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Glutaminergic signaling in the caudate nucleus is required for behavioral sensitization to methylphenidate

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ABSTRACT

Methylphenidate (MPD) is a widely prescribed psychostimulant for the treatment of attention deficit hyperactivity disorder, and is growing in use as a recreational drug and academic enhancer. MPD acts on the reward/motive and motor circuits of the CNS to produce its effects on behavior. The caudate nucleus (CN) is known to be a part of these circuits, so a lesion study was designed to elucidate the role of the CN in response to acute and chronic MPD exposure. Five groups of $n = 8$ rats were used: control, sham CN lesions, non-specific electrolytic CN lesions, dopaminergic-specific (6-OHDA toxin) CN lesion, and glutaminergic-specific (ibotenic acid toxin) CN lesions. On experimental day (ED) 1, all groups received saline injections. On ED 2, surgeries took place, followed by a 5-day recovery period (ED 3–7). Groups then received six daily MPD 2.5 mg/kg injections (ED 9–14), then three days of washout with no injection (ED 15–17), followed by a re-challenge with the previous 2.5 mg/kg MPD dose (ED 18). Locomotive activity was recorded for 60 min after each injection by a computerized animal activity monitor. The electrolytic CN lesion group responded to the MPD acute and chronic exposures similarly to the control and sham groups, showing an increase in locomotive activity, i.e. sensitization. The dopaminergic-specific CN lesion group failed to respond to MPD exposure both acute and chronically. The glutaminergic-specific CN lesion group responded to MPD exposure acutely but failed to manifest chronic effects. This confirms the CN's dopaminergic system is necessary for MPD to manifest its acute and chronic effects on behavior, and demonstrates that the CN's glutaminergic system is necessary for the chronic effects of MPD such as sensitization. Thus, the dopaminergic and glutaminergic components of the CN play a significant role in differentially modulating the acute and chronic effects of MPD respectively.

1. Introduction

Use of the psychostimulant methylphenidate (MPD; Ritalin, Concerta) has grown dramatically over the last decade (Dalsgaard et al., 2012; Visser et al., 2014; Frauger et al., 2016; Pauly et al., 2018; King et al., 2018). This has been driven by the rapid increase in patients diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) for which MPD is the drug of choice (Storebø et al., 2016; Fond et al., 2016; Stanford and Tannock, 2012; Froehlich et al., 2007; Accardo and Blondis, 2001; Goldman et al., 1998; Levin and Kleber, 1995; Solanto, 1998), as well as the rise in non-prescription use of MPD for academic enhancement and recreation (Cox et al., 2003; Greely et al., 2008; Wilens et al., 2008; Bogle and Smith, 2009; Fond et al., 2016; Djezzar et al., 2014). When properly administered to its target population, psychostimulants including MPD significantly improve symptoms and can be protective against the future development of a substance abuse disorder (Mannuzza et al., 2008; Kollins et al., 2009; Clavenna and Bonati, 2014; Paslakis et al., 2013; Gray et al., 2011). However, healthy individuals often abuse psychostimulants for their desirable effects of enhanced attention and focus (Clemow and Walker, 2014; Kollins et al., 2009), with MPD having a reported abuse rate of up to 35% in college aged individuals (Huss and Lehmkuhl, 2002; Wilens et al., 2008; Bjarnadottir et al., 2013). This growing illicit usage of MPD in non-ADHD populations is a cause for concern given that MPD remains less studied than its psychostimulant counterparts, amphetamine and cocaine.

With the increase in non-therapeutic MPD use by healthy subjects (Cox et al., 2003; Greely et al., 2008; Wilens et al., 2008; Bogle and Smith, 2009; Fond et al., 2016; Djezzar et al., 2014), further investigation is needed to elucidate MPD's mechanism of action on the brains of normal subjects. Chronic use of MPD has previously been reported to produce behavioral tolerance, withdrawal, and sensitization - the progressive augmentation of the drug effect produced by re-administration of previous doses in animals (Schreiber et al., 1976;

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Robinson and Berridge, 1993; Kuczenski and Segal, 1997; Gaytan et al., 2001; Yang et al. 2003a, 2006a, & 2007a; Claussen and Dafny, 2015; Dafny and Yang, 2006; Lee et al., 2008; Algahim et al., 2009; Claussen et al., 2012; Jones and Dafny, 2014; Claussen and Dafny, 2015, Karim et al. 2017 & 2018). Increases in behavioral expression, i.e. sensitization, following repeated doses of psychostimulant serves as one of the experimental biomarkers of MPD's potential to become a drug of abuse.

MPD shares a similar pharmacologic profile to other psychostimulants including amphetamine and cocaine (Kharas et al. 2019; Diaz Heijtz et al. 2004; Accardo and Blondis 2001; Kuczenski and Segal 1997; Teo et al. 2003; Volkow et al. 1995). They act by binding to the dopamine transporter and preventing reuptake of dopamine from the synaptic cleft into the presynaptic terminal, leading to increased dopamine activity at the postsynaptic neuron (Gatley et al. 1999; John and Jones 2007; Volkow et al. 1999).

The brain's reward/motive circuit is known to play a role in the development of reward-seeking behaviors involved in substance abuse disorders (Gardner et al., 1997; Kalivas et al. 1993; Wolf 1998; Woolverton and Johnson 1992; Volkow et al. 2006; Everiit and Robbins 2013). This circuit is made up of several central nervous system (CNS) nuclei that work in concert to facilitate communication between the limbic and motor circuits to ultimately produce the behavior of an organism (Oldehinkel et al. 2016; Dafny and Yang 2006; Chiara and Imperato 1988; Koob and Bloom 1988). This circuit includes the ventral tegmental area (VTA), the nucleus accumbens (NAc), the pre-frontal cortex (PFC), and the caudate nucleus (CN).

Psychostimulants such as MPD act on the reward/motive circuit to facilitate their long-term effects (Volkow et al. 2012; Manev and Uz 2009; Yang et al. 2007b). The CN belongs to both the extrapyramidal motor system and reward/motive circuit (Claussen et al. 2015; Claussen et al. 2012; Yang et al. 2006a&b; Rebec 2006), making it a unique structure of interest in the animal response to psychostimulants. The CN receives input from the VTA, the NAc, and the PFC which have been shown to be key participants in expressing behavioral sensitization following chronic psychostimulant administration (Pierce et al. 1996 & 1998; Pierce and Kalivas 1997; Reid and Berger 1996; Kalivas and Duffy 1998; Bell and Kalivas 1996; White et al. 1995a, b; Wolf 1998; Childress et al. 1999; Yang et al. 2006a, 2007a; Lee et al. 2008; Podet et al. 2010; Wanchoo et al. 2009, 2010; Claussen et al. 2012; Jones and Dafny 2014; Karim et al. 2017; Venkataraman et al. 2017).

The CN is composed primarily of dopaminergic medium spiny neurons which have been shown to be critical for the acute effect of MPD (Karim et al. 2017; Claussen et al. 2015; Claussen et al. 2012; Kelly et al. 1975; Creese and Iversen 1974), but it is however unknown what role the CN plays in the reward/motive circuit's response to chronic MPD use. Glutaminergic signaling has been shown to modulate the long-term response between other reward/motive circuit nuclei (Pierce et al. 1996 & 1998; Pierce and Kalivas 1997; Reid and Berger 1996; Kalivas and Duffy 1998; Bell and Kalivas 1996; White et al., 1995a, b; Wolf 1998; Childress et al. 1999; Yang et al. 2006a, 2007a; Lee et al. 2008; Podet et al. 2010; Wanchoo et al. 2009, 2010; Hemby et al. 2005; Hnasko et al. 2012; Claussen et al. 2012; Jones and Dafny 2014), and it has been shown that glutamate also modulates dopaminergic signaling within the CN (Cheramy et al., 1986; White et al. 1995a; Reid et al. 1997; Wang et al. 1999; Hong et al. 2005; Gabriele et al. 2012; Lorenz et al. 2015; Leurquin-Sterk et al. 2018). While altered glutaminergic and dopaminergic signaling in the CN have been implicated in the development of behavioral markers of substance abuse disorders, the precise role of glutaminergic signaling in the CN in response to chronic psychostimulant use remains incompletely understood.

