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The Ventral Tegmental Area (VTA), the Nucleus Accumbens (NAc), the Caudate Nucleus (CN) and the Prefrontal Cortex (PFC) role in the Response to Acute and Chronic Methylphenidate

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Abstract

Methylphenidate (MPD) is psychostimulant, similar to cocaine and amphetamine, that is commonly used to treat attention deficit hyperactivity disorder and is increasingly being abused by healthy subjects for its psychoactive effects such as memory retention cognitive enhancement for young, adult and the elderly and recreation. MPD's action on the brain reward/motive circuit is still under investigation, however it is known that in animals chronic use of MPD leads to behavioral sensitization, an experimental indicator associated with dependence. To investigate this neural circuit's role in response to acute and chronic MPD, three different lesions (non-specific, dopaminergic specific, and glutaminergic specific lesions) have been conducted at the nucleus accumbens (NAc), the ventral tegmental area (VTA), the caudate nucleus (CN), and the prefrontal cortex (PFC), to assess the structure, dopaminergic signaling, and glutaminergic signaling roles in response to MPD. The three types of lesions show that each one of the above four brain areas participate differently in the acute and chronic effect of MPD and have helped determine which type of signaling is critical for the acute and/or chronic behavioral adaptions to MPD.

Keywords: Methylphenidate, Specific lesions, VTA, NAc, CN, PFC, Motive circuit

Introduction

Methylphenidate (MPD; Ritalin®, Concerta®) is one of the first line treatments for patients with Attention Deficit Hyperactivity Disorder (ADHD), and is growing in illicit use for recreation or cognitive enhancement in normal subjects [1-6]. MPD has been shown to produce a variety of effects on the locomotive activity of normal and ADHD-model animals [7-23]. Acute exposure to MPD causes an increase in locomotor activity, while chronic use of MPD has been reported to produce behavioral tolerance [17,24,25], withdrawal [11], or sensitization [10, 17,19,21,25-27].

MPD shares a similar pharmacologic profile to other psychostimulants including amphetamine and cocaine [24,28-30]. It is effective in treating ADHD, in addition to disorders of alertness in children with learning difficulties and of sleep-wake cycles such as narcolepsy and chronic fatigue [31-33]. MPD has been shown to bind to the dopamine transporter preventing dopamine reuptake to the presynaptic terminal, similar to the mechanism of action of cocaine and methamphetamine [24,28,29]. Decreased dopamine reuptake increases dopamine in the synaptic cleft, leading to increased signaling in the postsynaptic neuron which underlies MPD's status as an indirect dopamine agonist [29,34,35]. This increase in dopamine is believed to be linked to the reinforcing effect of psychostimulants such as MPD [36,37].

Acute administration of psychostimulants such as MPD in normal and ADHD model animals results in an increase in locomotor activity [23,25-27,38]. At low doses, this manifests as a net increase in locomotive activity while at high doses it becomes repetitive purples movements termed stereotypic behavior [39-43]. Chronic administration of psychostimulants results in neural plasticity that will ultimately lead to the dependent state. In animal models, tolerance, withdrawal, and behavioral sensitization are used as experimental bioindicators of the abusive potential of a compound [24-27,32,39,44-47]. Behavioral sensitization, or the progressive augmentation of the drug effect produced by re-administration of previous doses, has been implicated as the physiologic underpinning of the symptom of drug craving [48,49], and serves as one of the experimental biomarkers that the drug under investigation has properties consistent with a drug of abuse [24,26,27,45,47,50].

Underlying these maladaptive responses to the effects of MPD is the brain's reward/motive circuit [49,51-54]. This circuit **(Figure 1)** is made up of central nervous system (CNS) structures that are members of the executive function, mesolimbic, and motor systems and work in concert to mediate the behavior of an organism [50,55] and includes the ventral tegmental area (VTA), the nucleus accumbens (NAc), the caudate nucleus (CN), and the pre-frontal cortex (PFC), [56,57]. Classically, the reward circuit is described as originating from the VTA which projected to the NAc, which then projected to the PFC [53,56,58]. However, there is now increased understanding that the projections from the VTA are diffuse to the ventral and dorsal striatum, including the CN, and that reciprocal connections between these and other CNS structures all contribute to the rewards system [53,56,58].

Understanding the neural pathways and their components that mediate the complex responses to MPD exposure remains incomplete. One of the methods used to study them is to ablate a specific brain area of an animal model's CNS structure or signaling pathway (non-specifically or specifically)

