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Single Body Parts are Processed by Individual Neurons in the Mouse Dorsolateral Striatum

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Abstract

Interest in the dorsolateral striatum (DLS) has generated numerous scientific studies of its neuropathologies, as well as its roles in normal sensorimotor integration and learning. Studies are informed by knowledge of DLS functional organization, the guiding principle being its somatotopic afferent projections from primary somatosensory (S1) and motor (M1) cortices. The potential to connect behaviorally relevant function to detailed structure is elevated by mouse models, which have access to extensive genetic neuroscience tool kits. Remaining to be demonstrated, however, is whether the correspondence between S1/M1 corticostriatal terminal distributions and the physiological properties of DLS neurons demonstrated in rats and non-human primates exists in mice. Given that the terminal distribution of S1/M1 projections to the DLS in mice is similar to that in rats, we studied whether firing rates (FRs) of DLS neurons in awake, behaving mice are related to activity of individual body parts. MSNs exhibited robust, selective increases in FR during movement or somatosensory stimulation of single body parts. Properties of MSNs, including baseline FRs, locations, responsiveness to stimulation, and proportions of responsive neurons were similar to properties observed in rats. Future studies can be informed by the present demonstration that the mouse lateral striatum functions as a somatic sensorimotor sector of the striatum and appears to be a homolog of the primate putamen, as demonstrated in rats (Carelli and West, 1991).

Keywords

Somatosensation; Single-unit; Basal Ganglia; Striatum; Mouse

Introduction, 2

The dorsolateral or sensorimotor striatum (DLS) (Flaherty and Graybiel, 1994) figures prominently in research on control of voluntary movement, sensorimotor integration, and

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neuroplasticity involved in procedural learning and habit formation. Also heavily researched are dorsal striatal dysfunctions in Tourette syndrome, obsessive compulsive disorder, psychomotor stimulant addiction, Parkinson's disease, and Huntington's disease. The DLS role in these processes is enlightened by knowing its anatomical-functional organization. Seminal neuroanatomical studies using then new tract tracing tools began to elucidate the long-sought topography of corticostriatal projections from primary somatosensory (S1) and motor (M1) cortices (Kunzle, 1975, 1977). These anatomical findings played a pivotal role in informing subsequent studies clarifying striatal function. For example, the findings were soon corroborated by physiological studies (Liles, 1979; Crutcher and DeLong, 1984a; Alexander and DeLong, 1985; Lyles and Updyke, 1985) that revealed clusters of medium spiny neurons (MSNs) whose activity is related to sensorimotor activity of individual body parts and that project into pallidothalamocortical reentrant loops (Alexander et al., 1986). Hence, the functional organization of the sensorimotor striatum became known as a patchy somatotopy (Flaherty and Graybiel, 1993). A sequence similar to these studies in monkeys soon followed in rats. Anatomical projections indicating a sensorimotor sector in the DLS (Cospito and Kultas-Ilinski, 1981; McGeorge and Faull, 1989) were corroborated by physiological studies demonstrating a patchy somatotopic functional organization in rats similar to that in primates (West et al., 1990; Carelli and West, 1991; Cho and West, 1997; West, 1998). In monkeys and rats, knowledge of DLS functional organization has facilitated both design and interpretation of detailed studies of striatal function, including single cell relations to movement parameters (Crutcher and DeLong, 1984b; Liles, 1985; Kimura, 1992), mechanisms by which psychomotor stimulants activate movement (Pederson et al., 1997; Tang et al., 2008; Pawlak et al., 2010; Ma et al., 2013), effects of reduced dopamine transmission on somatosensory responsiveness of single neurons (Prokopenko et al., 2004), effects of dopamine deafferentation on the functional organization (Cho et al., 2004), corticostriatal plasticity during motor learning (Carelli et al., 1997; Tang et al., 2007, 2009), and the differential roles of dorsal striatal regions in habitual vs goal-directed behavior (Yin et al., 2008; Thorn et al., 2010).