This study aims to elucidate how glutaminergic signaling within the CN modulates the behavioral response to acute and chronic MPD administration through lesion studies to the CN. Adult male Sprague-Dawley rats underwent non-specific CN electrolytic bilateral ablation, as well as specific neurotoxin-mediated lesions to either the dopaminergic or glutaminergic systems (Lee et al. 2008; Podet et al. 2010; Wanchoo et al. 2009, 2010) in the CN to investigate the mechanism of MPD's action on animal behavior using the open field assay (Podet et al. 2010; Yang et al. 2001, 2003a&b, 2006a, 2007a; Gaytan et al. 1997; Lee et al. 2008; Lee et al. 2009; Claussen et al. 2012; Wanchoo et al. 2009).

2. Methods

2.1. Animals

Forty 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 × 40.5 × 31.5 cm in dimension) in a soundproof room without disturbance to the experimental environment for 4–5 days to acclimate prior to experimentation. These cages served as the home and test cage. 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%. At the beginning of the experimental phase, the rats were weighed and randomly divided into 5 groups: CN-intact controls (n = 8), sham operation (n = 8), CN electrolytic ablation (n = 8), 6-hydroxy-dopamine (6-OHDA) toxic ablation of the dopaminergic system (n = 8), and ibotenic acid toxic ablation of the glutaminergic system (n = 8). This 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.

2.2. Experimental procedure (Table 1)

Rats were given 4–5 days to acclimate in their home cage before experimentation. On experimental day 1 (ED 1-Sal) animals were weighed and a normal saline bolus was administered intra-peritoneal (ip). All animals weighed 200-220 g at that time. Locomotive behavioral activity was recorded for 60 min post-injection to establish baseline. On experimental day 2, the lesion and sham groups underwent surgery and were then allowed to recover for 5 days (ED 3–7) after CN ablation. On experimental day 8, saline was re-administered (ED 8-Sal) and post-surgical locomotor activity was recorded for 60 min 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 mls of 0.9% saline were administer for 6 consecutive days (ED 9-MPD – ED 14-MPD), and activity recorded for 60 min 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 (Gaytan et al. 1997; Yang et al., 2003a, 2003b, 2006a, 2006b, 2007a, 2007b, 2010; Claussen et al. 2012; Jones and Dafny 2014; Claussen and Dafny 2015, Karim et al. 2017 & 2018). For 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 60 min (the expression phase). All boluses were given at approximately 07:30 in the morning in 0.8 ml volumes.

2.3. Surgical procedure (ED 2)

The rats were anesthetized with 50 mg/kg phenobarbital ip. then placed into the stereotactic apparatus. Their heads were shaved, an incision placed down the midline of the scalp, and the cranial muscles and connective tissue were then separated to expose the skull. Bilateral holes were drilled above the CN (0.5 mm anterior to bregma, 2.0 mm and 3.0 mm lateral from the midline) according to coordinates derived from the Paximos and Watson rat brain atlas (1986). A similar procedure was used for all animals.

Table 1
Methylphenidate administration schedule. The table shows the experimental treatment protocol for the 5 groups of rats used. Each group consisted of $N = 8$ rats. Displayed are the experimental days (ED's) either normal saline or methylphenidate (MPD) 2.5 mg/kg ip was administered according to injection protocol, in a standardized volume of 0.8 ml at 07:30. * indicates day rats were behaviorally recorded post-injection. The experiment lasted 18 experimental days. The experimental schedule began after several days of acclimatization of the rats to their home/experimental cages.

Group	Experimental schedule						
	ED 1*	ED 2	ED 3–7	ED 8*	ED 9*–14*	ED 15–17	ED 18*
Control	Saline			Saline	MPD	Washout	MPD re-challenge
Sham	Saline	Surgery	Recovery	Saline	MPD	Washout	MPD re-challenge
Electrolytic lesion	Saline	Surgery	Recovery	Saline	MPD	Washout	MPD re-challenge
6-OHDA lesion	Saline	Surgery	Recovery	Saline	MPD	Washout	MPD re-challenge
Ibotenic acid lesion	Saline	Surgery	Recovery	Saline	MPD	Washout	MPD re-challenge

2.3.1. CN electrolytic lesion

Bipolar 80 μm diameter stainless steel electrodes were lowered to a depth of 4.8 mm below the cranium through the holes and a DC current of 2 mA was applied for 120 s bilaterally. The electrodes were then removed, and the incision closed with wound staples.

2.3.2. CN dopaminergic system ablation

The procedure described above was performed, and a 30-gauge stainless steel cannula was introduced instead of a bipolar electrode to each hole. 8 μg of 6-hydroxydopamine (6-OHDA) was dissolved in 2 μl of 0.9% normal saline containing 0.2 mg/ml ascorbic acid (Claussen et al. 2012; Jackson et al. 1983). This solution was infused at a rate of 1 μl per minute at a depth of 4.8 mm below the cortex, then the cannula held in place for an additional 10 min to allow for complete diffusion to the CN. The cannula was then withdrawn in 1 mm steps. This was done bilaterally, then the scalp closed with wound staples. This procedure has been shown to sufficiently deplete dopaminergic neurons from the targeted area (Claussen et al. 2012; Jackson et al. 1983).

2.3.3. CN glutaminergic system ablation

The procedure described above was performed. 5 μg of ibotenic acid was dissolved in 5 μl of 0.9% normal saline (Braun et al. 1993; Jaskiw et al. 1990; Li and Wolf 1997; Li et al. 1999; Wanchoo et al. 2009), and was then infused at a rate of 1 μl/min to the CN. The cannula held in place for an additional 10 min before being lifted by 1 mm steps to allow for complete diffusion to the CN. This was done bilaterally, then the scalp closed with wound staples. This procedure has been shown to sufficiently deplete glutaminergic neurons from the targeted area (Braun et al. 1993; Jaskiw et al. 1990; Li and Wolf 1997; Li et al. 1999; Wanchoo et al. 2009).

2.3.4. Sham operation

The cranial vault was opened with bilateral holes as described previously, and the cannula was lowered to the designated CN target area for five minutes, but no toxin or current introduced.

2.4. Histology

At the conclusion of the experiment, animals were overdosed with sodium pentobarbital and perfused with 10% formaldehyde. The brains were removed and allowed to soak in formaldehyde for a minimum of 48 h. Coronal sections were cut at 60 μm thickness and dried for 24 h. Sections were scanned with a high-resolution scanner for lesion size and location and correlated to the CN using the Paximos and Watson rat brain atlas (1986) (Fig. 1).

2.5. Apparatus

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 2 arrays of 16 infrared light beams with sensors on the opposite side, spaced every 2.5 cm that cross orthogonally through the plexiglass cage. Sensor polling frequency was set at 100 Hz. Movement of the rats interrupted the beams of infrared light, 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 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 (NOS)- episodes of purposeless, repetitive movement in the upper level of the sensors separated by at least 1 s.