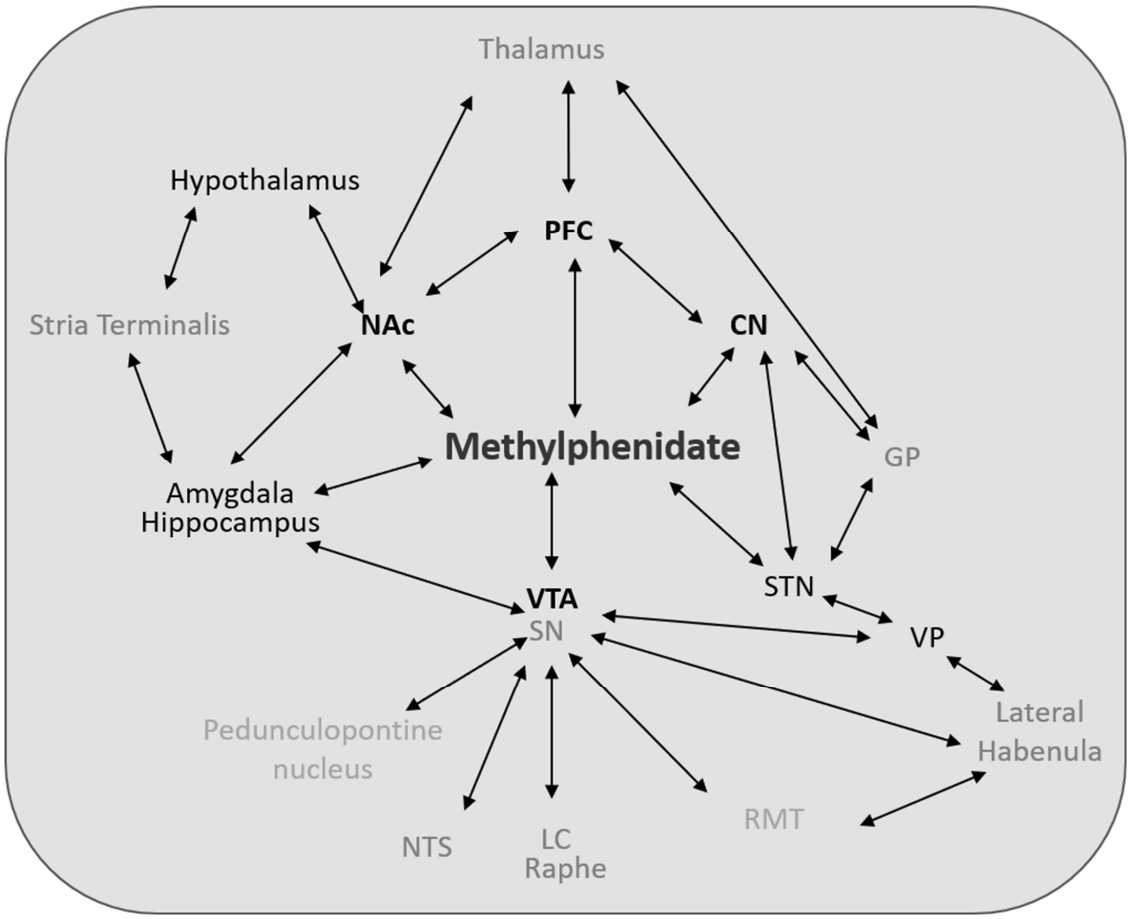

Figure 1. Figure 1 shows a representative diagram of the multiple interactions and pathways that mediate the acute and chronic effects of MPD in the rat CNS. Note that not all pathways are shown, nor is diagram meant to be anatomically to scale. Abbreviations not found in text: GP: Globus Pallidus; LC: Locus Ceruleus; NTS: Nucleus Tractus Solitarius; RMT: Rostromedial Tegmentum; STN: Subthalamic Nucleus; VP: Ventral Pallidum.

and challenge the subject to the substance. This manuscript reviews the non-specific electrolytic, dopaminergic specific, and glutaminergic specific lesions to the VTA (**Figure 3**) [59], to the NAc (**Figure 4**) [13,15,60], to the CN [4,7] (**Figure 5**) and to the PFC (**Figure 6**) [11,14,15], in the setting of acute and chronic MPD exposure that have been conducted. Bilateral non-specific lesions were conducted with electrolytic ablation [13,15,60], bilateral chemical dopaminergic specific lesions were obtained with local microinjection of the neurotoxin 6-hydroxydopamine (6-OHDA) [7,13,61-63], and bilateral glutaminergic specific ablation was obtained with local microinjection of the neurotoxin ibotenic acid [64-67] within the VTA, NAc, CN & PFC. Animal response to MPD was monitored and recorded with a computerized animal tracker in a behavioral open field assay, a means to track animal locomotive activity. It can track multiple movement parameters which can be analyzed by software to output distinct behavioral expression of locomotion which can then be followed over time to determine the acute and chronic effects of MPD. By drawing together current understandings of neural anatomy, circuitry, and these lesions' effects, we hope to offer a perspective on the current knowledge governing the effects of MPD.

Methods

The methods used in this review were published in detail [4,7,11,13-15,59,60,68,69]. In short, 160 male Sprague-Dawley rats weighing 170-180 g were obtained from Harlan Labs (Indianapolis, IN, USA). Animals were individually placed in plexiglass cages (40.5 x 40.5 x 31.5 cm in dimension) in a soundproof room for 4-5 days to acclimate prior to experimentation. These cages served as the home and test cage (**Figure 2**). Animals were maintained on a 12-hour light/dark cycle that began at 06:00. Food and water were provided ad libitum throughout the experiment, and the temperature was kept at 21 ± 2°C with a relative humidity of 37-42%. Each of the four-brain lesion consist five group each N=8 as follow: 1). Intact animals; 2). Shame operated; 3). Nonspecific bilateral electrolytic lesion; 4). 6-OH DA bilateral injection for dopamine signaling ablation and 5). Ibotonic acid bilateral injection for chemical ablation of the glutaminergic system (**Table 1**). This

Effect of surgery — Chronic effect of MPD

Group	Experimental Schedule								
	ED 1*	ED 2	ED 3-7	ED 8*	ED 9*	ED 10-13	ED 14*	ED 15-17	ED 18*
Control	Saline			Saline	MPD	MPD	MPD	Washout	MPD
Sham	Saline	Surgery	Recovery	Saline	MPD	MPD	MPD	Washout	MPD
Lesion	Saline	Surgery	Recovery	Saline	MPD	MPD	MPD	Washout	MPD

Acute effect of MPD — Sustained chronic effect of MPD

Table 1. Table 1 shows the experimental protocol of methylphenidate (MPD) administration and recording schedule. Displayed are the experimental days (ED's) either normal saline or MPD was administered. * indicates day rats were behaviorally recorded post-injection. Lesion refers to the electrolytic, 6-OHDA toxin, or ibotenic acid toxin administered on ED 2. Brackets show the comparisons that were made: the post-surgical effect (ED 8 vs. ED 1), the acute effect of MPD (ED 9 vs. ED 8), and the chronic effect of MPD- sensitization- that is seen after sustained administration (ED 14 vs. ED 9) and persists after washout (ED 18 vs. ED 9). Full methodology can be found in the original reports [4,7,11,13-15,27,59].

