

Cite this article as: Neural Regen Res. 2012;7(10):772-777.

Calcium-mediated paired pulse depression in juvenile rat dorsal striatum[☆]

Yufeng Xie¹, Michael F. Jackson^{1,2}, John F. MacDonald^{1,2,3}

¹Robarts Research Institute, University of Western Ontario, London, Ontario, Canada

²Department of Physiology and Pharmacology, University of Western Ontario, London, Ontario, Canada

³Department of Anatomy and Cell Biology, University of Western Ontario, London, Ontario, Canada

Abstract

As the major division of the basal ganglia, neostriatum forms mutual connections with multiple brain areas and is critically involved in motor control and learning/memory. Long-term synaptic plasticity has been widely studied in different species recently. However, there are rare reports about the short-term synaptic plasticity in neostriatum. In the present study, using field excitatory postsynaptic potentials recording, we reported one form of short-term synaptic plasticity that is paired pulse depression in juvenile rat dorsal striatum slices induced by stimuli of the white matter. The field excitatory postsynaptic potentials could be abolished by α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione, but not by gamma-aminobutyric acid type A receptor antagonist bicuculline or dopamine D1 receptor antagonist SKF-81297. The paired pulse depression in the corticostratial pathway was different from paired pulse facilitation in the hippocampal CA1 synapse. In addition, the paired pulse depression was not affected by bath application of gamma-aminobutyric acid type A receptor antagonist or dopamine D1 receptor antagonist. However, low calcium and high magnesium could attenuate the paired pulse depression. These findings suggest a more complicated plasticity form in the dorsal striatum of juvenile rats that is different from that in the hippocampus, which is related with extracellular calcium.

Key Words: paired pulses depression; dorsal striatum; calcium; juvenile rats

Abbreviations: fEPSP, field excitatory postsynaptic potentials; PPD, paired pulse depression; MSN, medium spiny projection neuron

Yufeng Xie[☆], Ph.D.,
Research associate, Robarts
Research Institute, University
of Western Ontario, London,
Ontario, Canada

Corresponding author: John
F. MacDonald, Ph.D.,
Professor, Robarts Research
Institute, University of
Western Ontario, London,
Ontario, Canada;
Department of Physiology
and Pharmacology,
University of Western
Ontario, London, Ontario,
Canada; Department of
Anatomy and Cell Biology,
University of Western
Ontario, London, Ontario,
Canada; Michael F.
Jackson, Ph.D., Adjunct
assistant professor, Robarts
Research Institute, University
of Western Ontario, London,
Ontario, Canada;
Department of Physiology
and Pharmacology,
University of Western
Ontario, London, Ontario
canadajfmacdonald@
robarts.ca;
mjackson@robarts.ca

Received: 2011-11-18
Accepted: 2012-02-24
(NY20111118001/H)

Xie YF, Jackson MF,
MacDonald JF.
Calcium-mediated paired
pulse depression in juvenile
rat dorsal striatum. Neural
Regen Res.
2012;7(10):772-777.

www.crter.cn
www.nrronline.org

doi:10.3969/j.issn.1673-5374.
2012.10.008

INTRODUCTION

The striatum, as the major division of the basal ganglia, is critically involved in motor control and learning/memory. The most common cell type in the striatum, medium spiny projection neurons (MSNs), receive glutamatergic inputs from the cerebral cortex and thalamus, serotonergic input from the raphe nuclei, dopaminergic input from the substantia nigra as well as cholinergic and gamma-aminobutyric acid input from striatal interneuron. In addition, MSNs also receive synapses from axonal collaterals from neighboring MSNs^[1], suggesting a more complicated circuit of the striatum. The neuroplasticity in the striatum controls the short-term and long-term selection and the differential amplification of cortical neural signals modulating the processes of motor and behavioral selection within the basal ganglia neural circuit^[2-3]. Synaptic plasticity at corticostratial synapses is proposed to contribute to motor learning and habit formation. Unlike hippocampal CA3-CA1 synapses, however, the corticostratial pathway differs regionally in direction of

plasticity in spite of the application of identical stimulation protocols: for example high frequency stimulation (100 Hz) induces long-term potentiation in the dorsomedial striatum but long-term depression in the dorsolateral striatum^[4-5]. In addition, paired pulses induce depression of excitatory postsynaptic potentials (EPSPs)^[6-7], and this differs from hippocampus CA3-CA1 synapses which exhibit facilitation in response to paired pulses^[8]. These results suggest that the mechanisms of long-term and short-term synaptic plasticity in the striatum may differ from those in the hippocampus.