2.6. Data analysis

Rat locomotive activity quantified by the three compiled indices of movement (HA, TD, NOS) was interpreted as the percent change from baseline for each of the indices. Data from the locomotor indices compiled the 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. That average for each index on a given experimental day was then calculated as a percent change from baseline activity. Baseline activity was defined as the average movement of an experimental group on the first experimental day post saline injection (ED1-Sal) for each locomotive index and thus experimental day 1 (ED1-Sal) had no percent change. Each of the indices of movement for each study-relevant day were calculated as a percent change from that baseline. 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 the comparisons was determined by generalized estimating equations (GEE). GEE predicted whether the type of surgical intervention (control, sham, electrolytic, O-6HDA, and Ibotenic acid) and the experimental time points (EDs 1, 8, 9, 14 and 18) significantly predicted the locomotor activity indices (HA, TD, and NOS). For comparisons between the matched samples to estimate changes between days within groups (assuming non-normal distribution), a Wilcoxon rank sum test was run. A p-value < 0.05 was considered statistically significant.

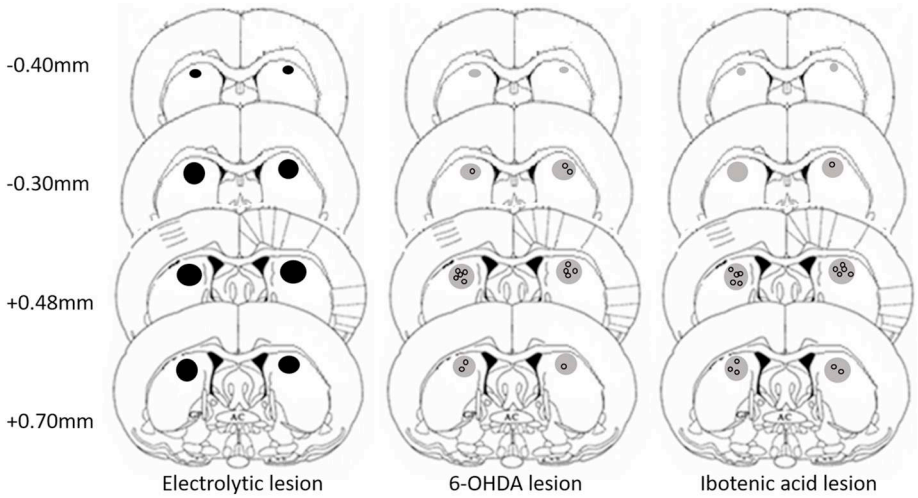


Fig. 1. Histological reconstruction of CN lesions. This figure shows the histologic reconstruction of the CN lesions, denoted below each series of sections, on rat atlas plates (Paximos and Watson, 1986) in relation to the anterior distance from bregma in millimeters (mm). The black fields in the Electrolytic lesion sections represent the size of the electrolytic lesions. The black rings in the 6-OHDA and Ibotenic acid lesion sections represent the canula placement for injection; the gray fields behind them represent the approximate area affected.

3. Results

3.1. Effect of surgery on baseline activity: ED 1-Sal vs. ED 8-Sal (Fig. 2)

Fig. 1 shows the results of surgical manipulation of the CN on the animals by comparing their pre-surgical and post-surgical indices of movement (ED 8-Sal vs. ED 1-Sal). Locomotive activity after the first saline injection pre-surgery (ED 1-Sal) was defined as the baseline for each group for data analysis. A generalized estimating equation (GEE) model was run for all locomotor indices: HA (Fig. 2A, $R^2 = 0.01$, $F = 49.9$, $p < 0.05$), TD (Fig. 2B, $R^2 = 0.54$, $F = 1180$, $p < 0.05$), and NOS (Fig. 2C, $R^2 = 0.26$, $F = 290$, $p < 0.05$). Surgery with or without chemical intervention to the CN (ED 8-Sal vs. ED 1-Sal) significantly predicted change in horizontal activity ($\beta = 0.01$, $p < 0.05$), TD ($\beta = -0.12$, $p < 0.05$), and NOS ($\beta = -0.01$, $p < 0.05$). Furthermore, the ED was predictive of TD ($\beta = 0.01$, $p < 0.05$) and NOS ($\beta = -0.02$, $p < 0.05$) activity. However, horizontal activity post-surgery was not significantly different across all groups ($\beta = 0.001$, $p = 0.30$). The control or sham group did not show significant change from baseline on ED 8 compared to ED 1 in HA, NOS, or TD (Wilcoxon rank sum, $p > 0.05$). This observation indicates that animal handling, injection volume, and injection procedure were consistent, and that surgical/chemical intervention did not modulate baseline activity.

3.2. Acute effect of methylphenidate: ED 9-MPD vs. ED 8-Sal (Fig. 3)

Fig. 3 shows the results of acute MPD administration to all groups by comparing their post-surgical intervention baseline to post-surgical MPD exposure (ED 9-MPD vs. ED 8-Sal). A GEE model significantly predicted activity changes in all three locomotive indices of movement HA: (Fig. 3A, $R^2 = 0.82$, $F = 14{,}900$, $p < 0.05$), TD (Fig. 3B, $R^2 = 0.67$, $F = 2270$, $p < 0.05$), and NOS (Fig. 3C, $R^2 = 0.67$, $F = 717$, $p < 0.05$) post-MPD injection on ED 9 for all of the groups (control, sham operation, electrolytic lesion, 6-OHDA, and ibotenic lesion) relative to their post-surgical baseline. The type of surgical intervention ($\beta = -0.01$, $p < 0.05$) and the experimental day ($\beta = 0.98$, $p < 0.05$) both significantly predicted an increase in HA locomotor activity (Fig. 3A). For TD, the type of surgical intervention ($\beta = -0.11$, $p < 0.05$) and the experimental day ($\beta = -0.06$, $p < 0.05$) both significantly predicted an increase locomotor activity (Fig. 3B). For NOS, the type of surgical intervention ($\beta = -0.05$, $p < 0.05$) and the experimental day ($\beta = -0.10$, $p < 0.05$) both significantly predicted an increase in locomotor activity (Fig. 3C). Control, sham, electrolytic, and ibotenic acid lesion groups all showed a statistically significant increase in locomotor activity upon post-surgical MPD exposure (ED 9-MPD) compared to post-surgical intervention baseline (ED 8-Sal) in all three indices of movement (HA, TD, & NOS, Fig. 3A, B, & C, respectively; Wilcoxon rank sum, $p < 0.05$). The 6-OHDA group did not show a statistically significant change in any of the indices of movement (Fig. 3A, B &C, Wilcoxon rank sum, $p > 0.05$).

