reward pursuit as a function of both the cost and strength of reward (Treadway et al., 2009). Thus, this task could achieve the same distinction as the reward-mountain method between variables acting at, or prior, to the input of the reward-growth function and variables acting at, or beyond, its output. However, such a distinction is possible only when the direction in which the mountain surface can be determined. A non-linear reward-growth function is required. The use of small monetary rewards may well fail to provide the required non-linearity. We speculate that the required non-linearity would be achieved if a reward that had to be consumed in the laboratory at the end of the session were substituted for the monetary payoffs. For example, a chocolate lover could be informed that they had the opportunity to earn various amounts of their preferred variety, with the proviso that they had to consume it within a given time period at the end of the session. The reward-growth function for such a payoff will saturate because the participant will know that amounts beyond a given mass will exceed what could reasonably be consumed and enjoyed within the available time.

Figure 3 illustrates how easy it is to prematurely adopt one of a set of convergent causes as the explanation for an observation and to ignore less-salient alternatives. As the figure shows, the reward-mountain method is indeed able to distinguish one set of potential causes, those acting at the input to the reward growth function, from a second set, those acting at or beyond the output. However, Figure 2 counsels caution. It shows that the mountain method fails to distinguish between the members of the second set of potential causes: multiple variables that can shift the mountain along the price axis,

including subjective estimates of opportunity costs, effort costs, and the value of alternate activities. Although we have established that at least one member of that second set depends on dopaminergic signaling (Hernandez et al., 2012; Trujillo-Pisanty et al., 2014), that does not prove that all the other members do as well. Thus, it would be unwise and unwarranted to leap to the premature conclusion that dopaminergic mechanisms underlie all shifts of the mountain along the price axis.

Convergent causation is no less germane to the interpretation of antidepressant effects of MFB stimulation in humans. Let us keep that in mind when we later address the putative role of dopamine signaling in the antidepressant effect of MFB stimulation.

3.8 Dependence of Intracranial Self-Stimulation of the Medial Forebrain Bundle on Direct Activation of Myelinated Descending Fibers

In parallel with the initial work that established the dependence of MFB self-stimulation on dopaminergic neurotransmission, detailed psychophysical studies were carried out to characterize the directly stimulated neurons responsible for the rewarding effect (Gallistel et al., 1981). The estimated characteristics include recovery from refractoriness (Yeomans, 1975, 1979; Bielajew et al., 1982), conduction velocity (Shizgal et al., 1980; Bielajew & Shizgal, 1982, 1986; Murray & Shizgal, 1996a,b), frequency following (Gallistel, 1978; Simmons & Gallistel, 1994; Solomon et al., 2015), and the behaviorally relevant direction of conduction (Bielajew & Shizgal, 1986). The results are consistent with the hypothesis that the principal constituents of the directly

activated substrate for MFB self-stimulation are neurons with descending myelinated axons. In contrast, the dopaminergic fibers in the rat MFB have slow-conducting (Feltz & Albe-Fessard, 1972; Takigawa & Mogenson, 1977; Guyenet & Aghajanian, 1978; German et al., 1980; Maeda & Mogenson, 1980; Yim & Mogenson, 1980), unmyelinated (Hattori et al., 1991) axons with relatively long refractory periods (Anderson et al., 1996) that ascend from the midbrain to the forebrain (Ungerstedt, 1971). The series-circuit hypothesis (Shizgal et al., 1980; Wise, 1980; Bielajew & Shizgal, 1986) was proposed to reconcile the pharmacological data implicating dopaminergic neurons in MFB self-stimulation with the portrayal that has emerged from the psychophysical studies.

3.9. The Series-Circuit Model of Intracranial Self-Stimulation

The series-circuit model attempts to accommodate both the psychophysical and pharmacological data by concatenating two sets of neurons. In that model, MFB-projecting neurons with myelinated axons dominate the directly stimulated stage. They do so because they are much more readily excited by electrical currents than the fine dopaminergic axons in the MFB, which have high threshold to electrical activation (Guyenet & Aghajanian, 1978; Yeomans et al., 1988; Anderson et al., 1996). Instead of being driven directly by MFB electrodes, the series-circuit model posits that midbrain dopamine neurons are excited mono- or poly-synaptically by input from the directly activated, myelinated fibers. Figure 4 provides a simplified sketch of this hypothesis. As explained above, the failure of the reward mountain to shift along the pulse-frequency

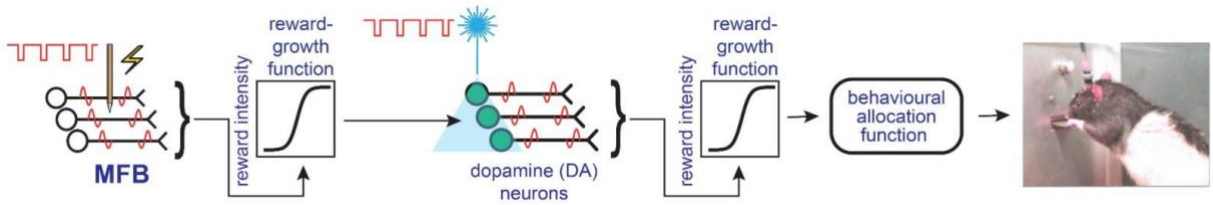


Figure 4. Simplified schematic depicting the basic components of the series-circuit model of brain reward circuitry, redrawn from Trujillo-Pisanty et al. (2020).

axis following blockade of the dopamine transporter or dopamine receptors implies that the drugs acted beyond the output of the reward growth function. Thus, a reward-growth function is positioned in Figure 4 between the output of the directly activated MFB neurons and the midbrain dopamine cells. The second reward growth function (beyond the output of the dopamine neurons) is required to accommodate data from an experiment in which rats worked for specific, optical stimulation of midbrain dopamine neurons (Trujillo-Pisanty et al., 2020).

3.10. Evidence Inconsistent with the Series-Circuit Model

The discovery that rodents will work for specific optogenetic stimulation of midbrain dopamine cells seems to fit the series circuit model nicely. However, application of the reward mountain method to optical self-stimulation places a seemingly insurmountable obstacle in the path of the series-circuit model.