Short-term synaptic plasticity, including short-term potentiation and depression, lasts from tens of milliseconds to several seconds, and plays an important role in neural encoding^[9]. Short-term depression can act as a low-pass filter contributing to spatial-temporal processing^[10], serving to control the gain between excitation and inhibition^[11], and contributing to the generation of synchronous network activity^[12]. Paired pulse depression (PPD), instead of paired pulse facilitation, is a form of short-term synaptic plasticity that was

observed in the striatum^[6, 13]. Although it has been suggested that PPD in the striatum involves presynaptic mechanisms and the concentration of external calcium^[6], the detailed mechanism of this form of plasticity is poorly understood.

RESULTS

Dorsal striatum field EPSP (fEPSP) is not affected by D1, gamma-aminobutyric acid type A or muscarinia receptor

Stimulation of the white matter induced two negative extracellular potentials (N1 and N2, Figure 1A) in the neostriatum, as previously described^[14-15]. The N2, also referred to population spike or fEPSP, was abolished by bath application of α -amino-3-hydroxy-5-methylizoxazole-4-propionic acid receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione, while the N1 was not affected by 6-cyano-7-nitroquinoxaline-2,3-dione (10 μ M) (Figure 1D), suggesting the N2 potential is generated mainly by excitatory postsynaptic currents^[14, 16]. The population spike (N2) of the striatum was not affected by blockade of gamma-aminobutyric acid type A receptors antagonist bicuculline (20 μ M) (Figures 1B, C), while in contrast the fEPSP in hippocampus CA1 synapses was significantly affected by blockade of gamma-aminobutyric acid type A receptor antagonist bicuculline (20 μ M) (Figures 2A–C) and paired-pulses induced facilitation, which is significant different from striatum (Figure 2D). In addition, the PS was not affected by D1 receptors antagonist SKF-81297 (20 μ M) or muscarinic receptors antagonist succinylcholine chloride (20 μ M) (Figures 3, 4), consistent with previous reports^[14].

The PPD is related with extracellular calcium

It is well known that paired pulse stimulation of the Schaffer collateral pathway induces facilitation of the fEPSP in the hippocampal CA1 area (Figures 2A, D). In contrast, using the identical conditions paired pulse stimuli of the corticostriatal pathway induced depression of the population spike/fEPSP (Figures 1A, B) in the slices of dorsal striatum. In addition, a series of paired pulses, including interstimulus intervals of 20, 40 and 80 ms, all produced depression of population spike/fEPSP (Figure 1B). In addition, we found that even longer interval as 150–1 000 ms also induced depression of population spike/fEPSP in rat dorsal striatum (Figure 2D, lower), which was significantly different from the hippocampus. We next investigated if blockade of gamma-aminobutyric acid, muscarinic or D1 receptors would alter paired pulse induced depression of population spike/fEPSP in striatal slices. Bath application of the gamma-aminobutyric acid type A receptor antagonist bicuculline (20 μ M), the muscarinic receptor antagonist succinylcholine chloride (20 μ M)^[17] or the D2 receptor antagonist SKF-81297 (20 μ M) had no effect on the PPD of population spike/fEPSP (Figures 3, 4), neither did any of these drugs alter the amplitudes of population spike/fEPSP.