3.3. Chronic effect of MPD- induction phase: ED 14-MPD vs. ED 9-MPD (Fig. 4)

Fig. 4 shows the results of chronic MPD administration to all groups by over six consecutive days by comparing the final day of chronic MPD exposure to the acute MPD exposure (ED 14-MPD vs. ED 9-MPD). A GEE model predicted that the administration of a repetitive 2.5 mg/kg MPD dose for an additional five consecutive days relative to the acute effect of MPD across all groups significantly predicted change in all three locomotive indices of movement: HA (Fig. 4A, $R^2 = 0.26$, $F = 1840$, $p < 0.05$), TD (Fig. 4B, $R^2 = 0.67$, $F = 3800$, $p < 0.05$), and NOS (Fig. 4C, $R^2 = 0.45$, $F = 292$, $p < 0.05$). For HA, the type of surgical intervention ($\beta = -0.02$, $p < 0.05$) and the experimental day ($\beta = -0.04$, $p < 0.05$) significantly predicted an increase in locomotor activity (Fig. 4A). For TD, the type of surgical intervention ($\beta = -0.14$, $p < 0.05$) and the experimental day ($\beta = -0.04$, $p < 0.05$) also significantly predicted an increase in locomotor activity (Fig. 4B). Lastly, for NOS, the type of surgical intervention ($\beta = -0.03$, $p < 0.05$) and the experimental day ($\beta = -0.33$, $p < 0.05$) significantly predicted an increase in locomotor activity (Fig. 4C). Control, sham, and electrolytic lesion groups all showed a statistically significant increase between the final day of chronic MPD exposure (ED 14-MPD) when compared to their acute MPD exposure (ED 9-MPD) in all three indices of movement (HA, TD, & NOS, Fig. 4A, B, & C, respectively; Wilcoxon rank sum, $p < 0.05$). This further augmentation in locomotive behavior following repeated exposure to MPD confirms that 2.5 mg/kg MPD induces behavioral sensitization. The 6-OHDA and ibotenic acid groups did not show a statistically significant change in any of the indices of movement following chronic exposure (HA, TD, & NOS, Fig. 4A, B, & C, respectively; Wilcoxon rank sum, $p > 0.05$).

3.4. Chronic effect of MPD-expression phase: ED 18-MPD vs. ED 9-MPD (Fig. 5)

Fig. 5 shows the effect of MPD re-challenge following washout by comparing the effect of MPD re-challenge to the acute MPD effect (ED 18-MPD vs. ED 9-MPD). A GEE model predicted that the re-challenge with the same 2.5 mg/kg MPD dose after a three-day washout period following chronic MPD exposure (six days of MPD administration) as compared to acute MPD administration across all experimental groups significantly predicted a change in all three locomotive indices of

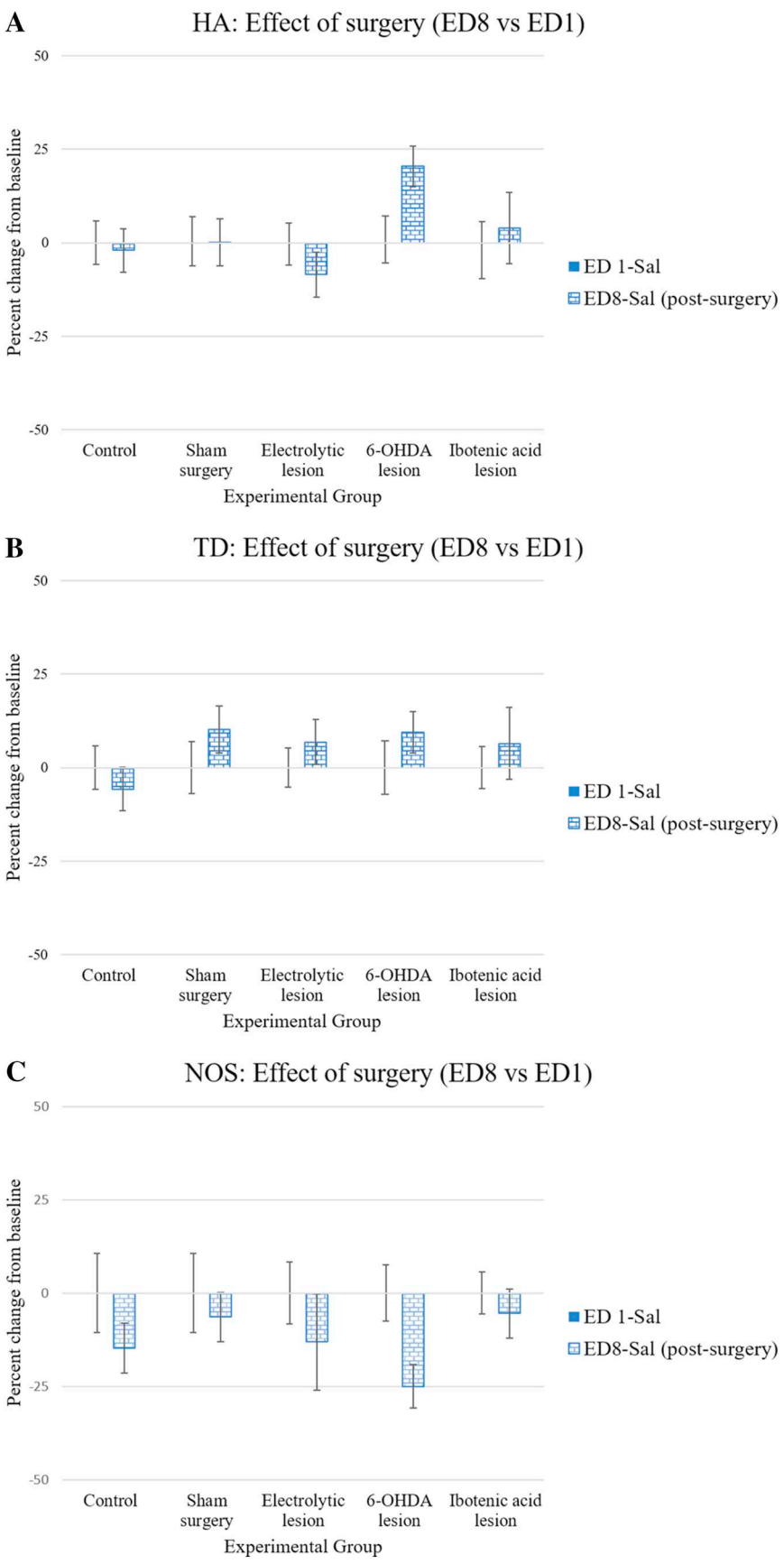


Fig. 2. Effect of CN surgery. This figure compares the three indices of movement following CN surgery (ED 1-Sal vs. ED 8-Sal). A: Horizontal Activity (HA); B: Total Distance (TD); C: Number of Stereotypic movements (NOS). None of the groups that underwent CN surgery (sham surgery, electrolytic lesion, 6-OHDA lesion, and ibotenic acid lesion) showed a statistically significant change in ambulation as measured by HA (1A), TD (1B), or NOS (1C) compared to their pre-surgical baseline. The scale has been altered on this figure to allow visualization of the data.