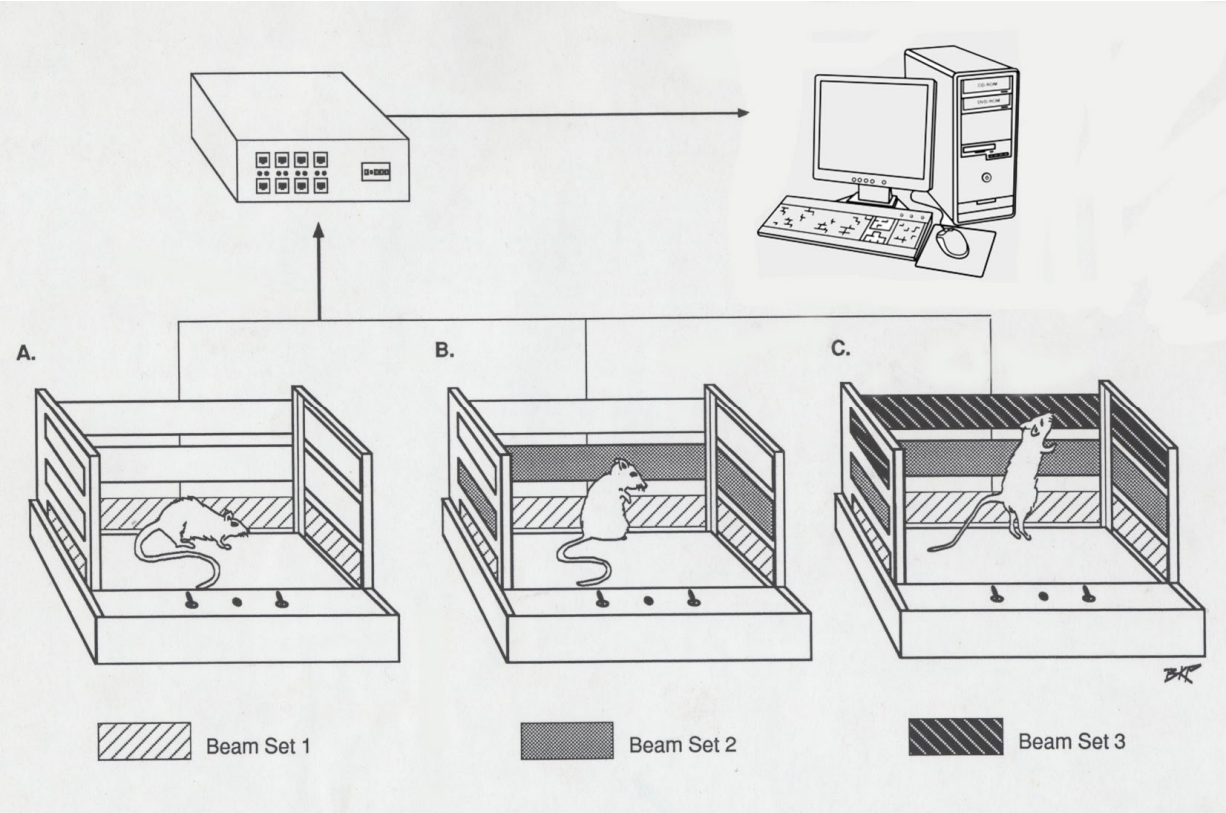

Figure 2: Figure 2 shows a schematic of the open field recording system used to monitor the animals and generate the indices of movement in the original reports [4,7,11,13-15,27,59].