Anatomical studies in mice (White and DeAmicis, 1977; Jinno and Kosaka, 2004; Hattox and Nelson, 2007; Tai and Kromer, 2014) have demonstrated a pattern of corticostriatal terminal distribution similar to that in rats, confirming that S1 and M1 cortices project selectively to the DLS. However, whether neurons in the DLS of awake, behaving mice exhibit selective responses to sensorimotor activity of individual body parts is unknown. Although such activity might be predicted because it follows logically from the above evidence, it cannot be presumed. Moreover, the importance of establishing the anatomical-functional organization of the mouse DLS is underscored because of the utility of mouse models in neuroscience research. Transgenic mice enable selective manipulation of genetically or anatomically defined specific cell types during behavior in a temporally precise manner, e.g., using optogenetic stimulation to study synaptic connectivity and circuit function (Ting and Feng, 2013; Warden et al., 2014; Marton and Sohal, 2015). Coupling the characterization of sensorimotor responsiveness of a recorded DLS neuron with specific information gained using optogenetic stimulation would enable an exciting synergy of both types of information, making the study of striatal SBP neurons particularly attractive. The present study aimed to establish evidence regarding DLS neuron responsiveness in the

awake, freely moving mouse, toward achieving the goal of enhancing the ability of future studies to connect behaviorally relevant function to detailed structure (Warden et al., 2014).

Results, 3

Of the 80 wires implanted, all wire tips were histologically verified to be located in the dorsolateral striatum (Fig. 1). Fifty-three wires yielded recordings of single neurons (Fig. 2). Of these, 52 exhibited characteristics of medium spiny neurons, and one exhibited characteristics of fast-spiking interneurons (Gage et. al., 2010). The FR of the putative FSI appeared to be modulated during locomotion, but was outside the scope of the present study. Of the 52 putative MSNs studied, 22 (42%) exhibited a response to stimulation of a single body part (SBP), termed the “related” body part.

All responses of the 20 SBP neurons consisted of an increase in FR relative to Baseline. SBP Baseline FRs ranged from 0.083 to 1.97 discharges/sec (median = 0.5915 discharges/sec) (Fig. 3). Responses were robust, exhibiting Stimulus FRs ranging from .2 to 21.9 standard deviations above Baseline FR (Fig. 3). Among all neurons exhibiting responsiveness to body part stimulation (N=22), none responded to stimulation of more than one body part, and SBP FR during stimulation of unrelated body parts was not significantly different from Baseline FR (KS test, $P>0.05$). Selective responses of individual neurons are displayed in raster-PETHs (Fig. 4). Selectivity extended beyond what is displayed in the figure, in that only two of the total number of unrelated body parts are depicted for each neuron. Of the 22 neurons exhibiting a selective response, the related body part was head/neck for six neurons (6), chin (4), snout (3), contralateral forelimb (3), contralateral vibrissae/buccal pad (3), chest (2), ipsilateral ear (1). Responses of some example neurons to stimulation of their related body parts was visualized in raster-PETHs (Fig. 5) and in real time videos of body exams and synchronized single unit activity (Vid. 1–5).

SBP neurons were observed throughout the entire anterior-posterior range of the DLS studied. The most anterior locations were at 1.1mm and the most posterior locations were at - 0.58mm A-P relative to bregma (Paxinos and Franklin, 2004). A relatively uniform density of SBP neurons was observed within this range, in the dorsolateral “quadrant” of the striatum, the only target of the present study.

The remaining 30 putative MSNs exhibited no relation to activity of any body part, and were not categorized further (“Uncategorized”). Their Baseline FRs ranged from 0.10 to 5.89 discharges/sec, with a median FR of 1.23 discharges/sec (Fig. 3). Uncategorized neurons’ FRs during stimulation of body parts were not significantly different from their Baseline FRs (KS test, $P>0.1$).