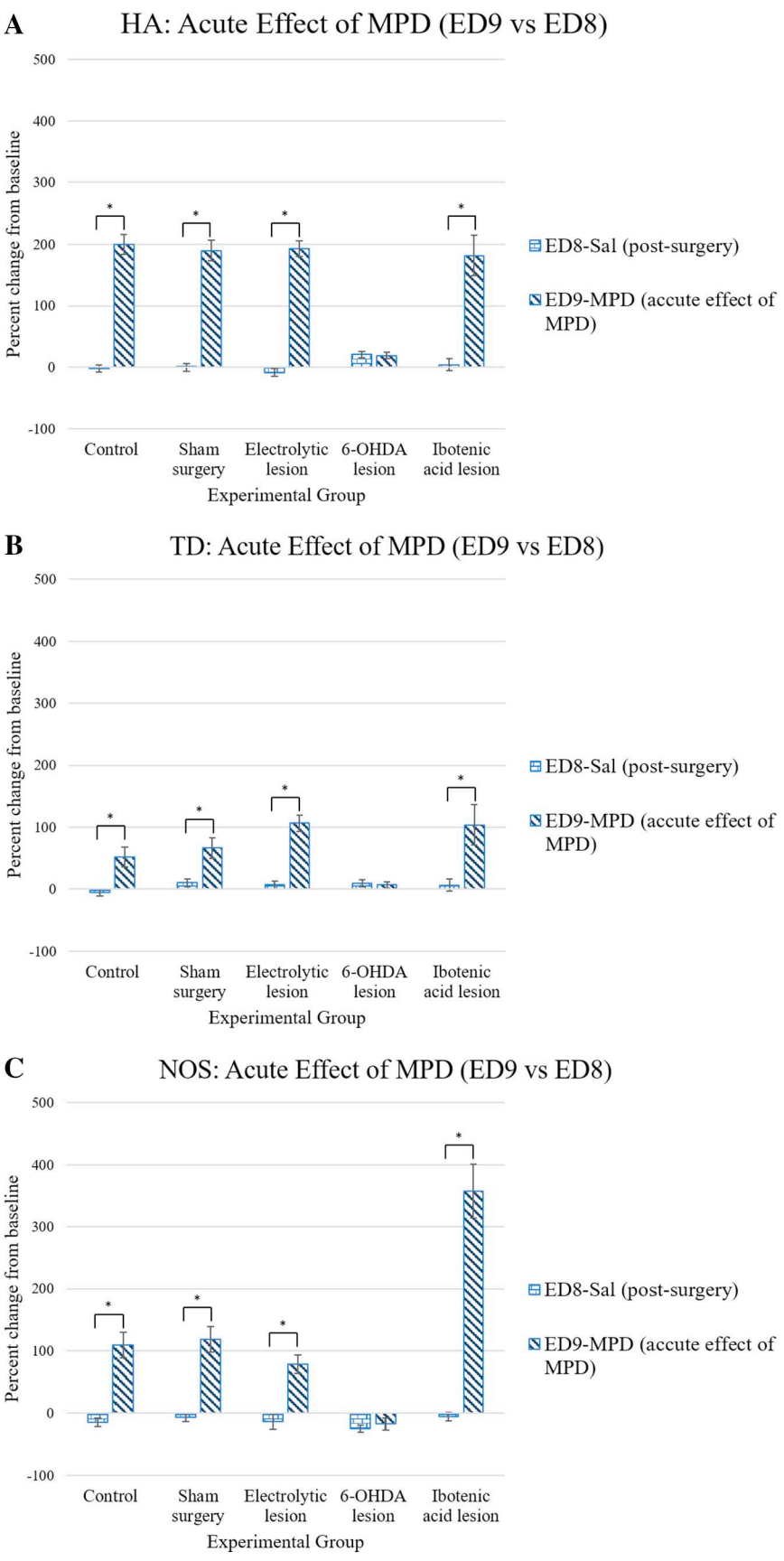
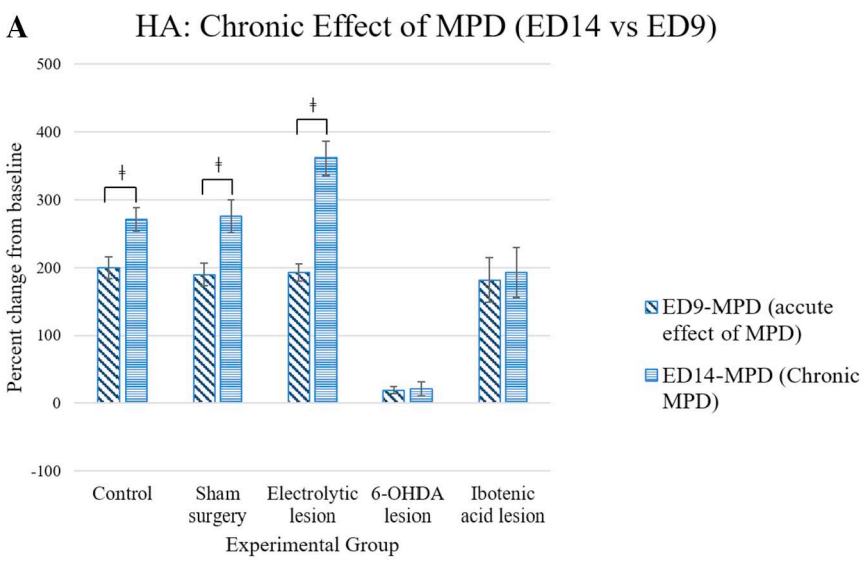
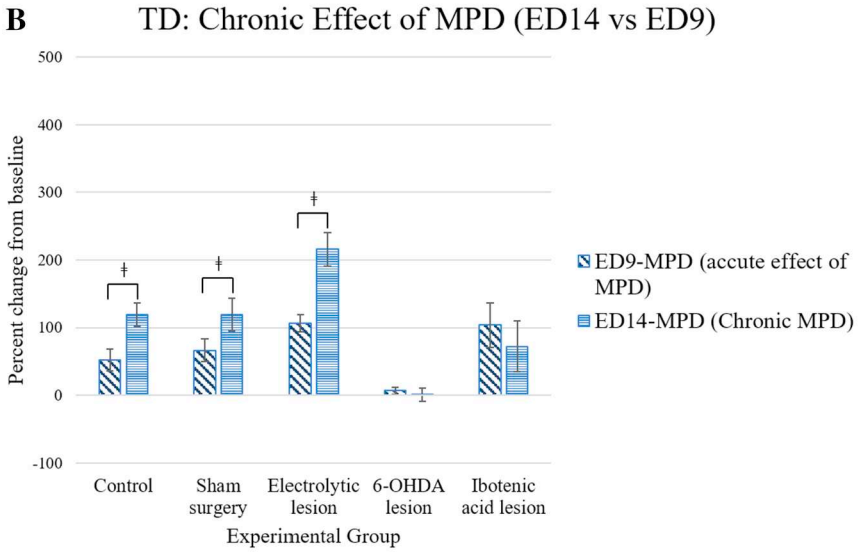


Fig. 3. Acute effect of MPD. This figure compares the three indices of movement following the acute administration of MPD (ED 9-MPD vs. ED 8-Sal). A: Horizontal Activity (HA); B: Total Distance (TD); C: Number of Stereotypic movements (NOS). * indicates a statistically significant (Wilcox rank sum $p < 0.05$) change. Control, sham lesion, electrolytic lesion, and ibotenic acid lesion groups all showed a statistically significant increase in all three indices (HA (2A), TD (2B), NOS (2C)) following acute MPD exposure. The 6-OHDA lesion group showed no appreciable response to acute MPD exposure. The ibotenic acid lesion group shows a unique increase in NOS (2C) acutely as compared to the MPD-responding groups (controls, sham surgery, and electrolytic lesion).