protocol was approved by our Animal Welfare Committee and carried out in accordance with the National Institute of Health Guide for Care and Use of Laboratory Animals. On experimental day 1 (ED 1-Sal) animals were weighed and 0.8 mL of 0.9% saline was administered intra-peritoneal (i.p). All animals weighed 200-220 g at that time. Locomotive behavioral activity was recorded for 120 minutes post-injection to establish a baseline prior to surgical manipulation. On experimental day 2 (ED 2), the lesion and sham groups underwent surgery and were then allowed to recover for approximately 5 days (ED 3-7). On experimental day 8, saline was re-administered (ED 8-Sal) and post-surgical locomotor activity was recorded for 120 minutes to compare with the pre-surgical baseline (ED 1-Sal). Starting on experimental day 9 (ED 9-MPD), daily injections of 2.5 mg/kg MPD (Mallinckrodt, Hazelwood MO) dissolved in 0.8 mL of 0.9% saline were administer for 6 consecutive days (ED 9-MPD to ED 14-MPD), and activity recorded for 120 minutes post-injection. This dose of 2.5 mg/kg MPD has been shown to be sufficient to elicit behavioral sensitization in rats in previous dose-response experiments [7-9,17-23,70-72]. For the next 3 days (ED 15-17), animals received no injections (the washout period). After the washout period (ED 18-MPD), the rats were re-challenged with MPD at the previous dose of 2.5 mg/kg and behavioral activity was observed for 120 minutes (**Table 1**). On ED 2, the sham operation group, the electrolytic lesion group, the 6-OHDA group, and the ibotonic acid group animals were anaesthetized with 60 mg/ kg pentobarbital and placed in the stereotactic apparatus. An incision was to expose the skull. For surgery, holes were drilled in the skull bilaterally as follows: for the PFC- anterior (A) from Bregma 3.7 mm, lateral (L) from midline 0.4mm; for the NAc A- 1.7 mm, L- 1.4 mm and 1.8 mm; for the CN posterior (P) from Bregma 0.2 mm, L- 2.0 mm and 3.0 mm; for the VTA P- 4.8 mm, L- 0.5 mm using the Paxinos and Watson "The Brain Atlas" [73] coordination. Bipolar stainless steel 80u electrode was used to make the non-specific electrolytic lesion with 2.0 mA DC current for 90 sec. at a depth of 3.2 mm and 4.2 mm; 1.0 mm and 1.6 mm; 4.0 mm and 5.2 mm and 8.2 mm and 8.5 mm within the PFC, NAc, CN and VTA respectively. For the chemical specific ablation of dopaminergic and glutamatergic neurons 8.0 ug 6OH DA (Sigma St. Louis, Mo, USA) dissolved in 2 uL of 0.9% Saline containing 0.2 mg/ml ascorbic acid and 4.0 uL of 1 ug/mL isotonic acid (Sigma St. Louis, Mo, USA) solution in depth similar to the non-specific electrolytic lesion for dopaminergic and the glutamatergic specific neurons ablation respectively. For the shame operation groups similar procedure (electrodes,

cannula and coordination) were used but no current or injection were given [4,7,13-15,59,60,69]. The cannulas and the electrodes were then removed, and incision closed with wound staples.

Behavioral locomotive activity was recorded using the open field computerized animal activity monitoring system (CAAM, Accuscan Instruments, Inc., Columbus OH). The CAAM system consists of 3 arrays of 16 infrared light beams with sensors on the opposite side, spaced every 2.5 cm that cross orthogonally through the plexiglass cage (**Figure 2**). Movement of the rats interrupted the infrared light beams, and each beam-break detected by a sensor was collected as an event by the Accuscan Analyzer and transferred to a computer. Events over a 5-minute period were summed, giving 12 5-minute bins for each hour of observation. These bins were transferred to the OASIS data collecting software and three indices of behavioral locomotion were compiled for each collection period: Total movement (TM), total travelling distance (TD)- all forward locomotion in cm, horizontal activity (HA)- the overall movement in the lower level of the cage, and the number of stereotypic movements (NOS)- episodes of purposeless, repetitive movement in the upper level of the sensors separated by at least 1 second. Only HA, TD, & Nos were published, TM not. At the conclusion of the experiment, animals were overdosed with sodium pentobarbital and perfused with 10% formaldehyde. The brains were removed and stored in 10% formaldehyde. 60 µm thickness coronal sections were cut, stained, and scanned with a high-resolution scanner to identify lesion size and location correlated to the NAc using the Paximos and Watson rat brain atlas [73].

Rat behavioral locomotive activity was quantified by four compiled indices of movement (TM, HA, TD, NOS) obtained in twelve 5-minute bins collected the hour after injections for each rat were averaged across each experimental group based on the experimental day to allow for comparisons. Post-surgical manipulation effects on baseline behavioral locomotor activity were determined by comparing the animal's activity after a saline injection before and after the surgical intervention (ED 8-Sal vs. ED 1-Sal). The acute effects of MPD were determined by comparing the first day of MPD administration to the post-surgical baseline (ED 9-MPD vs. ED 8-Sal). The effects of repetitive (chronic) MPD exposure over 6 consecutive days on behavioral locomotor activity were determined by comparing the final day of administration to the first, i.e. the induction phase (ED 14-MPD vs. ED 9-MPD). The effects of chronic MPD exposure following a washout period on behavioral locomotor activity were determined by comparing MPD re-challenge to the initial administration, i.e. the expression phase (ED 18-MPD vs. ED 9-MPD) (See **Table 1**). Significance of change among these within-group comparisons was determined by ANOVA, with repeated measures with adjustments for correlation among measurements within each animal. Post ad hoc comparisons were used to estimate changes between days within groups. A p-value<0.05 was considered statistically significant. The effects of each lesion were determined by comparing the treatment group to both the control and sham groups on each of the recording days (ED 1-Sal, ED 8-Sal, ED 9-MPD, ED 14-MPD, and ED 18-MPD). Significance of change among the between-group comparisons was determined with Turkey-Kramer Honest Significant Difference (HSD) post hoc test. A p-value<0.05 was considered statistically significant.

Result

The ventral tegmental area (Figure 3, VTA)

The VTA is a collection of primarily dopaminergic neurons distinct from the substantia nigra that gives rise to the dopaminergic projections of the mesocorticolimbic system which underlies the reward circuit and is critical for conditioned responses and chemical dependency [74-76]. Despite usually being considered a single entity, the VTA is quite heterogenous, and is comprised of four major divisions: the parafasciculus retroflex area (PFR), the ventral tegmental tail (VTT), the paranigral nucleus (PN), and the parabrachial pigmented area (PBP) [58]. The major outputs of the VTA are from the PN and PBP to the NAc and the PFC, which are critical for the initiation of reward functions via the mesolimbic system [19,58], and from the PFR and VTT to the diagonal band. The dopaminergic outflow of the VTA is thought to be modulated by its multiple afferent inputs, the most dominant being the glutamatergic input from the PFC [75]. Other inputs to the VTA originate from the NAc, the CN, the ventral pallidum, the rostromedial tegmental nucleus, the subthalamic nucleus, pedunculopontine tegmental and laterodorsal tegmental nuclei, the bed nucleus of the stria terminalis, and the superior colliculus [17,18,40,41,77-81].