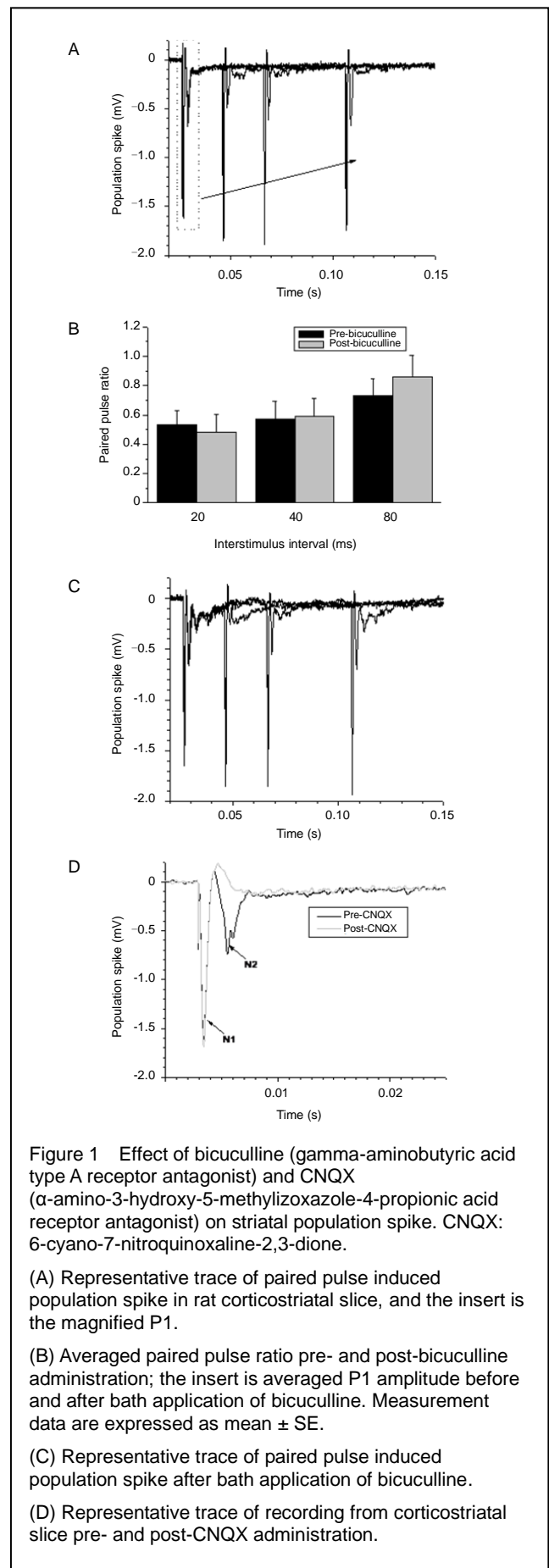


Figure 1 Effect of bicuculline (gamma-aminobutyric acid type A receptor antagonist) and CNQX (α -amino-3-hydroxy-5-methylizoxazole-4-propionic acid receptor antagonist) on striatal population spike. CNQX: 6-cyano-7-nitroquinoxaline-2,3-dione.

(A) Representative trace of paired pulse induced population spike in rat corticostriatal slice, and the insert is the magnified P1.

(B) Averaged paired pulse ratio pre- and post-bicuculline administration; the insert is averaged P1 amplitude before and after bath application of bicuculline. Measurement data are expressed as mean \pm SE.

(C) Representative trace of paired pulse induced population spike after bath application of bicuculline.

(D) Representative trace of recording from corticostriatal slice pre- and post-CNQX administration.

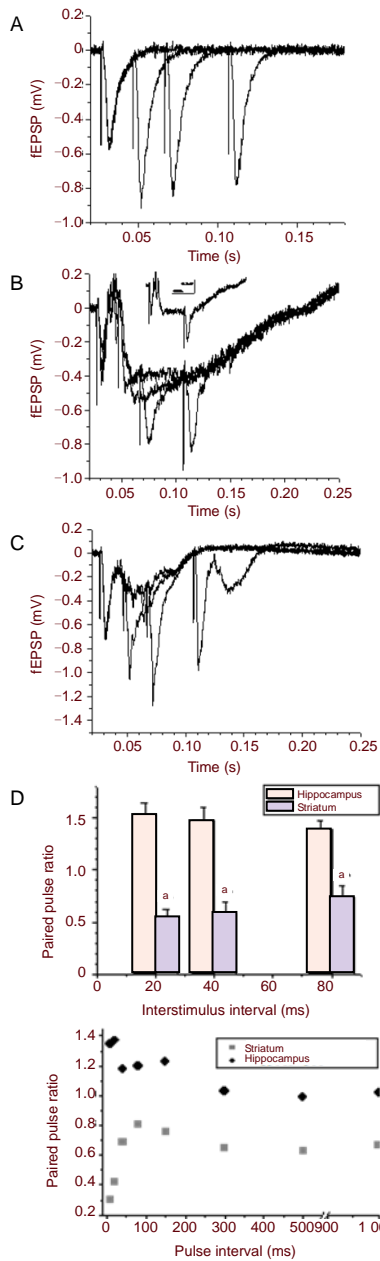


Figure 2 Effect of bicuculline on hippocampal field excitatory postsynaptic potentials (fEPSP) (A–C) and difference of paired pulse ratio between the hippocampus and striatum (D).