Discussion, 4

The main finding of the present study is that the dorsolateral striatum of the mouse, like that of rats and primates, contains neurons whose FRs increase selectively during sensorimotor activity of an individual body part. Generalizing from the similarity of corticostriatal terminal distributions in rats and mice, and from single unit recordings in rats, the entirety of the present findings might have been expected, but could not be assumed. Any one of the

many firing patterns of DLS SBP neurons demonstrated here to be similar to those observed in rats could have been found to be different. Instead, no noticeable differences were observed in their characteristically low baseline FRs, spike waveforms, inter-spike intervals, or in their somatic sensorimotor responsiveness. Specifically, responses to body part stimulation were uniformly excitations, occurred *during* the related movement, and were selective for a single body part. Locations of SBP neurons were distributed throughout all three dimensions of the DLS (the only region studied), including a lengthy anterior-posterior range, as observed in rats. Further studies are needed to assess the full range and distribution of SBP neurons in all three dimensions of the lateral striatum (dorsolateral and ventrolateral), and whether they exhibit somatotopy and clustering of neurons related to the same body part, as observed in rats and primates.

This new information in the mouse is necessary for ongoing and future studies of striatal function in mice. Knowledge of the specific sensitivity of each recorded neuron is critical in design and interpretation of single unit recording studies. For example, without knowledge of a recorded neuron's sensitivity, changes in firing may appear to encode a cognitive process when in fact they reflect merely a difference in the form of movement. Thus, such knowledge enhances precision in assessing the function(s) of the circuitry in which recorded neurons are connected, such as in studying the relationships of striatal forelimb neurons to force of forelimb movement as a function of trial-to-trial variations in demands (Crutcher and DeLong, 1984b; Liles, 1985) or as a function of overtraining in a force lever task (Carelli et al., 1997). In contrast to the present findings, one study in the mouse found that *all* recorded DLS MSNs responded to stimulation of the vibrissae (Reig and Silberberg, 2014). The explanation for this discrepancy may be related to their recording exclusively sub-threshold postsynaptic potentials, as opposed to action potentials of MSNs in the present study. One cannot rule out the possibility that MSNs that are selectively responsive to a single body part may receive inputs from multiple other body parts that do not reach threshold for firing under the conditions tested here.

Assessment of single body part sensitivity in mouse DLS neurons can synergize with knowledge gained via modern genetic neuroscience tool kits available for studies in mice. Only recently have researchers been able to unambiguously identify and manipulate neural subpopulations within the striatum. For example, D1 and D2 receptor expressing neurons, ostensibly belonging to the direct and indirect pathways, can be identified, recorded and manipulated during experiments in behaving animals (Kravitz et al., 2010; Cui et al., 2013). While studies like these have expanded our understanding of cell type specific functions in the striatum, they can be enhanced by combining this new information with information that is known every time a responsive DLS neuron is recorded: 1) a recorded neuron exhibiting a slow spike waveform and low baseline firing rate is nearly 100% likely to be an MSN; 2) of neurons meeting these criteria, those that exhibit activity related to sensorimotor activity of a single body part (SBP) are projection neurons (Kimura et al., 1990) receiving synaptic input from S1/M1 (Liles and Updyke, 1985). Interpretations from this type of study would be robust, as they would be firmly grounded in the knowledge of neuron type, the neuron's specific S1/M1 afferents, its efferents, as well as its receptor expression. Such studies can be further enhanced by the added ability to specifically target a neuron's related body part using a behavioral manipulation. That is, generating isolated, repetitive movement of a body part,