Both glutaminergic and dopaminergic signaling in the VTA have been shown to be critical for the animal response to MPD. Specific glutaminergic ablation of the VTA abolishes any response to MPD acutely or chronically, indicating that glutaminergic signaling with the VTA is critical for the acute and chronic behavioral responses to MPD (**Figure 3**) [59]. Dopaminergic ablation however only prevents the acute response to MPD, the chronic response of behavioral sensitization is left intact (**Figure 3**) [59]. Significant attention has been paid to the functions of the VTA's dopamine projections, which have been shown to initiate the mesocorticolimbic reward system [49,81-83], however this finding of glutamate in the VTA being critical is novel and presents a further nuance to the complexities of this nucleus. Notably, glutaminergic ablation of the prefrontal cortex also precludes behavioral sensitization [84,85], which agrees with the hypothesis that the PFC/VTA is the predominant pathway to regulating behavioral sensitization.

There is significant evidence that differing sections of the VTA induce different behavioral outcomes. The medial

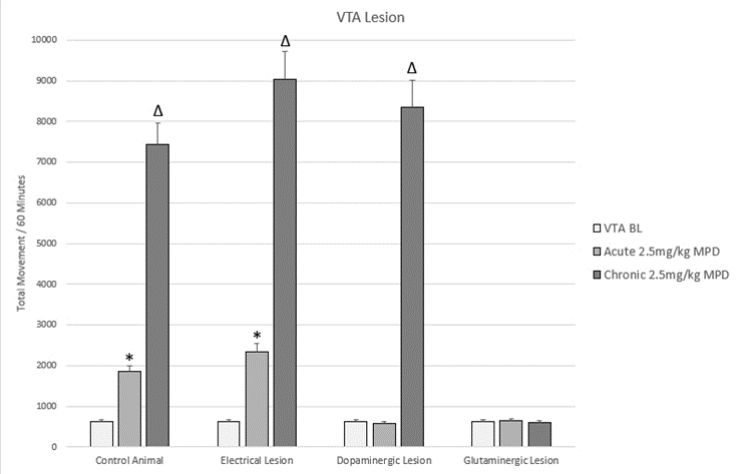

Figure 3. Figure 3 shows a representation of animal total movement (TM) following acute and chronic methylphenidate (MPD) in animals that were subjected to lesions to the VTA.

* = indicate significant p<0.05 different from experimental day 1 (ED 1) baseline (BL), (ED1 MPD/ ED1 BL); Δ = indicate significant p<0.05 different from experimental day 1 (ED 1) methylphenidate (MPD) 2.5mg/kg, i.e., (ED10 MPD/ ED1 MPD).

VTA is comprised of an inhibitory pathway that negatively regulates behavioral activities [14,81,86-88] while the lateral VTA appears to mediate reward functions such as behavioral augmentation [19,20,76,77]. Excitatory D1 receptors appear to be the predominant type in the lateral reward pathway [89], with inhibitory D2 making up the majority of the medial inhibitory pathway receptor type [90,91]. The functional and anatomic distinction with in the VTA would appear to explain the results of non-specific electrolytic ablation of the VTA causing an acute increase in behavioral activity with no change to the overall response to MPD administration (**Figure 3**) [59]. Ablation of the medial inhibitory VTA with an intact lateral reward VTA would produce larger behavioral increases while maintaining the response to MPD.

Identification and targeting of the VTA's subregions (medial vs. lateral, PFR vs. VTT vs. PN vs. PBP) has proved to be exceedingly difficult, even using in vivo electrophysiologic studies [92]. These studies of the heterogeneity of the VTA appear to disagree with the classical view of the VTA solely as the dopaminergic origin of the mesolimbic and mesocortical pathways, and hints at the higher order modulation required to produce complex behavioral responses. Further work using *in vivo* recording, lesions, and microinjections investigating the subdivisions of the VTA represent future avenues for understanding this nucleus.

The nucleus accumbens (Figure 4, NAc)

The nucleus accumbens (NAc) is critical for motivation, emotion, limbic functions, and motor execution. It is composed predominantly of dopaminergic median spiny neuron's (MSN's) and is divided into a shell and core that are anatomically and functionally distinct [93-95]. The NAc shell seems to mediate reward and addiction behaviors, while the core appears to modulate conditioned response and spatial learning [94,96,97]. The primary input to the NAc is from the VTA, but it also receives input from the substantia nigra, the amygdala, the hippocampus, and the PFC. The output from the NAc is via its MSN's to various basal ganglia and midbrain structures including (but not limited to) the substantia nigra, the VTA, the ventral pallidum, the thalamus, the globus pallidus, the subpallidus, and the stria terminalis [94,98,99].