(A) Representative trace of paired pulse facilitation in rat hippocampal slices before application of gamma-aminobutyric acid type A receptor antagonist bicuculline (20 μM).

(B) Representative trace of paired pulse facilitation in rat hippocampal slices after bath application of gamma-aminobutyric acid type A receptor antagonist bicuculline (20 μM); the insert is averaged P1 amplitude before and after bath application of bicuculline.

(C) Trace of paired pulse facilitation after washout of bicuculline.

(D) Averaged paired pulse ratio from rat hippocampal and corticostriatal slices. Measurement data are expressed as mean ± SE. ^a*P* = 0.001, 0.001 2, 0.03, vs. at the hippocampus 20, 40 and 80 interstimulus interval, respectively.

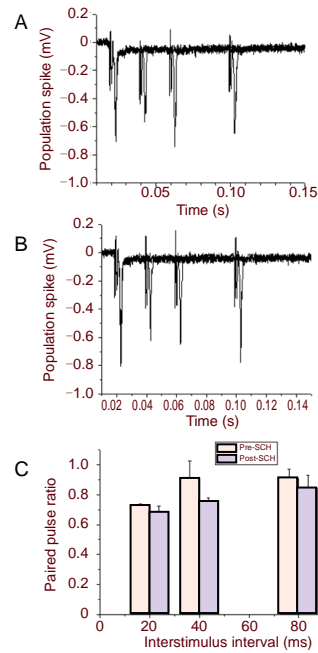


Figure 3 Succinylcholine chloride (muscarinic receptor antagonist) (20 μM) had no effect on the paired pulse depression of population spike/field excitatory postsynaptic potentials.

Representative trace of paired pulse depression in rat hippocampal slices before (A) and after (B) application of succinylcholine chloride. (C) Averaged paired pulse ratio pre- and post-succinylcholine chloride administration. Measurement data are expressed as mean ± SE.

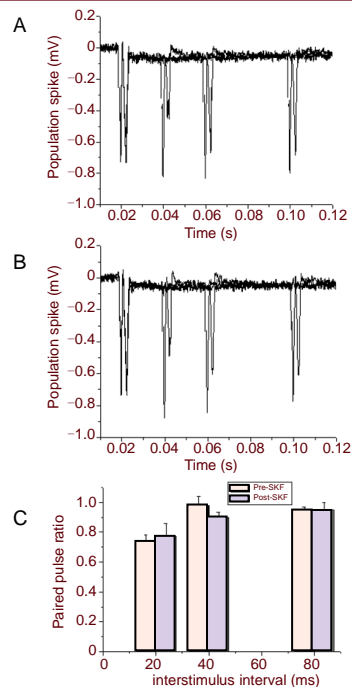


Figure 4 SKF-81297(dopamine D1 receptor antagonist) (20 μM) had no effect on the paired pulse depression of population spike/field excitatory postsynaptic potentials.

Representative trace of paired pulse depression in rat hippocampal slices before (A) and after (B) application of succinylcholine chloride. (C) Averaged paired pulse ratio pre- and post-SKF-81297 administration. Measurement data are expressed as mean ± SE.

Previous study indicated that the N2 potential was blocked in a perfusion medium containing a lower Ca^{2+} or a higher Mg^{2+} concentration than the standard solution^[15]. The result indicated that 0.5 mM but not 2.6 mM calcium containing solution can attenuate the PPD (Figure 5).