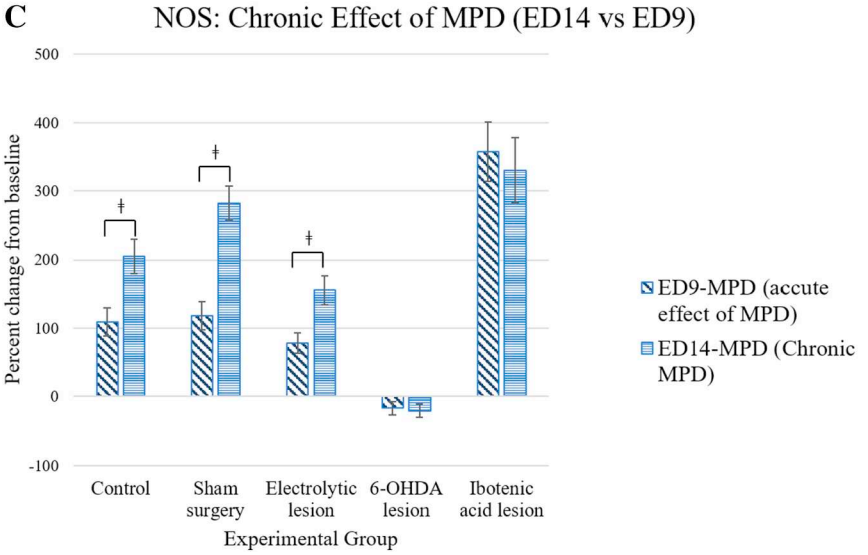
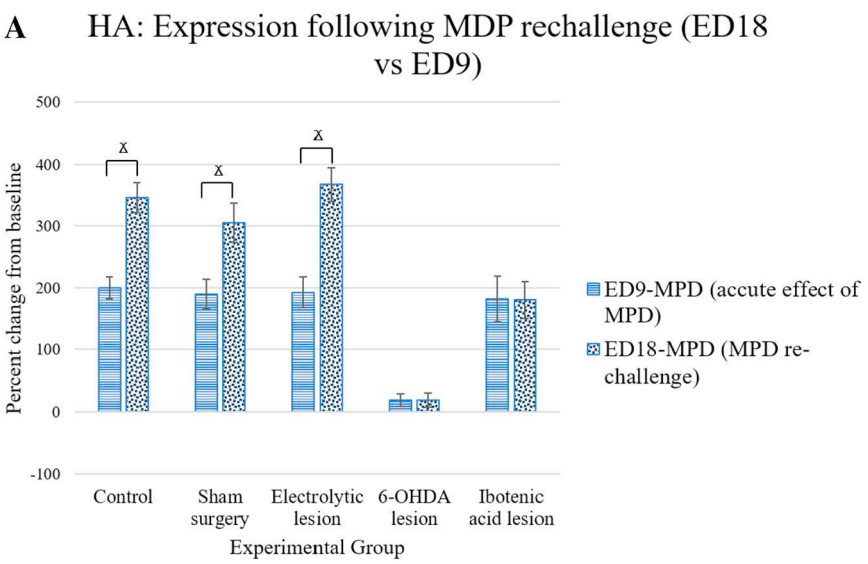
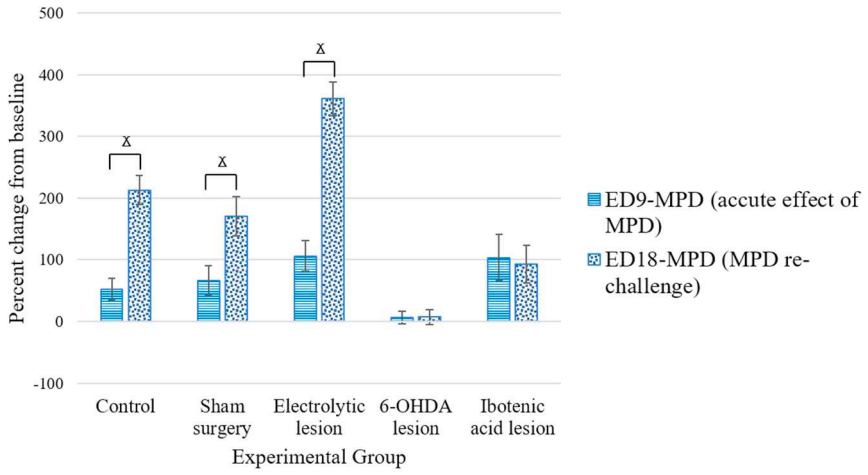


Fig. 4. Chronic effect of MPD (Induction phase). This figure compares the three indices of movement following the chronic administration of MPD (ED 14-MPD vs. ED 9-MPD). A: Horizontal Activity (HA); B: Total Distance (TD); C: Number of Stereotypic movements (NOS). ǂ indicates a statistically significant (Wilcox rank sum $p < 0.05$) change. Control, sham lesion, and electrolytic lesion groups all showed a statistically significant increase in all three indices (HA (3A), TD (3B), NOS (3C)) following chronic MPD exposure. The 6-OHDA lesion and ibotenic acid lesion groups showed no appreciable change in response to MPD following chronic exposure. The ibotenic acid lesion group responded similarly to MPD exposure as measured by motor activity on the final day (ED 14-MPD) of consecutive MPD exposure as they did to the acute exposure (ED 9-MPD).

movement: HA (Fig. 5A, $R^2 = 0.35$, $F = 3640$, $p < 0.05$), TD (Fig. 5B, $R^2 = 0.80$, $F = 7560$, $p < 0.05$), and NOS (Fig. 5C, $R^2 = 0.56$, $F = 471$, $p < 0.05$). For HA, the type of surgical intervention ($\beta = -0.03$, $p < 0.05$) and the experimental day ($\beta = 0.04$, $p < 0.05$) significantly predicted an increase in locomotor activity (Fig. 5A). For TD, the type of surgical intervention ($\beta = -0.17$,





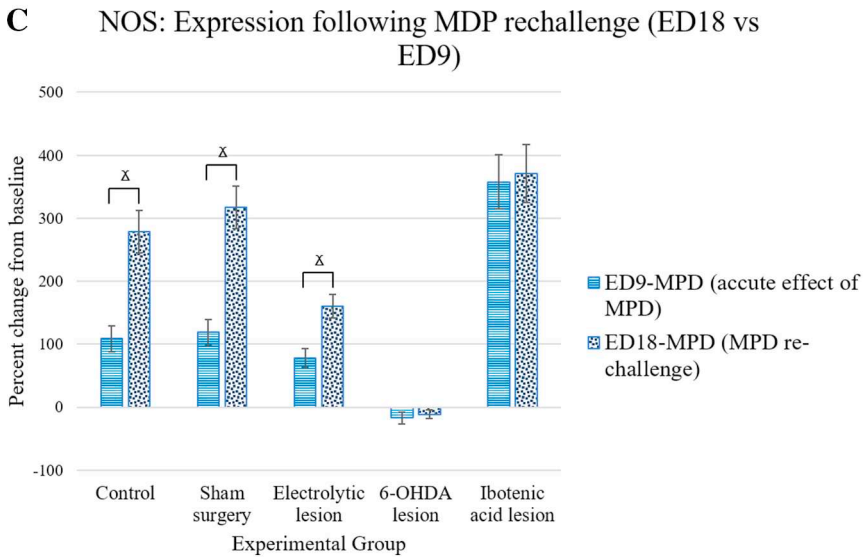


Fig. 5. Effect of MPD following re-challenge (Expression phase). This figure compares the three indices of movement following the re-challenge with MPD after washout (ED 18-MPD vs. ED 9-MPD). A: Horizontal Activity (HA); B: Total Distance (TD); C: Number of Stereotypic movements (NOS).Ⱪ indicates a statistically significant (Wilcox rank sum $p < 0.05$) change. Control, sham lesion, and electrolytic lesion groups all showed a statistically significant increase in all three indices (HA (4A), TD (4B), NOS (4C)) following MPD re-challenge. The 6-OHDA lesion and ibotenic acid lesion groups showed no appreciable change in response to MPD following re-challenge. The ibotenic acid lesion group responded similarly to MPD exposure as measured by motor activity upon MPD re-challenge (ED 18-MPD) as they did to the acute exposure (ED 9-MPD).