Trujillo-Pisanty et al. (2020) used the reward-mountain method to test the effect of dopamine-transporter blockade on reward-mountain measurements obtained from rats working for direct, specific optogenetic activation of midbrain dopamine. As in the case of electrical self-stimulation, the rewarding effect (particularly following administration of the specific dopamine transporter blocker, GBR-12909) started to saturate at pulse frequencies well within the frequency-following capabilities of the dopamine neurons. This implies that a saturating reward growth function is positioned downstream of the activated dopamine neurons (Figure 4). In contrast to the results obtained with the same drug on electrical self-stimulation of the MFB, they found that the mountain was shifted leftwards along the pulse frequency axis by dopamine

transporter blockade. That result implies that the rewarding effect was boosted by an action at or before the *input* to the reward-growth function. This finding refutes the series-circuit model, because positioning a reward growth function downstream from the dopamine neurons predicts that perturbation of dopaminergic neurotransmission would also shift of the reward mountain along the pulse frequency axis in rats working for electrical MFB stimulation, whereas Hernandez et al. (2012) and Trujillo-Pisanty et al. (2014) showed that it does not. In order to accommodate both sets of results, Trujillo-Pisanty et al. (2020) proposed a new architecture: the convergence model.

3.11. The Convergence Model

A simplified summary of the convergence model is provided in Figure 5. The full model and extensive computer simulations supporting it are provided in the report by Trujillo-Pisanty et al. (2020). Supplementary Figure 1 provides an update to this full model to address potential effects of continuous MFB stimulation. In this architecture, the myelinated MFB axons and the midbrain dopamine neurons have parallel access to the final common path for reward pursuit. The convergence model thus elevates the state of the myelinated pathway. In the series-circuit model, the stimulated MFB axons are merely one of many sets of inputs to the midbrain dopamine neurons (Watabe-Uchida et al., 2012), which are the gatekeepers to the final common path for reward estimation and pursuit. In contrast, the convergence model gives the myelinated pathway an independent voice in the chorus vying for control over the behavioral final

common path, one that can dominate under the conditions of electrical self-stimulation experiments.

The convergence model accommodates a number of prior findings that fit poorly with the series-circuit model. These include the results of studies employing radical ablation methods that eliminated most of the forebrain terminations of ascending dopamine neurons (Huston & Borbély, 1973; Pritzel et al., 1983), a study of the effect of cytotoxic lesions of the nucleus accumbens terminal field (Johnson & Stellar, 1994), and a comparison between frequency following in midbrain dopamine neurons and the substrate for the rewarding effect of electrical MFB stimulation (Cossette et al., 2016).

Research on the role of dopaminergic neurons in reward seeking has accomplished so much and achieved such prominence as to overshadow the established and potential contributions of other neural populations. The ascending dopaminergic projection from the midbrain is merely one of over 50 distinguishable components of the MFB (Nieuwenhuys et al., 1982). Which of the others contribute to the evaluation and pursuit of rewards and in what ways? The convergence model encourages us to give greater consideration to the non-dopaminergic components, which include descending projections that pass through or near the midbrain region housing dopamine cell bodies and continue deeply into the brainstem (Nauta et al., 1982).

Rompré and Milliaressis (1985, 1987) have described an array of electrical self-stimulation sites that runs longitudinally along the core of the mesencephalon, well caudal to the dopamine cells bodies clustered in the ventral tegmental area (VTA). Boye

and Rompré (1996) demonstrated that axons contributing to the rewarding effect directly link sites in this mesencephalic array with the VTA and lateral hypothalamus. Although the behaviorally relevant direction of conduction in these fibers is unknown, the finding of Boye and Rompré could arise from reward-related MFB projections that pass through the VTA en route to more caudal regions. Such projections would be suitable candidates for the long-sought descending path and for the channel in the convergence model that parallels the midbrain dopamine neurons en route to the behavioral final common path for reward seeking. Indeed, Huston (1982) has long interpreted the results of radical ablation experiments carried out by his team (e.g., Huston and Borbély, 1973; Pritzel et al., 1983) to imply that the critical circuitry underlying self-stimulation, and reinforcement of operant behavior more generally, lies in the deep brainstem.

3.12. Finding the Parallel Path

Most of the research that gave rise to the series-circuit model was carried out in the 1970s and 1980s. The reader may well ask why the neurons with myelinated axons implicated by this work as the directly stimulated substrate for MFB self-stimulation have not since been found. In our view, this is due principally to the nature of the tools that were available until recently for anatomical tracing and for determining the necessity and causal role of identified neural pathways in behavioral effects of brain stimulation. Painstaking manual methods, typically applied to small numbers of selected tracer-injection sites, were long required to trace axonal trajectories between their cell-body

origins and postsynaptic targets (Cowan et al., 1972; Veening et al., 1982; Wouterlood et al., 2014). Applying such methods required prior knowledge of the origin and/or termination of a given pathway. In the absence of such prior information, researchers studying effects of electrical brain stimulation had few options for tracing axons coursing past the stimulation site (e.g., Fink & Heimer, 1967; Honig & Hume, 1989).

An array of recently developed trajectory-tracing technologies greatly enhances feasibility, accuracy, specificity, and speed (Wouterlood et al., 2014; Lanciego & Wouterlood, 2020). Tissue-clearing methods (Tian et al., 2020; Ueda et al., 2020; Richardson et al., 2021) render entire rodent brains optically transparent. Via stochastic electrotransport (Kim et al., 2015), fluorescent antibodies can be driven efficiently into cleared rodent brains to label specific neural populations. Via lightsheet microscopy (Mano et al., 2018; Migliori et al., 2018; Chakraborty et al., 2019; Hillman et al., 2019), the cleared tissue can be sectioned optically, thus eliminating registration issues and the need for manual manipulation of delicate tissue sections. Segmentation and image-analysis software makes it possible to trace single axons throughout the labeled, cleared brain (Berger et al., 2018; Gao et al., 2019). Achieving this for individual myelinated axons, such as those coursing through MFB self-stimulation sites, is no longer a dream. (For an example of long-distance tracing of fluorescently labeled myelinated axons in cleared tissue, see Gao et al., 2019). The new methods not only provide detailed information about connections (origins and terminations of neural projections), they also trace trajectories, which is crucial to identifying the directly activated neurons subserving behavioral effects of deep-brain stimulation.

Once the trajectories of the axons of interest have been traced, optogenetic methods (Yizhar et al., 2011) can render the neurons that give rise to particular MFB components optically excitable, thereby making it possible to determine whether driving these cells produces rewarding and/or motivating effects. Identification of the terminal fields of the MFB-projecting neurons, coupled with optogenetic silencing methods (Yizhar et al., 2011; Wiegert et al., 2017) provide complementary means for assessing the necessity of these neurons for the rewarding effect of MFB stimulation. By recording the activity of these neurons in response to rewarding MFB stimulation, it can be determined whether the properties of their axons correspond to the psychophysically derived portrait of the fibers subserving MFB self-stimulation (e.g., Rompré & Shizgal, 1986; Shizgal et al., 1989; Murray & Shizgal, 1996b; Cossette et al., 2016).