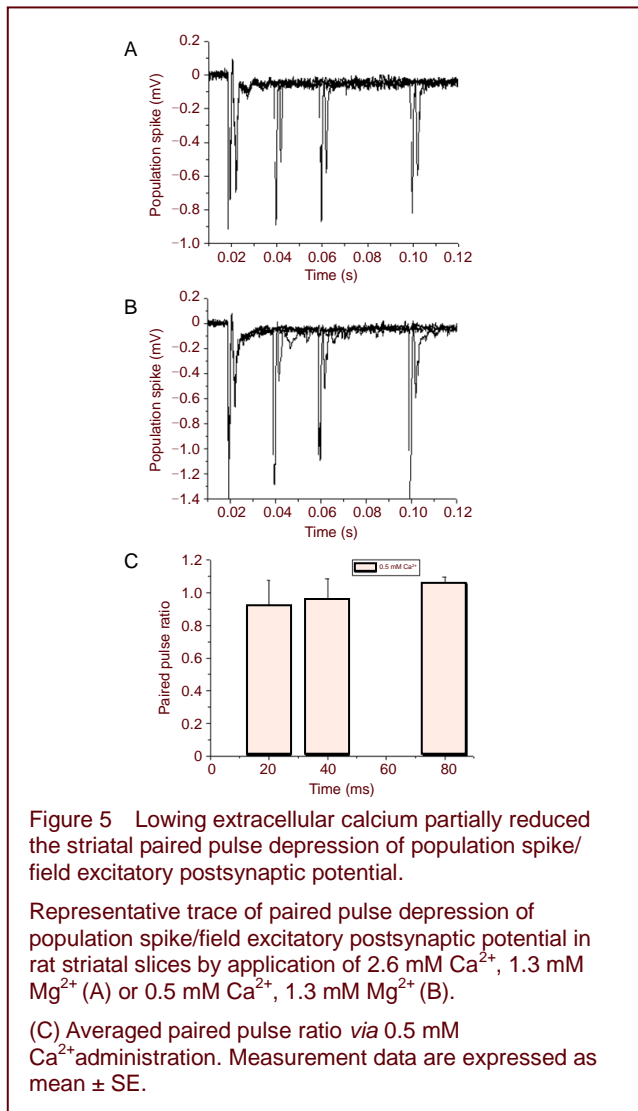


Figure 5 Lowering extracellular calcium partially reduced the striatal paired pulse depression of population spike/field excitatory postsynaptic potential.

Representative trace of paired pulse depression of population spike/field excitatory postsynaptic potential in rat striatal slices by application of 2.6 mM Ca^{2+} , 1.3 mM Mg^{2+} (A) or 0.5 mM Ca^{2+} , 1.3 mM Mg^{2+} (B).

(C) Averaged paired pulse ratio via 0.5 mM Ca^{2+} administration. Measurement data are expressed as mean \pm SE.

DISCUSSION

The dorsal striatum is a large forebrain region involved in action initiation, timing, control, learning and memory. Modulation of corticostriatal synaptic transmission plays a large part in controlling the input to as well as the output from MSNs^[3]. Both long-term plasticity and short-term plasticity have been identified in the neostriatum using different experimental conditions^[18-21] and the alterations in striatal synaptic plasticity might be implicated in Parkinson's disease and Huntington's disease^[16, 21]. It was proposed that long-term changes of synaptic transmission were often associated with a modification of short-term synaptic plasticity^[22]. Two forms of short-term plasticity at inhibitory synapses, PPD

and synaptic augmentation, were studied in adult rat striatal slices using intracellular recordings and were suggested to modify the output of striatum and thus might be an important component of information processing during behaviors involving the striatum^[19]. While in the present study, we observed one PPD at the corticostriatal slices mediated by excitatory synapses since the N2 potential (population spike/fEPSP) can be abolished by α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist 6-cyano-7-nitroquinoline-2,3-dione. Using whole-cell configuration, Mori *et al*^[6] recorded the PPD in MSNs of neonatal Wistar rat corticostriatal slices and suggested the PPD involved presynaptic mechanism. Their findings were not same with the present study in that they found the PPD was not detected when the second pulse was 100 ms after the first pulse while our data showed that even with 500 ms interstimulus interval the PPD was still present. Similar controversy was confirmed by studies from Akopian and Walsh that the PPD existed during the interstimulus interval was 1 second in Fisher rats^[23] and from Lighthall indicating that the PPD was gone when interstimulus interval was longer than 30 ms in adult Long-Evans rats^[7]. However, one similar PPD was showed up in adult rat striatal inhibitory synapses when interstimulus intervals at several hundred milliseconds when the authors studied other project and they did not give further attention^[19], which was similar to the present study.

The striatal MSNs receive glutamatergic input from the cerebral cortex and thalamus, serotonergic input from the raphe, dopaminergic input from the substantia nigra and cholinergic and gamma-aminobutyric acidergic input from striatal interneuron^[1]. There are two distinct inhibitory gamma-aminobutyric acidergic circuits in the neostriatum: feedforward circuit and feedback circuit. The feedforward circuit consists of a relatively small population of gamma-aminobutyric acidergic interneurons that receives excitatory input from the neocortex and exerts monosynaptic inhibition onto striatal MSNs. The feedback circuit comprises the numerous spiny projection neurons and their interconnections via local axon collaterals. This network has long been assumed to provide the majority of striatal gamma-aminobutyric acidergic inhibition and to sharpen and shape striatal output through lateral inhibition, producing increased activity in the most strongly excited spiny cells at the expense of their less strongly excited neighbors^[24]. However, our data did not support the role of inhibitory gamma-aminobutyric acidergic circuits in the PPD since bicuculline had no effect on the PPD or the population spike. In addition, although MSNs also receive D1 receptor innervations and may be involved in synaptic plasticity in the neostriatum^[25], our data did not support their involvements in the PPD. It was indicated that glutamatergic synapses in the neostriatum were capable of expressing a form of synaptic depression that may involve decreased