Changes in accumbal dopamine have been shown to be critical for reward circuit responses. Psychostimulants such as MPD have been shown to cause an increase in dopaminergic transmission from the VTA to the NAc, and increased dopamine within the NAc has also been shown to lead to increased locomotion [100-102]. It has been consistently reported that direct chronic microinjection of other dopaminergic agonists such as amphetamine, cocaine, or morphine into the NAc can induce behavioral sensitization [103-105], suggesting that the NAc is involved in the induction of behavioral sensitization. Psychostimulant exposure increases dendritic branch points and spines of the NAc's MSN's, and MPD has been shown to cause increased spine formation in excitatory MSN-D1 dopamine receptors but not inhibitory MSN-D2 dopamine receptor spines [106,107]. This excitatory effect of psychostimulants is greatest in the shell [108-110], indicating this component of the NAc is critical to mediating chronic psychostimulant effects.

Lesions to the NAc have confirmed its role in responding to acute and chronic MPD. Non-specific electrolytic lesions to the NAc have resulted in an exaggerated acute response to MPD and a loss of behavioral sensitization with chronic exposure (**Figure 4**) [13]. This indicates that in addition to its role in the

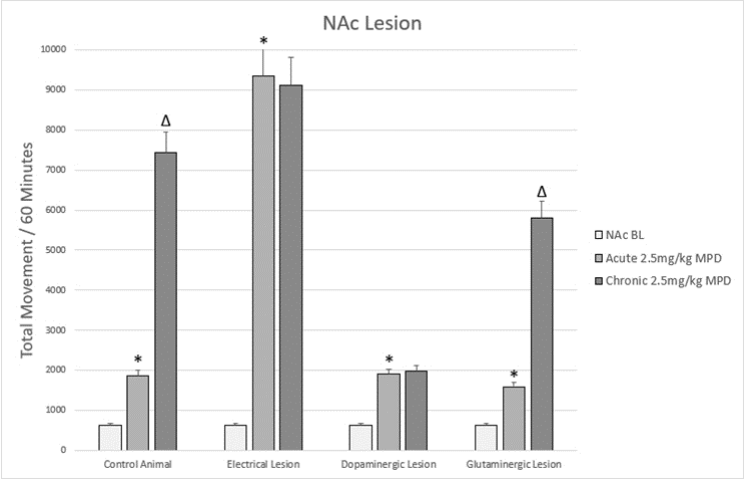

Figure 4. Figure 4 shows a representation of animal TM following acute and chronic methylphenidate (MPD) in animals that were subjected to lesions to the NAc.

* = indicate significant p<0.05 different from experimental day 1 (ED 1) baseline (BL), (ED1 MPD/ ED1 BL); Δ = indicate significant p<0.05 different from experimental day 1 (ED 1) methylphenidate (MPD) 2.5mg/kg, i.e., (ED10 MPD/ ED1 MPD).

response to MPD, the NAc serves as an inhibitor of behavioral activity [111]. The NAc's inhibitory role in behavioral activity can be seen following treatment with dopamine modulators that attenuate activity [112,113], and could serve as an autoregulatory system to control excessive dopaminergic signaling.

Selective lesions to the dopaminergic signaling of the NAc also resulted in a loss of behavioral sensitization to cocaine, amphetamine, and MPD (**Figure 4**) [15,114,115]. One study showed two distinct responses in rats following dopaminergic lesions of the NAc. While some animals exhibited no increase in locomotor activity after the acute injection of MPD, others showed a significantly elevated locomotor activity following MPD and this difference persisted throughout the length of the study [15]. Those animals that showed an increase in behavioral activity following acute MPD did not develop behavioral sensitization, i.e. a further increase beyond the acute effect, while those that showed no behavioral change following the dopaminergic lesion did show behavioral sensitization following repetitive (chronic) MPD exposure [15]. This work seems to verify that NAc dopamine is a critical component of the behavioral response both acutely and chronically to MPD, but the heterogeneity of responses raises more questions than it answers. The author notes that the accuracy of the lesion (core, shell or both) is unknown as the lesions could not be verified independently and therefore it is possible that the difference in acute response to psychostimulant administration may be due to differences in the size or location of the lesion [15].

The glutaminergic signaling of the NAc appears to also modulate the effect of MPD. Selective lesions to the glutaminergic NAc signaling system do not lead to a gross disturbance in the acute or chronic response to MPD **(Figure 4**) [60], however when broken down into different locomotor expression of movement (horizontal activity vs. total distance vs. stereotypic movements), a significant difference is seen between groups [60]. Specifically, more goal directed forward movement as measured by horizontal activity (HA) was attenuated while stereotypic activity as measured by the number of stereotypic movements (NOS) was augmented following glutaminergic ablation of the NAc; total distance (TD) traveling remained unchanged [60]. This work seems to indicate that it is volitional movement that is modulated by glutaminergic signaling in the NAc, which fits with glutaminergic input from the PFC being critical to movement [116-120], and with a more global picture of glutaminergic signaling being critical to modulating the motor outcomes of the rewards circuit [4,7,19,21,70,87].

However, this lesion was centered in the NAc core and did not differentiate from the core versus the shell. The specific attenuation of volitional movement corroborates with other work showing that in addition to the shell/core distinction, different pathways within the NAc govern motivation and behavioral actions [121,122]. And while the NAc shell was initially thought to govern the response to psychostimulants, the NAc core has also been shown to participate in the response as well [109,123,124], further reinforcing the evidence that the anatomic distinctions are really secondary to the signaling pathways within the NAc. This all hint at the differing roles of the NAc core, shell, and the circuits between them.