4. Implications for Research on The Antidepressant Effect of Deep-Brain Stimulation

4.1. Stimulation Parameters

Before we discuss the implications of the convergence model for research on the antidepressant effect of deep-brain stimulation, it is important to address the issue of how the stimulation parameters employed in the rodent research are related to those employed in the therapeutic intervention in humans. The pulse duration employed in the deep brain stimulation of the human MFB is 60 ms, which is even shorter than the 100 ms duration typically employed in studies of intracranial self-stimulation in rats.

Chronaxies of unmyelinated axons are typically longer than those of myelinated axons (West & Wolstencroft, 1983). Thus, the short pulse duration employed in deep-brain stimulation of the human MFB would render such stimulation even less likely to directly activate unmyelinated dopamine axons than the stimulation employed in the rodent studies.

The maximum firing frequency of human dopamine neurons has yet to be determined, as far as we know. That said, the pulse frequency employed in the deep-brain stimulation of the human MFB, 130 Hz, is well above the maximum firing frequency that dopaminergic neurons can sustain in the rodent (Tsai et al., 2009; Witten et al., 2011; Covey & Cheer, 2019).

4.2. The Centrality of the Dopamine Neurons?

The papers detailing the antidepressant effect of MFB stimulation have consistently acknowledged the anatomical and neurochemical heterogeneity of the MFB (Coenen et al., 2011, 2012; Schlaepfer et al., 2013). However, after a tipping of the hat toward this incontestable neuroanatomical reality, the discussion in the early papers rapidly gravitates toward a dopamine-centered (“dopacentric”) view analogous to the series-circuit model in Figure 4. The authors recognize that the dopaminergic axons are less excitable to extracellular stimulation than the larger, myelinated MFB fibers interspersed among them. Thus, they have proposed that the directly stimulated elements subserving the rewarding effect are corticofugal afferents to VTA dopamine

neurons (Schlaepfer et al., 2013, 2014; Coenen et al., 2021). These glutamatergic fibers excite their post-synaptic targets: the midbrain dopamine cells. The psychological and behavioral effects of the MFB stimulation are largely attributed to that excitation, as in the series circuit model. In the case of MFB self-stimulation in rats, the series-circuit model has been falsified by recent evidence (Trujillo-Pisanty et al., 2020) and fits poorly with an array of prior findings (Huston & Borbély, 1973; Pritzel et al., 1983; Johnson & Stellar, 1994; Cossette et al., 2016). This is what motivated the development of the convergence model (Figure 5 and Supplementary Figure 1) in which the activity of non-dopaminergic MFB fibers accessed the final common path for reward pursuit in parallel with the firing of midbrain dopaminergic neurons.

The failure of psychomotor stimulants to serve as an effective monotherapy for depression invites reconsideration of a series-circuit model of the antidepressant effect of MFB stimulation. An alternative, analogous to the convergence model of intracranial MFB self-stimulation, would include multiple, convergent pathways. On that view, non-dopaminergic MFB components may contribute to the therapeutic effect in parallel to, in synergy with, or even instead of, a dopaminergic component. To assess those possibilities, we must look in more detail at the neuroanatomical complexity of the region where MFB stimulation is effective in relieving treatment-resistant depression and at the methods that have been used to link that effect to particular fiber bundles.

4.3. Which Neurons Are Activated Directly by Therapeutically Effective Stimulation of the Medial Forebrain Bundle, and Which Are Responsible for the Antidepressant Effect?

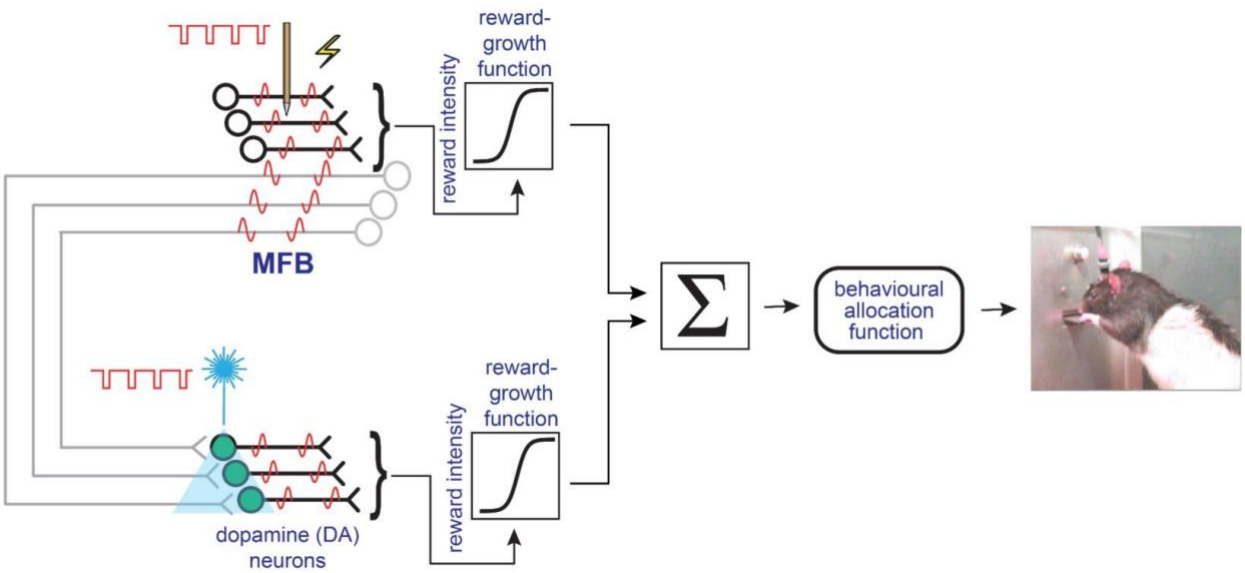


Figure 5. Simplified depiction of the convergence model, redrawn from Trujillo-Pisanty et al. (2020). See Supplementary Figure 1 for an updated version of the full model.

Evidence continues to accumulate that deep-brain stimulation of the MFB provides relief from depression that has resisted other forms of treatment (Schlaepfer et al., 2013; Fenoy et al., 2016, 2021; Coenen et al., 2018, 2019; Kilian et al., 2019). The effective stimulation site lies in a neuroanatomically complex region. Which of the local neural elements is directly activated by the electrical stimulation and gives rise to the therapeutic effect: local cell bodies, their afferents, fibers of passage, or some combination thereof?