e.g., forelimb lever pressing (Carelli et al., 1997), vertical head movement (Tang et al., 2007; Pawlak et al., 2010) or licking (Mittler et al., 1994) would involve somewhat selective increased firing of the particular striatal neurons related to that movement. This selective activation could be used to both label the cells and insert Channelrhodopsin for later reactivation. One could target the MSNs of c-fos-tTA transgenic mice with a tetracycline-responsive element - channelrhodopsin 2 - enhanced yellow fluorescent protein (TRE-ChR2-EYFP) adeno associated virus (AAV). This approach couples the c-fos promoter, an immediate early gene associated with recent neuronal activity, to the tetracycline transactivator (tTA). This system allows for inducible gene expression through doxycycline (Lui et al., 2012). The presence of doxycycline inhibits c-fos-promoter-driven-tTA from binding to a tetracycline-responsive element (TRE) site on the AAV, which in turn prevents it from driving ChR2-EYFP expression. In the absence of doxycycline, behaviorally-induced neuronal activity would selectively label active c-fos-expressing MSNs with ChR2-EYFP, which could then be manipulated by light as desired. Such experiments would open more possibilities, and would further strengthen understanding of striatal neuron function in health and disease.

Methods and Materials, 5

Surgery and Recording, 5.1

Five adult, female mice (25–30g) were anesthetized and surgically prepared for chronic, extracellular single unit recording as described previously (Root et al., 2012; Barker et al., 2014; Coffey et al., 2014). Each animal was implanted with an array of 16 microwires (2×8; Micro-Probes, Gaithersburg, MD, USA) aimed at the right dorsolateral striatum. Arrays were implanted through a rectangular craniotomy with the following corners (ML mm, AP mm) relative to bregma [(1.8, 1.3) (2, 1.3) (2.7, −0.5) (2.9, −0.5)]. Arrays were constructed from 25-μm stainless steel microwires quad coated in Teflon insulation. Arrays were constructed with 200 μm spacing between rows and columns. Arrays were lowered using a motorized stereotaxic device (Coffey et al., 2013) at a rate of 200 μm/min and to a depth of 2.75 mm below the surface of the skull. The array was sealed to the surface of the skull with cyanoacrylate. The wires led to a connector strip embedded in dental cement on the skull. Animals were given one week to recover from surgery, and had ad lib access to food and water at all times. When recording commenced, a recording harness (Triangle Biosystems, Durham, NC) connected to a commutator was attached to the connector strip on the skull, allowing free movement within the Plexiglas recording chamber (12"×12"). Signals were amplified and filtered (450 Hz to 10 kHz; roll off 1.5 dB/octave at 1 kHz and −6 dB/octave at 11 kHz), and digitized (50 kHz sampling frequency per wire) for off-line analysis (DataWave Technologies, Loveland, CO). Protocols were performed in compliance with the *Guide for the care and use of laboratory animals* (NIH Publication 865-23) and were approved by the Institutional Animal Care and Use Committee, Rutgers University.

Body exam, 5.2

Procedures for conducting the somatosensorimotor exam were the same as those used in studying rats, as described in detail in Carelli and West (1991) and Cho and West (1997). Animals were trained to remain still, resulting in low baseline firing rates of DLS neurons.

Exams were conducted and video recorded over several sessions (approximately 2 hr/session). All accessible body parts (head, vibrissae, paw, chest, chin, snout, ear, shoulder, cheek pad, and trunk) underwent stimulation in a variety of types, e.g., cutaneous touch, passive manipulation, and active movement. A stimulus was defined as any active or passive movement of, or experimenter contact with, a particular body part. Multiple stimuli (at least 10) of each type were applied to each body part. Thus, responses to all types of stimulation of all body parts by all neurons on the 16 wires could be analyzed post-hoc. Video recordings (Datawave Video Bench) obtained during the exam enabled unambiguous identification of the onset and offset of each individual stimulus using post-hoc frame-by-frame (30 frames/sec) analysis.

Body Part Sensitivity Analysis, 5.3

Rasters and peri-event time histograms (PETHs) displaying firing rate (FR) of individual neurons were constructed using video-defined nodes. For each neuron, raster-PETHs corresponding to all examined body parts were created. The mean Stimulus FR was defined as the average firing rate during body part stimulation, i.e., between all onset-to-offset times set during video analysis. The mean and standard deviation for Baseline FR were calculated during all periods of non-stimulation by the experimenter, during which time the animals were not moving. Average FR during the Stimulus was compared to Baseline FR and Baseline variance. Each neuron was tested for sensitivity to 10 body parts, so the alpha value for determining sensitivity was Bonferroni corrected from 0.05 to 0.005. Any Stimulus FR exceeding the neuron's 99.5% confidence interval for Baseline FR was deemed as body part sensitive.