$p < 0.05$) and the experimental day ($\beta = 0.08$, $p < 0.05$) also significantly predicted an increase in locomotor activity (Fig. 5B). Lastly, for NOS, the type of surgical intervention ($\beta = -0.03$, $p < 0.05$) and the experimental day ($\beta = -0.43$, $p < 0.05$) significantly predicted an increase in locomotor activity (Fig. 5C). Control, sham, and electrolytic lesion groups all showed a statistically significant increase in

locomotion between MPD re-challenge (ED 18-MPD) compared to their acute MPD exposure (ED 9-MPD) in all three indices of movement (HA, TD, & NOS, Fig. 5A, B, & C, respectively; Wilcoxon rank sum, $p < 0.05$). This continued augmentation of the response to MPD even after drug washout is the continued expression of sensitization to chronic psychostimulant use, i.e. the expression phase. The 6-OHDA and ibotenic acid groups did not show a statistically significant change in any of the indices of movement following MPR re-challenge (HA, TD, & NOS, Fig. 5A, B, & C, respectively; Wilcoxon rank sum, $p > 0.05$).

4. Discussion

Methylphenidate has been less widely studied than other psychostimulants despite its wide use as a therapy for ADHD patients (Accardo and Blondis 2001; Goldman et al. 1998; Levin and Kleber 1995; Solanto 1998), and growing use as a cognitive enhancer and recreational drug (Cox et al. 2003; Wilens et al. 2008; Greely et al. 2008; Bogle and Smith 2009; Hildt et al. 2015; Fond et al. 2016). Previous work has shown that MPD treatment can elicit behavioral sensitization in rats (Yang et al. 2003a, 2006a, 2007a; Gaytan et al. 2001), an experimental biomarker in animals for the symptoms of substance abuse disorders.

MPD is considered an indirect dopamine agonist. It has been shown to bind to the dopamine transporter preventing dopamine reuptake at the presynaptic terminal, similar to the mechanism of action of cocaine and methamphetamine (Kuczenski and Segal 1997; Teo et al. 2003; Volkow et al. 1995). Decreased dopamine reuptake following MPD binding to the dopamine transporter increases dopamine in the synaptic cleft, leading to increased signaling in the postsynaptic neuron (Gatley et al. 1999; John and Jones 2007; Volkow et al. 1999). Increased dopamine within the mesolimbic system and the CN is implicated in the formation of substance abuse behaviors (Corrigall et al. 1992; Pierce and Kumaresan 2006; Pontiere et al., 1995). The reward/motive circuit includes the ventral tegmental area (VTA), the nucleus accumbens (NAc), the pre-frontal cortex (PFC), and the caudate nucleus (CN). The CN belongs to both the motor system and reward/motive circuit (Yang et al. 2006a; Rebec 2006; Claussen and Dafny 2015), making it a key link for the expression of locomotive behaviors in response to psychostimulant exposure. This study aimed to elucidate the role of glutaminergic signaling the CN in response to acute and chronic MPD exposure by non-specific destruction of the CN, and selective destruction of the dopaminergic or glutaminergic system of the CN.

This experiment utilized five groups of rats: intact control, sham CN lesion, non-specific electrolytic CN lesion, dopaminergic system specific CN lesion (6-OHDA toxin), and glutaminergic system specific CN lesion (ibotenic acid toxin) groups. This study found that the surgical operation had no effect on animal locomotive behavior as measured by the HA, TD, or NOS (ED 8-Sal vs ED 1-Sal, Fig. 2) in any group. When the groups received their first exposure to MPD (ED 9-MPD), the intact controls, sham lesion, non-specific electrolytic lesion, and glutaminergic-specific ibotenic acid lesion groups all responded similarly to acute MPD exposure, showing an increase in locomotive behavior (ED 9-MPD vs. ED 8-Sal, Fig. 3). The dopaminergic-specific 6-OHDA lesion group failed to show a response to acute MPD exposure as compared to their ED 8-Sal baseline (ED 9-MPD vs. ED 8-Sal, Fig. 3). The intact control, sham lesion, and non-specific electrolytic lesion groups all showed further increases in locomotion following chronic administration of MPD as compared to the initial exposure (ED 14-MPD vs ED 9-MPD, Fig. 4). They continued to show this increase in locomotion following MPD re-challenge after a three-day washout period (ED 18-MPD vs 9-MPD, Fig. 5). Therefore, the intact control, sham lesion, and non-specific electrolytic lesion groups all showed the induction of sensitization to chronic MDP exposure. The dopaminergic system specific (6-OHDA toxin) CN lesion group failed to respond to both chronic MPD exposure (ED 14-MPD vs ED 9-MPD, Fig. 4) and MPD re-challenge following the three-day washout (ED 18-MPD vs ED 9-MPD, Fig. 5). The glutaminergic system specific (ibotenic acid toxin) CN lesion group showed no further increase in locomotive behavior after chronic administration of MPD (ED 14-MPD vs ED 9-MPD, Fig. 4), or MPD re-challenge after the three-day washout (ED 18-MPD vs ED 9-MPD, Fig. 5).

Bilateral electrolytic lesions of the CN had no effect on locomotion after acute and chronic exposure to MPD. These findings are consistent with previous work that has shown that non-specific electrolytic lesions to the CN, PFC, or the NAc do not considerably alter the locomotive activity in response to stimulants such as MPD or amphetamine (Claussen et al. 2012; Lee et al. 2008; Podet et al. 2010; Tang et al. 2009; McKenzie 1972). Electrolytic lesions are non-specific lesions that physically destroy the neuropil, including all the ascending, descending, excitatory, and inhibitory tracts within it. Thus, when the CN was electrically ablated, both the dopaminergic and glutaminergic systems within it should be destroyed. The lack of a significant change in response to MPD exposure after bilateral CN ablation as compared to control groups suggests that either the lesion was insufficient to destroy all pathways in the CN (DiChiara, 1995; Podet et al. 2010; Robinson and Berridge 1993; Sullivan and Brake 2003), or that there is/are a bypass tract(s) around the CN that are uncovered when the CN is destroyed, allowing normal responses to MPD in the face of CN destruction. Given that chemical ablation of specific tracts in the CN dramatically affects the response to MPD exposure while non-specific electrolytic ablation does not lends plausibility to the possibility that there is simply insufficient destruction of the CN neuropil with electrolytic ablation as described here. An incomplete, non-specific lesion to the CN would leave some tracts unaffected allowing an altered response to MPD as compared to intact controls. This possibility is supported by the observation that the response to MPD exposure in animals with electrolytic lesions to the CN varies as compared to the control and sham groups based on the index of movement (Figs. 3B, 4A, B, & C, 5B & C). Further work is required to determine the optimal parameters for total CN ablation by electrolytic lesions.