The groups that are carrying out the neurosurgical work and following up on its consequences apply diffusion weighted magnetic-resonance imaging tractography ("diffusion tractography") to address this question (Thomas et al., 2014; Jbabdi et al., 2015; Maier-Hein et al., 2017). This non-invasive, inferential method is used extensively both in the surgical positioning of deep-brain stimulation electrodes and in interpreting the effects of the stimulation. It is based on the differential ease with which water molecules diffuse along and across fiber tracts. The volume elements (voxels) that constitute the spatial units of the structural MRI data from which the inferences about fiber trajectories are drawn are large compared to the diameters of individual axons, and multiple assumptions must be made in order to link the imaging data to its anatomical interpretation. As Haber et al. (2021) have noted: "multiple configurations of axon populations can give rise to similar diffusion profiles."

The plausibility of findings obtained by means of diffusion tractography has been evaluated in non-human primates. In such studies, fiber tracts are visualized post-mortem by means of well-established neuroanatomical tract-tracing methods with high spatial resolution. The results are registered and compared to high-resolution, *ex vivo*

diffusion tractography results obtained from the same subjects (Grisot et al., 2021). Such rigorous comparisons provide both good and not-so-good news: the two methods yield correspondence that is substantial but imperfect, particularly where projections from different sources cross, branch, abut, and/or bend (Grisot et al., 2021; Haber et al., 2021, 2022). One such location is the MFB in the vicinity of the VTA, the location of the MFB site where deep-brain stimulation can relieve treatment-resistant depression. Haber and colleagues note that:

"This complex midbrain area contains tightly packed intermixed myelinated bundles. As such, it likely modulates descending and ascending STN (subthalamic nucleus), ZI (zona incerta), and VTA/substantia nigra fibers entering and exiting the IC (internal capsule). The area also contains striato-brainstem, pallido-midbrain, cortico-brainstem, and hypothalamo-brainstem fibers" (Haber et al., 2021; acronym definitions added in parentheses).

The fibers coursing toward the brainstem are of particular interest given the evidence cited above for a reward-related pathway that parallels the midbrain dopamine projections (Trujillo-Pisanty et al., 2020), for reward-related fibers linking self-stimulation sites in the rat caudal to the midbrain dopamine neurons axonal to the VTA and lateral hypothalamus (Boye & Rompré, 1996), and for the view that the fundamental circuit subserving intracranial self-stimulation is located in the caudal brainstem (Huston, 1982).

Do the brain sections obtained to trace corticofugal fibers in the non-human primates contain additional information pertinent to identifying the neurons directly

activated by electrical stimulation in humans that produces therapeutic effects? For example, how do the diameters and myelination of corticofugal fibers terminating in the VTA compare to those of corticofugal fibers that continue caudally as well as to those of brainstem-projecting fibers arising in the diencephalon and basal forebrain? Pertinent neuroanatomical methods for addressing such questions are addressed in a recent manuscript (Yendiki et al., 2021). Although a single hull is typically drawn around a therapeutically effective stimulation site to enclose the volume within which the stimulation triggers action potentials, a broad distribution of fiber diameters and myelination would require a Russian-doll-like depiction consisting of multiple concentric hulls, each corresponding to a different neural population defined on the basis of its excitability (Kringelbach et al., 2007). How does the appropriate Russian-doll-like depiction map onto the complex anatomy of the therapeutically effective MFB stimulation site?

Single-unit electrophysiology provides the most definitive means for determining whether particular neurons are directly excited by electrical stimulation. For example, the collision test (Bishop et al., 1962) establishes that an axon activated by a stimulation electrode at one brain site arises from a cell body in a second site. Can the pertinence of such studies in the non-human primate to identifying the directly stimulated neurons activated by MFB stimulation in humans be increased, perhaps by employing the same type of stimulation electrode and scaling the stimulation current to reflect the different dimensions of non-human-primate and human brains and axons? Could pertinent information be derived from post-mortem imaging of axons linking the stimulation and recording sites? Can such work tell us whether stimulation at the site homologous to the

therapeutically effective locus in humans activates neurons that project to deep brainstem sites beyond the midbrain dopamine cell bodies?

In recognition of the differential excitability of dopaminergic axons and larger, myelinated fibers that also course through the therapeutically effective stimulation site, Coenen, Schlaëpfer and colleagues (referred to below as the “Freiburg group”) proposed that the antidepressant effect of MFB stimulation arises from the direct excitation of glutamatergic, corticofugal afferents to VTA dopamine neurons (Schlaepfer et al., 2013, 2014). In a recent paper (Coenen et al., 2021), their team aligned *in vivo* and *ex vivo* diffusion-tractography data, the latter acquired at higher resolution. The post-mortem specimen was stained to highlight nerve fibers and to visualize neurons expressing tyrosine-hydroxylase. The data were interpreted as support for the proposition that direct activation of corticofugal VTA afferents gives rise to the therapeutic effect. It is not clear whether this work puts to rest all the concerns voiced by the researchers who have compared diffusion tractography and neuroanatomical tracing methods in the non-human primate (Grisot et al., 2021; Haber et al., 2021, 2022). To their concerns, we add some questions of our own.

We wonder whether additional information about fiber diameter spectra and axonal trajectories in the vicinity of the effective stimulation site could be extracted from the existing *ex vivo* human specimen or from additional such specimens examined by means of higher-resolution methods (Yendiki et al., 2021). There now appears to be agreement (Coenen et al., 2021; Haber et al., 2021, 2022) that the axons of the midbrain dopamine neurons in the human ascend in the classic MFB, as they do in the non-human primate, and that these axons do not join the internal capsule. Do we

understand correctly that what the Freiburg group calls the superolateral MFB consists of contifugal fibers that occupy a quadrant of the anterior limb of the internal capsule and reach the VTA via the lateral hypothalamus? If so, to what degree are these fibers intermingled with those of the classic MFB en route from the lateral hypothalamus to the VTA (Coenen et al., 2021)? Is the VTA their sole terminal field, or are there branches or sub-components of the bundle that continue caudally?

Although dopaminergic activation is central to their account of the antidepressant effect of MFB stimulation, the Freiburg group has also considered another impact on cortical functioning, one due to antidromic propagation of the stimulation-induced firing of corticofugal fibers (Coenen et al., 2021). Presumably, the antidromic action potentials could invade cortical collaterals that drive local inhibitory interneurons. That proposal is of particular interest given a recent report linking maladaptive stress-induced glutamatergic responses in the medial prefrontal cortex in depressed patients to pessimistic expectations (Cooper et al., 2021). That said, the report from the Freiburg group emphasizes orbitofrontal efferents, rather than medial prefrontal ones. Electrophysiological data from non-human primates obtained using electrodes and stimulation sites homologous to the ones employed in the human clinical work would be of particular interest in this regard.