glutamate release^[20] and that depolarization during the first N-methyl-D-aspartate receptor response caused facilitation of the second one by removing voltage-dependent block of N-methyl-D-aspartate receptors by Mg²⁺ and by activating voltage-dependent Ca²⁺ channels^[26]. However, another study suggested that N-methyl-D-aspartate application depressed the population spike/fEPSP in mouse corticostriatal slices in a gamma-aminobutyric acid-independent manner and that the depression was not affected by removal of the cortex^[27]. Previous studies have indicated that calcium plays an important role in synaptic transmission at corticostriatal synapses mediated by N-type calcium channels^[28]. Although the present study also indicated that lowering the extracellular calcium concentration could reduce the PPD but we still did not see obvious paired pulse facilitation, which was not consistent with Dr Wang's report that lower calcium with the calcium/magnesium ratio at 1:2 could introduce obvious paired pulse facilitation in C57BL/6 mice aged 2–5 months^[29] and suggested that the PPD in juvenile rat corticostriatum was related with calcium. The difference may be related with protocols, species and age, etc., which need to be further studied.

MATERIALS AND METHODS

Design

An *in vitro* electrophysiological study.

Time and setting

This study was performed at the University of Western Ontario, Canada from November 2010 to March 2011.

Materials

Animals

Wistar rats of either sex, aged 2 weeks, were provided by the Animal Center at University of Western Ontario, Canada.

Reagents

6-cyano-7-nitroquinoxaline-2,3-dione, SKF-81297, bicuculline (Tocris), succinylcholine chloride dehydrate (Sigma) and (+)- α -methyl-4-carboxyphenylglycine (MCPG, Sigma) were applied *via* the bathing solution.

Methods

Slice preparation

The rats were decapitated under anesthesia with esoflurane and the whole brain was removed, immersed in ice-cold cutting solution containing (in mM): sucrose 194, NaCl 30, KCl 4.5, MgCl₂ 1, NaHCO₃ 26, NaH₂PO₄ 1.2, glucose 10, bubbled with 95% oxygen and 5% CO₂. The coronary striatum containing cortex and the transverse hippocampus were cut into 350 μ m slices using a vibratome (LeicaVT 1200S). The slices were incubated for at least 1 hour at room temperature in artificial cerebrospinal fluid containing (in mM): NaCl 124, KCl 3.0, NaH₂PO₄ 1.25, glucose 10, NaHCO₃ 26, CaCl₂ 2.6, MgCl₂ 1.3, bubbled with 95% oxygen and 5% CO₂.

Electrophysiological recording

Recordings were performed at 31°C. A slice was

transferred to the recording chamber using a Pasteur pipette and continuously perfused with artificial cerebrospinal fluid saturated by 95% O₂ and 5% CO₂ at a flow rate of 3 mL/min. A glass microelectrode filled with artificial cerebrospinal fluid (4–6 M Ω) was placed in the dorsal striatum (Figure 6A) or hippocampal CA1 stratum radiatum (Figure 6B). The depth of the electrode was adjusted to obtain a maximal response. Population spike or fEPSP were evoked by constant current stimuli (0.1 ms) *via* a tungsten concentric bipolar electrode (tip-diameter: 25 μ m; MCE-100, David Kopf Instruments, MD, USA) placed in the white matter for striatum recording (Figure 6A) or Schaffer lateral pathway for hippocampus recording (Figure 6B). Variable paired-pulses with different interstimulus intervals (20, 40, 80, or 150, 300, 500, 1 000 ms) were applied to evoke half of the maximal field potential (population spike or fEPSP). The signals were recorded (Digidata 1440A, Molecular Device, USA), amplified (MultiClamp 700B, Molecular Device, USA) and filtered at 5 kHz. Data were analyzed offline using Clampfit 10 (Axon Instruments). The paired pulse ratio refers to the amplitude of the second population or fEPSP relative to that of the first population spike or fEPSP.