Bilateral administration of 6-OHDA to the CN extinguished any response to MPD acutely and chronically. This finding agrees with prior work showing that dopaminergic-specific 6-OHDA lesions to the CN prevent any response to acute and chronic MPD or amphetamine exposure (Claussen et al. 2012; Kelly et al. 1975; Creese and Iversen 1974). 6-OHDA is a neurotoxin that is taken up by catecholaminergic neurons then oxidized by MAO-A to hydrogen peroxide, which is cytotoxic to cells (Iversen 1973; Luthman et al. 1989; Cadet and Brannock 1998; Blum et al. 2001). 6-OHDA that is infused into the CN is taken up preferentially by the catecholaminergic neurons which are subsequently destroyed by the oxidative stress of hydrogen peroxide. The CN is comprised primarily of catecholaminergic dopaminergic medium spiny neurons (MSN's) that express excitatory D1-dopamine receptors and inhibitory D2-dopamine receptors. These neurons project via two distinct pathways- the direct pathway via the ansa leticularis and the indirect pathway via the lenticular fasiculus (Carpenter 1976) to modulate movement. The indirect pathway expresses primarily inhibitory D2-dopamine receptors and exerts its effects via the globus pallidus externa and subthalamus, while 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 (Calabresi et al. 2014; Gerfen and Surmeier 2011; Kreitzer and Malenka 2008; Zhang et al. 2004). The cumulative action of both pathways is to regulate movement. MPD is thought to exert its stimulatory motor effects by activating this dopaminergic basal ganglia motor system, thus increasing movement. Our finding of neither acute nor chronic response the MPD after 6-OHDA administration is consistent with that of previous work showing the dopaminergic neurons of the CN are necessary for MPD to exert its motor effects acutely and chronically (Claussen et al. 2012; Kelly et al. 1975; Creese and Iversen 1974).

Ibotenic acid lesion of the glutaminergic system of the CN blunted the effect of chronic MPD exposure, i.e. the expression of behavioral

sensitization. Administration of ibotenic acid to the CN selectively ablates the glutaminergic neurons that serve as the primary excitatory neurons of the central nervous system (Schwarcz et al. 1979; Kouvelas et al. 1992; Meldrum 2000; McEntee and Crook 1993; Shigeri et al. 2004). Previous work has shown that glutaminergic tracts within and between other reward/motive circuit nuclei, including the NAc, PFC, and VTA, are involved in long-term neurocognitive changes such as sensitization in response to chronic psychostimulant administration (Pierce et al. 1996 & 1998; Pierce and Kalivas 1997; Reid and Berger 1996; Kalivas and Duffy 1998; Bell and Kalivas 1996; White et al., 1995a, b; Wolf 1998; Childress et al. 1999; Yang et al. 2006a, 2007a; Lee et al. 2008; Podet et al. 2010; Wanchoo et al. 2009, 2010; Hemby et al. 2005; Hnasko et al. 2012; Faget et al. 2016). However, to date only dopaminergic signaling within the CN has been shown to affect the behavioral response to chronic psychostimulant use. While the MSN's of the CN are primarily dopaminergic, they have been shown to express both glutamate and dopamine receptors (Wang et al. 1999; Nair et al. 2014). Glutamate, representing glutaminergic signaling, has also been shown to modulate dopaminergic signaling within the CN (Chéramy et al., 1986; White et al. 1995a; Wang et al. 1999; Hong et al. 2005; Lorenz et al. 2015), and increases in both dopaminergic and glutaminergic signaling can be seen following exposure to substances with addictive potential (Gabriele et al. 2012; Leurquin-Sterk et al. 2018). Increased glutaminergic signaling in the CN has been shown to strengthen learned behavior (Mckee et al., 2010; Packard 1999), but no work has investigated the role of glutaminergic signaling in the sensitization of animal behavior in response to chronic psychostimulant administration.

This study shows that the ablation of glutamate signaling within the CN prevents the chronic effect of MPD behavioral sensitization but does not affect the acute effect of MPD. This suggests that the glutaminergic signaling in the CN is active in the response to chronic psychostimulant use, manifesting as the development of behavioral sensitization. This modulation of the effect of MPD is lost when the dopaminergic tracts of the CN are ablated, suggesting the effect is local to the CN. Therefore, glutaminergic signaling, likely from throughout the reward/motive circuit, appears to act on the MSN's to increase dopamine synthesis, resulting in increased dopamine signaling with chronic exposure that ultimately manifests as behavioral sensitization. This agrees with the observations that glutamate modulates dopamine signaling in the CN and that both are upregulated when substances with abusive potential are administered (Chéramy et al., 1986; White et al. 1995a; Reid et al. 1997; Wang et al. 1999; Hong et al. 2005; Gabriele et al. 2012; Lorenz et al. 2015; Leurquin-Sterk et al. 2018). More significantly, this work links glutaminergic signaling to a behavioral outcome, the development of behavioral sensitization, in response to chronic psychostimulant exposure. Behavioral sensitization to MPD serves as a marker of abusive potential (Schreiber et al. 1976; Robinson and Berridge 1993; Kuczenski and Segal 1997; Gaytan et al. 2001; Yang et al., 2003a, 2006a, 2007a; Claussen and Dafny, 2015; Dafny and Yang 2006; Lee et al. 2008; Algahim et al. 2009; Claussen et al. 2012; Jones and Dafny 2014; Claussen and Dafny 2015, Karin et al., 2017; Venkataraman et al. 2017), which encompasses the diverse behaviors associated with substance abuse disorders. The lack of behavioral sensitization after glutaminergic ablation indicates that glutaminergic signaling within the CN might be involved with long-term learning associated with chronic MPD use that helps drive substance abuse disorders. This is supported by evidence showing glutamine infusion into the CN strengthens response learning, and that *N*-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptors, in the CN are required for operant learning in rats (Mckee et al., 2010; Packard 1999). So while glutaminergic signaling in the CN mediates behavioral sensitization to chronic MPD in an animal model, it might also mediate the learned behaviors an individual exhibits in association with chronic psychostimulant use.

If glutaminergic signaling is critical to the formation of the behavioral changes linked to substance abuse disorders, as this work suggests, it could be a potential pharmacologic treatment target. This agrees with work showing administration of non-specific systemic glutamate antagonists can reduce the stereotyped behavioral responses to psychoactive substances (Karler et al. 1989; Battisti et al. 2000; Cousins et al. 2014). However, given that glutamate is the most prevalent neurotransmitter in the CNS, it would likely be unwise to non-specifically blockade its receptors in the treatment of substance abuse disorders. Rather, with an enhanced mechanistic understanding of the neurobiological processes potentially underpinning abuse disorders, future work could identify and target the specific glutaminergic receptor subtypes likely involved to achieve a better therapeutic yield. Substance abuse disorders represent the outcome of a diverse neural network which includes glutaminergic signaling, and therapy targeting it more likely should be a part of a multi-targeted and multi-modal treatment plan.

Further work is needed to investigate the precise role of glutaminergic signaling in the CN. This could involve self-administration assays to complement the ablation study offered here to elucidate if the behavioral sensitization effect produced by glutaminergic signaling in the CN is linked to self-reinforcement and learning. Additionally, it is clear that further research is necessary to characterize the neuronal constituents of the CN beyond the MSN's that were previously thought to mediate the majority of its output. Finally, broad and narrow spectrum pharmacologic targeting of the glutaminergic system in the CN could illuminate the excitatory and/or inhibitory roles it plays in the reward/motive and motor circuits of the CNS. Such work would complement the findings here and help build a better understanding of how the CNS modulates behavior, learning, and motivation.

5. Conclusion

These results indicate the dopaminergic signaling pathways of the CN are necessary targets of MPD's action to increase locomotor movement because their ablation eliminates any response to MPD, acute or chronically. More significant, we show that the glutaminergic signaling within the CN regulates the chronic effects of psychostimulant exposure such as the expression of behavioral sensitization. Ablation of the glutaminergic neurons does not affect the acute effect of MPD but eliminates long-term sensitization. Previous work has focused on the dopaminergic MSN's that are the main constituent of the CN but here we show that glutaminergic signaling is critical to the chronic effect of MPD exposure, i.e. behavioral sensitization, the biomarker for substance abuse disorder symptoms. Further research should be directed to investigate the glutaminergic system of the CN and how it fits into the larger context of the reward/motive circuit.

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