5. Conclusion

In many of the papers describing their pioneering work on the use of MFB stimulation in humans to relieve treatment resistant depression, the Freiburg group has tied their analysis to longstanding research on intracranial self-stimulation of the rodent MFB. Jaak Panksepp is a co-author of several of the early papers (Coenen et al., 2009b, 2011, 2012), which adopt his qualitative perspective. When viewed through the lens of Panksepp's SEEKING system, the midbrain dopamine neurons are *primi inter pares* among the constituents of the MFB that subserve self-stimulation. Outside the field of view of this lens is over 40 years of parallel quantitative work implicating non-dopaminergic components of the MFB in reward and appetitive motivation (e.g., Gallistel et al., 1981; Yeomans, 1990; Shizgal, 1997). The series-circuit hypothesis attempts to reconcile the dopacentric, qualitative view with the quantitative, psychophysical and electrophysiological work. However, the series-circuit hypothesis has foundered following the incorporation of optogenetic methods into the quantitative approach (Trujillo-Pisanty et al., 2020). The new convergence model arises from that work. In that model, the directly activated, non-dopaminergic fibers access the final common path for reward pursuit via circuitry that partially parallels the dopaminergic projections. On that view, the midbrain dopamine neurons remain vitally important, but they have company in the form of a parallel route to the behavioral final common path. We speculate on how emerging methods will lead to the identification of the parallel pathway, and we make a plea to keep interpretative filters open in evaluating potential contribution to the antidepressant effect of MFB stimulation by non-dopaminergic fibers coursing through or near the effective stimulation site. We also question why, if the deep-brain stimulation produces its therapeutic benefit by "tuning up" the ascending

dopaminergic pathways (Döbrössy et al., 2021), does administration of psychomotor stimulants fall short of achieving the same ends?

In agreement with the Freiburg group and Panksepp, we hold that research on MFB self-stimulation in rodents will continue to have translational implications. We hope that future research into this seminal phenomenon, coupled with allied experimental work in non-human primates and humans, will yield a fuller understanding, both of the psychological and neural mechanisms underlying the antidepressant effect of deep-brain stimulation, and of the neural foundations of reward and motivation.

6. Data Availability Statement

This manuscript refers to a publicly available dataset. This data can be found here: https://spectrum.library.concordia.ca/id/eprint/986807/.

7. Ethics Statement

The animal study that generated the publicly available dataset was reviewed and approved by the Animal Research Ethics Committee, Concordia University.

8. Author Contributions

VP and PS: conceptualization and writing. Both authors contributed to the article and approved the submitted version.

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11. Supplementary Material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2022.851067/full#supplementary-material

GENERAL DISCUSSION

Motivation is involved in several critical functions spanning adaptive behaviour to psychopathology. The discovery of the brain reward system galvanized a concentrated investigation of the function and neuroanatomy of substrates that underlie motivated action. This effort was advanced considerably by the development of selective neuromodulation techniques, including optogenetics (Bi et al., 2006; Deisseroth, 2011). The use of optogenetics allowed researchers to overcome the ambiguity inherent in the indiscriminate neural excitation induced by electrical stimulation (Deisseroth, 2011). Using optogenetics, it was confirmed that selective activation of midbrain dopamine neurons suffices to elicit instrumental behaviour (Adamantidis et al., 2011; Witten et al., 2011, Ilango et al., 2014). This finding appeared to align well with the series-circuit model, according to which activation of midbrain dopamine neurons is a necessary phase of the neural signal causing reward seeking. However, the gain of tools permitting selective neuromodulation also contributed to uncovering previously obscured layers of information, attesting to the functional and electrophysiological complexity of the dopamine system (de Jong et al., 2022; Knowlton et al., 2021; Lammel et al., 2014; Morales & Margolis, 2017; Otomo et al., 2020). Over a decade after the seminal experiments of optogenetic ICSS, a lot remains to be known about how optical stimulation translates into the neural signal that causes instrumental behavior. Serving a parallel research effort, the seven decades of BSR literature can be leveraged to provide insights on how neuromodulation, including deep brain stimulation, treats psychopathology. Here, two experiments and a theory article are presented that add to both of these domains of research.

In the first two Chapters two operant, trade-off experiments are described, which combine rewarding optical stimulation of midbrain dopamine neurons with psychophysical inference. These two experiments are added to studies investigating how optical stimulation parameters influence ChR-2-mediated dopamine neuron activation and, by extension, operant behavior. Behavioral measurements are provided, which suggest that there are important differences between in-vitro and in-vivo measurements of electrophysiological properties of midbrain dopamine neurons (Arias-Gil et al., 2016). Together, the findings from these two experiments broaden the understanding of the experimentally useful stimulation parameter space for optical excitation of midbrain dopamine cells. Both empirical guidelines for a priori stimulation parameter selection and practical information for computational modeling of VTA dopamine firing are provided.

In the third Chapter, insights from the basic literature of brain stimulation are intersected with clinical studies of deep brain stimulation for refractory depression. This paper impinges on the selection of the MFB as the stimulation site both in basic BSR experiments and in clinical studies. It is proposed that, analogously to the convergence model of the reward system, there may be non-dopaminergic contributions to the antidepressant effect induced by MFB stimulation. The evolution of anatomical models of the brain reward system is described, emphasizing the easily concealed role of convergent causation in the measurement of brain-stimulation-dependent phenomena. The rationale of potential non-dopaminergic contributions in clinical MFB stimulation is outlined by reviewing the ineffectiveness of psychostimulants in treating depression, the

role of motivation in depression, and the efficacy of consistent engagement with rewarding activities in treating depression. A functional hypothesis for the antidepressant effect of MFB stimulation is outlined based on its potential effects on engagement with reward pursuit.

Implications for the Design of Optogenetic Experiments

In the first Chapter, the trade-off function between power and pulse duration in the optical excitation of midbrain dopamine neurons is described. For an experimentally useful range of powers (~12.6–31.6 mW), pulse duration and optical power were shown to undergo a lawful reciprocity in determining operant behavior. This reciprocity approximates the temporal summation described by Bloch's Law in human vision. Higher optical powers (>31.6 mW) are either ineffective or counter-productive at improving the stimulation's behavioral effectiveness. This upper power threshold does not appear to be caused by brain tissue heating. To contextualize these findings, one may consider that although microbial opsins, such as ChR-2, differ in several ways from animal opsins, fundamental processes including light absorption and retinal isomerization are homologous (Ernst et al., 2014; Zhang et al., 2011). The present results add to the notion that temporal summation, the dependence of stimulus detectability on duration, is virtually a universal phenomenon of sensory systems (Marks, 2014).