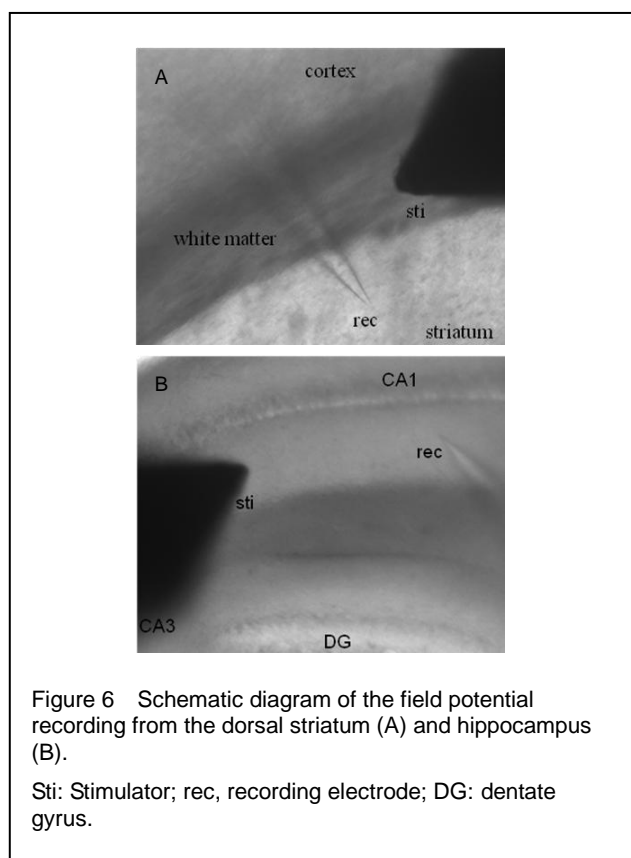


Figure 6 Schematic diagram of the field potential recording from the dorsal striatum (A) and hippocampus (B).

Sti: Stimulator; rec, recording electrode; DG: dentate gyrus.

Statistical analysis

Data were expressed as mean \pm SE. Statistical analyses were performed using one-way analysis of variance followed by the Bonferroni test or two-way repeated analysis of variance, using software of Origin7.

Funding: The study was supported by a grant from the Canadian Institutes of Health Research, No. 15514 & 44008.

Author contributions: Yufeng Xie designed, performed and wrote the manuscript. Michael F. Jackson and John F. MacDonald conceptualized, supervised the project and contributed to the design of experiments and wrote the manuscript. All authors read and approved the final manuscript.

Conflicts of interest: None declared.

Ethical approval: The experiment was approved by the Animal Ethics Committee of the University of Western Ontario, Canada.