The caudate nucleus (Figure 5, CN)

The caudate nucleus (CN) is unique in that it belongs to both the extrapyramidal motor system and reward/

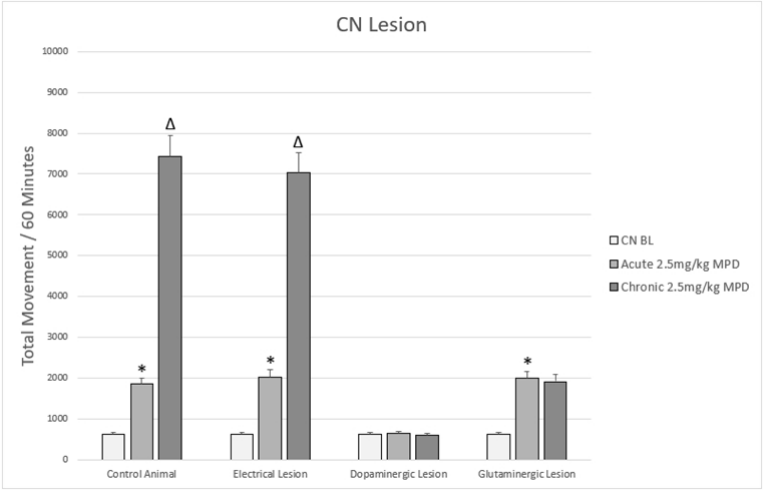

Figure 5. Figure 5 shows a representation of animal TM following acute and chronic methylphenidate (MPD) in animals that were subjected to lesions to the CN.

* = indicate significant $p<0.05$ different from experimental day 1 (ED 1) baseline (BL), (ED1 MPD/ ED1 BL); Δ = indicate significant $p<0.05$ different from experimental day 1 (ED 1) methylphenidate (MPD) 2.5mg/kg, i.e., (ED10 MPD/ ED1 MPD).

motive circuit [19,20,125,126]. In rats, who lack an internal capsule, the caudate is blended with the putamen forming the caudoputamen or dorsal striatum which can similarly be divided into a medial and lateral component. The CN is comprised primarily of catecholaminergic dopaminergic medium spiny neurons (MSNs) that were originally thought to be inhibitory regulators of movement [127,128], however further work showed its functions to more complex [129]. The MSN's of the CN express excitatory D1-dopamine receptors and inhibitory D2-dopamine receptors [130,131]. These neurons project via the direct pathway, the ansa leticularis, and the indirect pathway, the lenticular fasiculus, [125] to modulate movement. The indirect pathway expresses primarily inhibitory D2-dopamine receptors and exerts its effects via the globus pallidus externa and subthalamus. The direct pathway primarily expresses stimulatory D1 receptors to inhibit the globus pallidus interna. From there, both pathways project to the motor nuclei of the thalamus then to the cortex [125,130,132,133]. The CN receives input from other reward circuit nuclei such as the VTA, the NAc, and the PFC which assist in mediating behavioral sensitization following chronic psychostimulant administration [13-15,19,-21,134,135].

The dopaminergic and glutaminergic signal pathways of the CN have been shown to be critical for the effects of MPD. Increased dopamine transmission in the CN in response to psychostimulant exposure contributes to the increased locomotive activity that is characteristic of psychostimulants (**Figure 5**) [4,7,8,136]. Specific lesions to the dopaminergic neurons of the CN extinguishes any response to MPD both acutely and chronically, and specific antagonism of the D1 receptor can prevent the motor response to MPD, indicating that the excitatory pathway is the primary target of MPD (**Figure 5**) [4,7,136,137]. Glutamate signaling regulates the output of the MSN's to produce the chronic effects of MPD as shown by ablation of glutaminergic signaling within the CN that preventing the chronic effect of MPD such as behavioral sensitization, but not the acute effect (**Figure 5**) [4]. Co-localized glutamate and dopamine receptors on a subset of MSN's and an alteration of dopamine synthesis capacity in response to local CN glutamate could explain the modulatory role of glutaminergic signaling, however more work would need to done to verify this [135,138-141].

The CN has been shown to be critical for learning and memory, mediated by several pathways. Several studies have shown that animal memory is enhanced by increased CN dopamine and impaired by dopaminergic lesions [142,143], consistent with the theory of dopamine-mediated memory consolidation. However, glutaminergic signaling in the CN has also been shown to participate in long-term learning as well. Glutamine infusion into the CN has been shown to strengthen learned behavior, and N-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptors, in the CN are required for operant learning in rats [144,145]. Additionally, non-specific systemic glutamate antagonists can reduce the stereotyped behavioral responses to psychoactive substances [146,147], and although this work is not CN specific it lends credence to a glutaminergic component to learning. The lack of behavioral sensitization to MPD after specific glutaminergic ablation supports glutaminergic signaling within the CN as mediator of long-term learning and substance abuse associated with chronic MPD use [4]. These findings seem to indicate a concomitant neuromodulatory role of CN glutamate

and dopamine for learned behaviors an individual exhibit in association with chronic psychostimulant use. And while evidence exists for some anatomic and function divisions between the medial and lateral CN in cognitive and association functions respectively [143], no work has been targeted enough to examine if the dopaminergic and glutaminergic mediated learning pathways are similarly separated.

Non-specific electrolytic lesions to the CN have failed to affect the acute or chronic response to MPD (**Figure 5**) indicating that current electrolytic lesion targeting both afferent, the direct excitatory and the indirect inhibitory circuit and supports the CN as a heterogenous structure in both form and function [4,7].

The prefrontal cortex (Figure 6, PFC)

The prefrontal cortex (PFC) is a large territory of tissue at the anterior pole of the brain. It is critical to a diverse range of cognitive functions such as emotion, conscious decisions, and memory [148]. The PFC serves as a significant source of the excitatory amino acid glutamate, which it projects to the VTA and NAc to modulate dopaminergic signaling at these nuclei [48,49,149-151].