In the second Chapter, methodological insights from the first Chapter are applied to estimate the in-vivo firing fidelity of midbrain dopamine neurons. Drawing from the design used by Solomon and colleagues (2015) to estimate firing fidelity of MFB neurons, a spatial parameter (i.e., pulse duration; scaling the number of dopamine neurons fired) was traded off against a temporal parameter (i.e., pulse frequency; scaling the stimulated neurons' firing rate). Increases in stimulation pulse frequency improved the behavioral effectiveness of optical stimulation of VTA dopamine neurons up to an upper limit, lying between 28-40 Hz. Higher stimulation pulse frequencies (>40 Hz) were either ineffective or counter-productive at improving the stimulation's behavioral effectiveness. This original psychophysical estimation of frequency following of VTA dopamine neurons provides practical estimates of their in-vivo firing fidelity and their upper firing capacity using ChR-2.

The results from the first two Chapters are added to past findings (Trujillo-Pisanty et al., 2020) to support that rewarding optical stimulation of VTA neurons conforms to a simple, counter-model-like integration. This inference appears to be analogous to results from electrical BSR studies using the MFB as a stimulation site. Similarly to electrical ICSS, parametric control of optical stimulation supports that there is a monotonic relationship between induced neural firing and operant response. This idea was outlined in a review for electrical ICSS (Gallistel, Shizgal & Yeomans, 1981). The authors suggested that if the final outcome (in this case, operant behavior) of a sequence of neural stages scales in a lawful, monotonic manner with at least one of the parameters of the input (in this case, the optical stimulation), then, via back-

propagation, every stage lying between the input and output must also scale monotonically. As such, measuring the quantitative functions describing how variations in the optical stimulation parameters lead to changes in instrumental response can provide meaningful insights into the function of the brain reward system and the role of the midbrain dopamine system therein.

The value of using trade-off and within-subject designs in behavioral optogenetic experiments is showcased in the first two Chapters. As seen in Figures 3 in Chapter 1 and Chapter 2, identical stimulation parameters can lead to drastically different behavioural outcomes across subjects. Indeed, the behavioral effectiveness of a given optical stimulation train can vary substantially across subjects based on factors such as implant placement and opsin-expression density (Trujillo- Pisanty et al., 2020; Witten et al., 2011). Complicating interpretations further, the functional heterogeneity of midbrain dopamine neurons showcases that they do not all contribute homogeneously to reward processing (de Jong et al., 2022; Lammel, Lim, & Malenka, 2014; Morales & Margolis, 2017).

Even if optical fiber placement variation is random, within-subject designs can be used to circumvent averaging of data points caused by variable aggregate firing rates, which are induced across stimulation sites. As shown in the first two Chapters, experimenters using optogenetics can subvert this issue by customizing the stimulation parameters by subject based on a priori outcome criteria (e.g., magnitude of reward seeking or another emergent behavior). This is a process embraced by both the

electrical ICSS literature and by clinical studies of deep brain stimulation (Drobisz & Damborská, 2019). Even with the sophisticated brain imaging methods and predictive models used in human stereotaxic surgery, implant placements vary across patients, leading to observable outcome-based personalization of finalized placements and of the stimulation parameters (Riva-Posse et al., 2020; Roediger et al., 2022). Overall, in both basic and clinical studies, the within-subject approach to parameter adjustment is experimentally meaningful because, instead of relying on the physical properties of the stimulation, it holds final outputs (e.g., antidepressant efficacy, operant response) as the equalising factor across subjects and participants.

Interpretation of the findings of the first two Chapters is tied closely to the selection of opsin used to modulate dopamine neurons. The choice of ChR-2 was based on the common use of this opsin in neuroscience (Britt, McDevitt, & Bonci, 2015; Cho et al., 2019), and the consequent high external validity of the findings in relation to several applications within the field. That said, a limitation of using ChR-2 in the present experiments relates to the opsin's relatively slow kinetic profile (Boyden, Zhang, Bamberg, Nagel, & Deisseroth, 2005; Darrow et al., 2015). The frequency following of ChR-2 starts dropping off at stimulation frequencies of 10 Hz, and spike fidelity declines to 20% at stimulation frequencies of 80 Hz (Adamantidis et al., 2011; Klapoetke et al., 2014; Villaruel et al., 2018). The upper pulse frequency threshold described in the second Chapter may be influenced by factors determining the maximal temporal response of ChR-2 to optical stimulation. An extension of the current findings would be to replicate the experiment using opsins with faster kinetic profiles (Klapoetke et al.,

2014). Candidate opsins include ChEta and Chronos, two opsins that have been used in classical and instrumental conditioning experiments (Christoffel et al., 2021; Hung et al., 2017; Sweis, Larson, Redish, & Thomas, 2018). This extension can parse out to what extent the upper threshold value of pulse frequency detected in the second Chapter was influenced by the electrophysiological properties of dopamine neurons and by the biophysical properties of ChR-2.

Implications for the Antidepressant Effect of MFB Stimulation

A conceptual junction between the use of deep brain stimulation for depression and the basic neuroscience of motivation is provided by the impact of depression on reward seeking. As reviewed in Chapter 3, patients with depression provide similar hedonic ratings for freely delivered sucrose solutions compared to healthy controls (Amsterdam et al., 1987; Berlin et al., 1998; Dichter et al., 2010). Systems related to pleasure perception, at least pertaining to taste and smell, may be unchanged in depression. It has been suggested that motivational as opposed to hedonic deficits may underlie depressive symptomatology (Zald & Treadway, 2017). Studies spanning the entire development of major depressive disorder suggest that depression negatively affects parameters of reward processing, learning, and seeking (Keren et al., 2018). Such reward-related disruptions affect healthy individuals who are at a higher genetic risk for developing depression (Olino et al., 2014), patients with active symptoms (Halahakoon et al., 2020), and patients in remission (Ubl et al., 2015).

Irregularities in motivation can be conceptualized as both risk and maintenance factors for major depressive disorder. This view aligns neatly with transdiagnostic, dimensional models, which assess psychopathology using continuous constructs that exist across hierarchical levels of analysis (Insel et al., 2010). These models provide a baseboard for formulating and testing hypotheses about how deep brain stimulation of the MFB alleviates symptoms of refractory depression. To this end are reports of clinical studies supporting that an immediate, intraoperative effect of MFB stimulation is an increase in appetitive motivation (Coenen et al., 2018; Coenen et al., 2022). It is asked, here, whether and how this boost in motivation may drive the clinical property of the stimulation, which similarly has a rapid onset (Döbrössy et al., 2021; Fenoy et al., 2022).