REFERENCES

- [1] Smith AD, Bolam JP. The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. *Trends Neurosci*. 1990;13(7):259-265.
- [2] Di Filippo M, Picconi B, Tantucci M, et al. Short-term and long-term plasticity at corticostriatal synapses: implications for learning and memory. *Behav Brain Res*. 2009;199(1):108-118.
- [3] Lovinger DM. Neurotransmitter roles in synaptic modulation, plasticity and learning in the dorsal striatum. *Neuropharmacology*. 2010;58(7):951-961.
- [4] Dang MT, Yokoi F, Yin HH, et al. Disrupted motor learning and long-term synaptic plasticity in mice lacking NMDAR1 in the striatum. *Proc Natl Acad Sci U S A*. 2006;103(41):15254-15259.
- [5] Partridge JG, Tang KC, Lovinger DM. Regional and postnatal heterogeneity of activity-dependent long-term changes in synaptic efficacy in the dorsal striatum. *J Neurophysiol*. 2000;84(3):1422-1429.
- [6] Mori A, Takahashi T, Miyashita Y, et al. Two distinct glutamatergic synaptic inputs to striatal medium spiny neurones of neonatal rats and paired-pulse depression. *J Physiol*. 1994;476(2):217-228.
- [7] Lighthall JW, Park MR, Kitai ST. Inhibition in slices of rat neostriatum. *Brain Res*. 1981;212(1):182-187.
- [8] O'Mara SM, Commins S, Anderson M. Synaptic plasticity in the hippocampal area CA1-subiculum projection: implications for theories of memory. *Hippocampus*. 2000;10(4):447-456.
- [9] O'Donovan MJ, Rinzel J. Synaptic depression: a dynamic regulator of synaptic communication with varied functional roles. *Trends Neurosci*. 1997;20(10):431-433.
- [10] Fortune ES, Rose GJ. Short-term synaptic plasticity as a temporal filter. *Trends Neurosci*. 2001;24(7):381-385.
- [11] Varela JA, Song S, Turrigiano GG, et al. Differential depression at excitatory and inhibitory synapses in visual cortex. *J Neurosci*. 1999;19(11):4293-4304.
- [12] Tsodyks M, Uziel A, Markram H. Synchrony generation in recurrent networks with frequency-dependent synapses. *J Neurosci*. 2000;20(1):RC50.
- [13] Nisenbaum ES, Berger TW, Grace AA. Presynaptic modulation by GABAB receptors of glutamatergic excitation and GABAergic inhibition of neostriatal neurons. *J Neurophysiol*. 1992;67(2):477-481.
- [14] Cordingley GE, Weight FF. Non-cholinergic synaptic excitation in neostriatum: pharmacological evidence for mediation by a glutamate-like transmitter. *Br J Pharmacol*. 1986;88(4):847-856.
- [15] Misgeld U, Okada Y, Hassler R. Locally evoked potentials in slices of rat neostriatum: a tool for the investigation of intrinsic excitatory processes. *Exp Brain Res*. 1979;34(3):575-590.
- [16] Calabresi P, Pisani A, Mercuri NB, et al. The corticostriatal projection: from synaptic plasticity to dysfunctions of the basal ganglia. *Trends Neurosci*. 1996;19(1):19-24.
- [17] Jonsson M, Dabrowski M, Gurley DA, et al. Activation and inhibition of human muscular and neuronal nicotinic acetylcholine receptors by succinylcholine. *Anesthesiology*. 2006;104(4):724-733.
- [18] Akopian G, Musleh W, Smith R, et al. Functional state of corticostriatal synapses determines their expression of short- and long-term plasticity. *Synapse*. 2000;38(3):271-280.
- [19] Fitzpatrick JS, Akopian G, Walsh JP. Short-term plasticity at inhibitory synapses in rat striatum and its effects on striatal output. *J Neurophysiol*. 2001; 85(5):2088-2099.
- [20] Lovinger DM, Tyler EC, Merritt A. Short- and long-term synaptic depression in rat neostriatum. *J Neurophysiol*. 1993;70(5):1937-1949.
- [21] Gustafson N, Gireesh-Dharmaraj E, Czubayko U, et al. A comparative voltage and current-clamp analysis of feedback and feedforward synaptic transmission in the striatal microcircuit in vitro. *J Neurophysiol*. 2006;95(2):737-752.
- [22] Abbott LF, Nelson SB. Synaptic plasticity: taming the beast. *Nat Neurosci*. 2000;3 Suppl:1178-1183.
- [23] Akopian G, Walsh JP. Reliable long-lasting depression interacts with variable short-term facilitation to determine corticostriatal paired-pulse plasticity in young rats. *J Physiol*. 2007;580(Pt 1):225-240.
- [24] Tepper JM, Wilson CJ, Koos T. Feedforward and feedback inhibition in neostriatal GABAergic spiny neurons. *Brain Res Rev*. 2008;58(2):272-281.
- [25] Martella G, Tassone A, Sciamanna G, et al. Impairment of bidirectional synaptic plasticity in the striatum of a mouse model of DYT1 dystonia: role of endogenous acetylcholine. *Brain*. 2009; 132(Pt 9):2336-2349.
- [26] Akopian G, Walsh JP. Corticostriatal paired-pulse potentiation produced by voltage-dependent activation of NMDA receptors and L-type Ca(2+) channels. *J Neurophysiol*. 2002;87(1):157-165.
- [27] Schotanus SM, Chergui K. NR2A-containing NMDA receptors depress glutamatergic synaptic transmission and evoked-dopamine release in the mouse striatum. *J Neurochem*. 2008; 106(4):1758-1765.
- [28] Lovinger DM, Merritt A, Reyes D. Involvement of N- and non-N-type calcium channels in synaptic transmission at corticostriatal synapses. *Neuroscience*. 1994;62(1):31-40.
- [29] Wang Y. Differential effect of aging on synaptic plasticity in the ventral and dorsal striatum. *Neurobiol Learn Mem*. 2008;89(1):70-75.

(Edited by Zhu LQ, Zhao MG/Wang L)