The PFC is critical in mediating behavioral sensitization to psychostimulants. Non-specific ablation of the rat PFC as well as dopaminergic specific lesion did not prevent the MPD acute effect while, prevent the MPD repetitive (chronic) effect eliciting behavioral sensitization in response to chronic MPD administration (**Figure 6**) [11,69]. However, glutaminergic specific ablation has been shown to prevent MPD-induced hyperactivity acutely, however the chronic response of sensitization is maintained and even exaggerated (**Figure 6**) [14]. These differing responses to non-specific electrolytic lesions as compared to a selective chemical lesion is likely due to the numerous different neuronal pathways affected by a non-selective lesion [11,14]. They are consistent with the known glutamatergic efferents to the VTA and NAc. Glutamate from the PFC excites VTA dopaminergic neurons, which increases dopamine release in the NAc [118-120]. Increased dopamine within the NAc disinhibits motor inhibition, thus leading to increased locomotion [151,152]. This finding has been replicated with other psychostimulants, further implicating glutamate from the PFC as a key component of the neuroadaptive response to psychostimulants [80,151,153-157]. The enhanced chronic response following MPD in the setting of glutaminergic specific ablation is likely due to the persistence of non-glutaminergic pathways that are uncovered following the specific lesion but destroyed in the non-specific lesion, and further indicates the diverse neuronal populations in the PFC [11,14]

The PFC cytoarchitecture however is highly heterogeneous, containing norepinephrine, dopamine, α2 adrenoreceptors, and GABA in addition to its primary glutaminergic neurons [158-160]. There are two subgroups of DA receptors: excitatory D1 and inhibitory D2 receptors, with D1 DA receptors are expressed in a higher density compared to D2 DA in the PFC [161,162]. These receptors have been shown to modulate the excitability of PFC neurons, with D1 receptor activation being able to directly excite PFC neurons [162-164]. One study has shown that specific dopaminergic ablation of the PFC did not alter the acute behavioral change to MPD, but

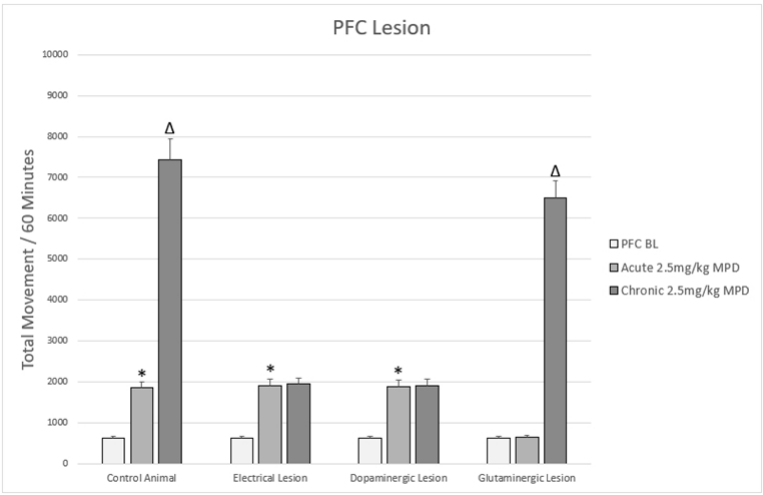

Figure 6: Figure 6 shows a representation of animal TM following acute and chronic methylphenidate (MPD) in animals that were subjected to lesions to the PFC.

* = indicate significant p<0.05 different from experimental day 1 (ED 1) baseline (BL), (ED1 MPD/ ED1 BL); Δ = indicate significant p<0.05 different from experimental day 1 (ED 1) methylphenidate (MPD) 2.5mg/kg, i.e., (ED10 MPD/ ED1 MPD).

did prevent behavioral sensitization following chronic MPD (**Figure 6**) [15]. However, reports of dopaminergic lesions to the PFC are mixed: with some reporting behavioral changes consistent with the prior study [114,165,166], while others report inconsistent motor activity changes following the lesion [166,167]. While these differences could certainly have been due to methodology, all the reports indicate that PFC dopamine plays a role in regulating both the motor response to acute MPD and the neuroadaptation to chronic MPD characteristic of the expression of behavioral sensitization.

However, rodent studies of the PFC should be considered with the recognition that they are poor surrogates for the human counterpart. The human PFC contains multiple divisions, of which only a few share homologies with a rodent counterpart [148,168]. Indeed, this is readily apparent from the lack of higher order social, emotional, and cognitive functions in rodents. So, while these studies of pathways and signaling in the rodent are not directly translatable to man, they provide an important understanding of the primitive pathways that drive complex neurocognitive functions such as behavioral sensitization and substance abuse. Further work in this region promises to deliver even more complete understanding of the basis of volitional and non-volitional motivation.

Conclusions

The NAc, VTA, CN, and PFC have been shown to be critical in the acute and chronic response to MPD. Through specific and non-specific lesions (**Figures 3-6**), the functions of the nuclei and their composite signaling pathways is better understood. But as more is learned, further questions are raised regarding anatomic and functional distinctions of the various subdivisions noted. Further refinement of *in vivo* identification and targeting of these subdivisions will allow for a more accurate understanding of the reward circuit and its response to psychostimulants such as MPD.

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Declarations

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Conflict of interest

There are no conflicts of interest among any of the listed authors.

Consent for publication

All authors have approved the manuscript and agree with its submission.

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