It has been suggested that deep brain stimulation of the MFB obtains antidepressant efficacy primarily via the activation of the dopamine system (Döbrössy et al., 2021; Fenoy et al., 2022). This view falls in line with the series-circuit model of ICSS, according to which dopamine activation is a necessary step for the neural processing of rewards. However, as reviewed in the third Chapter, other methods of increasing synaptic dopamine availability (e.g., psychostimulant administration), do not provide an effective treatment for depression. Notably, vanoxerine, a drug with particularly strong and selective affinity for the dopamine transporter has also failed to demonstrate clinical utility for depression (Obejero-Paz et al., 2015). This drug, otherwise known as GBR-12909, was the agent Trujillo and colleagues (2020) used to outline the convergence model of the brain reward system. The ineffectiveness of a pharmacological boost of tonic dopamine firing in treating depression brings into

question how MFB stimulation, which induces reliable release of dopamine (Michael, Ikeda, & Justice Jr, 1987; Coenen et al., 2022; Gale et al., 2013; Schluter, et al., 2014; Yoshimi et al., 2011), achieves its clinical effect. As the mapping of the precise neural circuitry involved in MFB stimulation continues, we can turn to functional hypotheses that are informed by the BSR literature to answer this question.

The Reward Platform Hypothesis of the Antidepressant Effect of MFB Stimulation

Here, I propose that constant stimulation of the MFB may be treating depression by facilitating a consistent pursuit of rewards. As shown in studies of Behavioral Activation (Lewinsohn, 1975), such a reliable involvement with goal-oriented actions is a potent treatment for depression with equivalent or greater efficacy than other evidence-based psychotherapies (e.g., Cognitive Behavior Therapy; Jacobson et al., 1996) and pharmacotherapies (Dimidjian et al., 2006; Tindal et al., 2017). Considering the antidepressant function of reward seeking, we can appraise whether the neural signal induced by the continuous MFB stimulation provides a raised “platform”, from which participation in goal-directed activities becomes easier.

It is theorized that MFB DBS may decrease the threshold required to pursue rewards, which increases the likelihood to engage in sustained reward seeking. This proposed functional mechanism of the reward platform hypothesis of MFB stimulation could be mediated by a number of ways. First, engagement in rewarding activities may be driven by a higher reward value, produced by a summation of the value of MFB stimulation with the value of other available rewarding activities. Second, the stimulation

could promote engagement with rewarding activities by reducing the subjective effort required to engage in reward seeking. Third, the constant MFB activation may work to increase the salience of rewards by inducing a priming effect (Gallistel, 1966; Reid, Hunsicker, Kent, Lindsay, & Gallistel, 1973). Forth, by increasing the proclivity to invest effort in reward seeking and the consumption of response-contingent rewards, MFB stimulation may help to offset pessimistic reward expectations that are theorized to underlie depression (Huys, Daw, & Dayan, 2015). Figure 1 depicts a schematic of the reward platform hypothesis.

Psychophysical experiments in clinical populations and animal models can be used to evaluate the potential unique and overlapping contributions of the aforementioned hypotheses. Providing some early indications to this end, Walker and Fouriezos (1995) demonstrated that continuous background MFB stimulation improved the vigor of operant behavior only when the stimulation overlapped with the delivery of response-contingent BSR. In other words, the pulses of the continuous MFB stimulation summated with the response-contingent stimulation pulses to amplify reward seeking. It has also been shown that BSR and natural rewards summate and compete with one another (Conover & Shizgal, 1994a, 1994b). Whether and to what extent the effect documented by Walker and Fouriezos is driven by reward value summation, subjective effort reduction, or another property of reward seeking, is open to investigation by psychophysical experiments.