Fluorescent Immunohistochemical labelling, 5.4

Following all recordings (~30 days after surgery) animals received an overdose of sodium pentobarbital and were perfused transcardially with 0.9% phosphate buffered saline followed by 4% paraformaldehyde. Brains were post-fixed for 48 hours in 4% paraformaldehyde and transferred to a 30% sucrose solution. Brains were sliced into 30 μ m coronal sections. Fluorescent immunohistochemistry was performed on free floating brain tissue. Slices were incubated for one hour in a 4% Bovine Serum Albumin (BSA) and 0.3% Triton X-100 in phosphate buffer. Sections were rinsed and incubated overnight in a 4% BSA with rabbit anti- GFAP antibody. Next, tissue was rinsed and incubated in anti-rabbit secondary antibody conjugated to a red fluorophore (Alexa Fluor[®] 555). Subsequently, tissue was washed with phosphate buffer and mounted on a slide using mounting medium containing Dapi (nucleic acid stain), which served as a counter stain. All slices were photographed and recorded with a Zeiss Axiovert 200M, Fluorescence microscope. The presence of astrocytes with upregulated GFAP along the entire length of microwires allowed tracing of microwire tracks by staining for GFAP protein (Polikov, 2006; Fig. 1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DLS	dorsolateral striatum
MSNs	medium spiny neurons
FR	firing rate

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- A Significant amount of clinical and preclinical research focuses on the striatum.
- DLS neurons respond selectively to sensorimotor activity of individual body parts.
- This is in concordance with S1/M1 corticostriatal terminal distributions in mice.
- Mouse DLS MSNs are similar to rats and non-human primates.
- These findings further validate the mouse DLS as a preclinical model.

Figure 1. Histology

Atlas Plates (Paxinos and Franklin, 2004) showing the approximate locations of all wire tips exhibiting an isolated neuronal waveform. Green/white dots: wire tips which recorded a Single Body Part Neuron (SBP); red dots/open: wire tips which recorded an Uncategorized Neuron. The actual histology slice (lower right) shows histochemical staining for activated astrocytes (GFAP), which surround wires. Wires can easily be tracked from their entrance into cortex until their tips in striatum.

Total Implanted Wires (80) **Single Body Part Neurons (22)** **Figure 2. Wires**

Pie charts showing the proportion of wires that recorded either an SBP Neuron, or an Uncategorized Neuron, or nothing (left), as well as the proportion of SBP Neurons that represented each identified body part.

Figure 3. Average Firing Rates

1 Box Plots Show the Median, inter-quartile range, and outlier FR for both SBP and Uncategorized type neurons. 1) Baseline FR for Uncategorized Neurons. 2) Movement/stimulation FR for Uncategorized Neurons. 3) Baseline FR for SBP Neurons. 4) Movement/stimulation FR for SBP Neurons. 5) Movement/stimulation of unrelated body part FR for SBP Neurons.

Figure 4. Selectivity of SBP Neurons

Raster/PETHs show single unit activity during body part movement/stimulation. Dashed line: onset of movement/stimulation, red/grey dots: offset of movement/stimulation. Each raster row represents a single movement/stimulation (trial); action potentials are depicted as vertical ticks. PETH shows summations of action potentials on all trials (bin = 50ms). Each row of three raster/PETHs depicts a single neuron's activity during three different body part stimulations. Green boxes highlight the selectivity of each neuron to its related body part.

For example, snout neuron discharges during snout touch but not during ear touch or paw movement, etc.

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Neurons Sensitive to Body Part Movement or Touch

Figure 5. Single Body Part Representation

Each *raster*/PETH shows a single neuron's response to stimulation of its related body part.

Responses are always increases in FR and are typically robust.