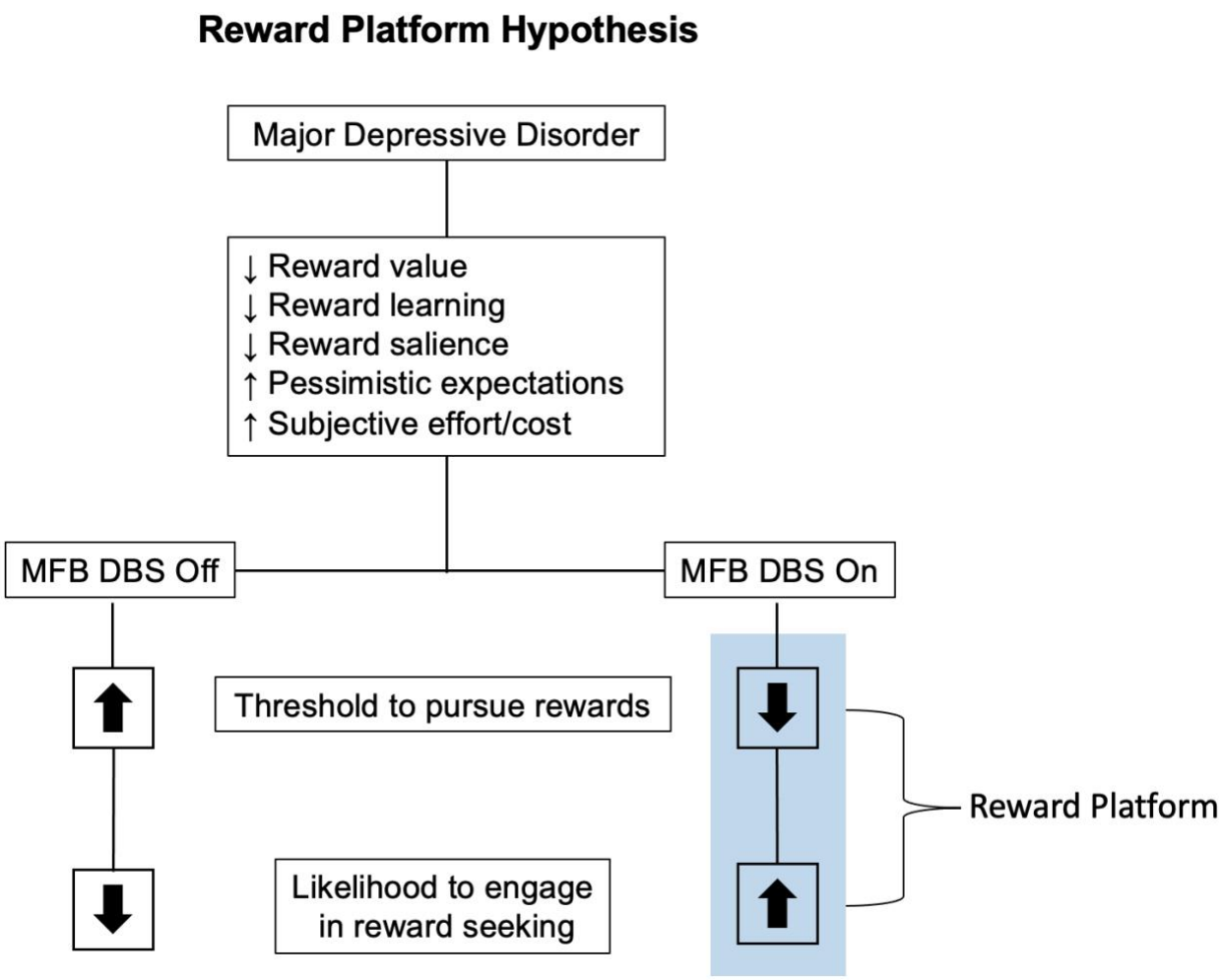

Figure 1. Diagram depicting the reward platform hypothesis. A non-exhaustive list of variables related to motivation that are affected by major depressive disorder is noted. According to the reward platform hypothesis, it is suggested that MFB DBS may decrease the threshold to pursue rewards and increase the likelihood of engaging in reward seeking. This may be mediated by changes in variables related to motivation (e.g., reward value summation, reduction of subjective effort) caused by the stimulation. In place of MFB DBS, other ways to create sustained firing in substrates related to reward seeking can be tested, such as vagus nerve stimulation and psychostimulants.

In humans, vagus nerve stimulation has been related to reinforcement learning and reward seeking (Han et al., 2018; Weber et al., 2021). In one such experiment, vagus nerve stimulation boosted the effort for pursuing rewards (Neuser et al., 2020). As vagus nerve stimulation is implicated in reward seeking and can modulate dopamine firing (Fernandez et al., 2020; Han et al., 2018), it provides a non-invasive paradigm that can be used to study the effects of neuromodulation of the reward system on instrumental behavior. Interestingly, vagus nerve stimulation is an approved, evidence-based intervention for depression (Austelle et al., 2022).

Whether the antidepressant effect of MFB stimulation is tied to continuous stimulation can be explored in both pre-clinical and clinical models. This pattern of neuromodulation for psychiatric disorders was laterally adopted from the application of deep brain stimulation in movement disorders, including Parkinson's Disease, Dystonia, and Essential Tremor (Larson, 2014). Whether the treatment of refractory depression by deep brain stimulation is also dependent on continuous stimulation is open to investigation by appropriate psychophysical experiments.

Depression is associated with many symptoms (Fried et al., 2016). Assessment of the effect of deep brain stimulation for depression relies commonly on two psychometric measures that are not validated for refractory depression and evaluate only a subset of symptoms (Fried, 2017). Rabin and colleagues (2020, 2022) have proposed several ways to improve the measurement of effects of functional neurosurgery, including developing population-specific measures, assessing functional

changes, conducting patient interviews, setting goals, and using technological tools (e.g., smartphone applications for high-frequency symptom assessment, closed-loop real-time electrophysiology). Measures evaluating aversive learning (e.g., skin conductance test) have been used to assess the effects of functional neurosurgery (Hamani et al., 2022; Wickramasuriya, Amin, & Faghih, 2019). It is proposed here that measures of motivation-related constructs can complement the assessment of the effects of deep brain stimulation for depression. For example, the Effort Expenditure for Rewards Task (Treadway et al., 2009) can be used to measure effort-based decision-making, the Balloon Analogue Risk Task (Lejuez et al., 2002) can be used to evaluate risk taking behaviour, and the Iowa Gambling Task (Bechara et al., 1994) can be used to assess probabilistic learning related to monetary rewards and punishments.

The reward platform hypothesis is founded on the idea that an increase in background neural activity of substrates involved in reward processing enables and supports reward seeking. This has long been showcased in the basic BSR literature, wherein the administration of psychostimulants, which increase dopamine tone, is shown to facilitate the vigor of electrical ICSS (Franklin, 1978; Gallistel & Karras, 1984; Wise & Rompré, 1989). In the clinical context, the prediction that increasing the background firing of reward-implicated substrates will invigorate reward seeking can be tested using neuromodulatory techniques other than deep brain stimulation. For example, vagus nerve stimulation or extended-release formulations of psychostimulants can be used to boost dopamine tone. It can be evaluated whether combining targeted use of psychostimulants or vagus nerve stimulation with Behavioral Activation provides

a more effective treatment of depression (i.e., greater magnitude, faster onset, greater response rate, longer duration) than use of Behavioral Activation alone. This proposed study can evaluate whether a tonic boost of dopamine induces a synergistic treatment effect with Behavioral Activation. This way, potential pharmacological/neuromodulatory interventions for depression can be founded on functional endpoints, and not on generalized and unspecified antidepressant properties.

The search for more effective antidepressant medications remains urgent. A remarkable 85% of individuals treated with antidepressants show equivalent improvement with patients receiving placebo (Stone et al., 2022). This finding is superimposed over questioning of established antidepressants' neurobiological rationale (Cowen, 2008; Cowen & Browning, 2015; Moncrieff et al., 2022; Lacasse & Leo, 2005; Leo & Lacasse, 2008), their consequential unwanted effects (Schweitzer, Maguire & Ng, 2009; Wang et al., 2018), and suggestions of iatrogenesis that prolongs the chronicity and worsens the severity of affective disorders (Cosci & Chouinard, 2020; Fava, 1994; Fava, 2020; Fava et al., 2015; Lejoyeux et al.,1996).

The striking antidepressant potency of MFB deep brain stimulation provides a steadfast reminder that symptoms of mental disorders are amenable to biological interventions. Understanding what drives this effect can direct the development of novel interventions, such as pharmacotherapies and non-invasive brain stimulation applications, which can scale to serve appreciably the 280 million of individuals estimated to have depression (Institute of Health Metrics and Evaluation, 2021). Here, it

is outlined that hypotheses guiding this effort and paradigms to test them can be derived readily from the BSR literature.

Conclusion

To account for stochasticity and complexity embedded in open systems, including biological and social ones, biologists Driesch (Valsiner, 2016) and von Bertalanffy (1950, 1968) described equifinality, the principle dictating that an end state can arise via different means. According to equifinality, the same – or similar – endpoints can be achieved through different antecedents and in several ways.

Equifinality operates freely both in the laboratory measurement of operant behavior and in the clinical assessment of psychopathology. Brain stimulation trains composed of different parameters that activate separate branches of the reward system can converge on equivalent operant behaviors. Remarkably different interventions (e.g., psychotherapy, pharmacotherapy, nervous system stimulation) can treat the same mental disorder. Equifinality reveals that the precise ways in which outcomes arise are not easily discernible from the researcher's or the clinician's viewpoints. Instead, the opacity of constructs operating under convergent causation is conducive to inferences about causality. The researcher and the clinician should evaluate these inferences carefully and in their own right. Ultimately, it is endorsed here that psychophysical designs can refine insights stemming from the measurement of operant behavior, and theory-driven, testable hypotheses for the antidepressant effect of MFB stimulation are provided.

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