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Comparison of Normal and Parkinsonian Microcircuit Dynamics in the Rodent Striatum

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1. Introduction

Experimentally, depriving the basal ganglia (BG) from their dopaminergic innervation, dramatically changes the behavior of all their circuits, neurons, and synapses in multiple ways. Dopamine afferents are received by all BG nuclei (Rommelfanger and Wichmann, 2010). In the absence of DA, BG generate enhanced pathological oscillatory patterns in the external segment of the striatum: globus pallidus (GPe), internal segment of the globus pallidus (GPi), subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr) (Blandini et al., 2000). These pathological oscillatory patterns are expressed as increased cortical beta frequency coherence (Costa et al., 2006; Fuentes et al., 2009; Kozlov et al., 2009; Walters and Bergstrom, 2009) and are reflected as the inability to select, change or initiate motor actions (Magill et al., 2001; Ni et al., 2001; Wilson et al., 2006), as though all neurons were trapped in a massive oscillation that does not allow the selection of any circuit or action. Behaviorally, circuit disfunction is accompanied by bradykinesia, akinesia, tremor and muscular rigidity (Brown, 2007; Hammond et al., 2007; Galvan and Wichmann, 2008; Fuentes et al., 2009; Walters and Bergstrom, 2009; Zold et al., 2009).

One question is what are the manifestations of these changes at the level of the striatal microcircuitry (Alexander and Crutcher, 1990; Middleton and Strick, 2002), given that its neurons are the principal entrance to the BG (Alexander and Crutcher, 1990; Middleton and Strick, 2002), and DA is particularly concentrated in this nucleus (striatum); more than in any other BG nuclei (Bjorklund and Dunnett, 2007). To answer this question, here we show how the striatal microcircuit functions before and after DA depletion. The changes observed may be fundamental to understand BG activity during Parkinsonism.

2. Activity in the striatal microcircuit

The striatum integrates inputs from the cortex, the intralaminar thalamic nuclei, the dopaminergic afferents from the *substantia nigra pars compacta* (SNc) and other nuclei (Smith et al., 1994; Parr-Brownlie et al., 2009). The basic elements that configure the striatal microcircuit are the medium spiny projection neurons (MSNs) and its interneurons (Kreitzer, 2009). MSNs are the major cell population commonly being in a resting state with a polarized membrane potential (ca., -80 mV) and relatively low input resistance (ca., 100

MΩ in adult neurons) (Bargas et al., 1988; Reyes et al., 1998). Upon depolarization, these neurons fire tonically due to persistent voltage-activated K^+-currents (Galarraga et al., 1989; Nisenbaum and Wilson, 1995; Bargas et al., 1999), with a long latency to first spike due inactivating K^+-currents (Surmeier et al., 1988; Bargas et al., 1989), inward rectification (Galarraga et al., 1994; Nisenbaum and Wilson, 1995), and interspike intervals partially dependent on Ca^{2+}-activated K^+-currents (Pineda et al., 1992; Bargas et al., 1999), among other outward currents (Nisenbaum and Wilson, 1995; Shen et al., 2005).

MSNs can be classified as striatopallidal or indirect pathway neurons and striatonigral or direct pathway neurons, based on their axonal projections, receptors and peptide expression (Gerfen et al., 1990; Smith et al., 1998). Striatopallidal fibers target the GPe and striatonigral axons target the output nuclei of the BG: GPi and SNr. Interneurons are divided into genres with much intrinsic, still not-well studied variation: i) the parvalbumin-immunoreactive (PV+) or fast spiking interneurons (FS), ii) the somatostatin (SS), neuropeptide Y (NPY), tyrosine hydroxylase (TH), nitric oxide synthase (NOS)-immunoreactive populations of cells that fire with a low threshold calcium spike (LTS), iii) large cholinergic or tonic active neurons (TANs), and iv) calretinin-immunoreactive neurons (Wilson et al., 1990; Kawaguchi et al., 1995; Tepper et al., 2004; Kreitzer, 2009; Ibáñez-Sandoval et al., 2010; Tepper et al., 2010). A challenge is to find out how all these neurons process striatal inputs into coherent spatio-temporal patterned outputs: what is their role in microcircuitry processing. Thus, as a first approach we decided to observe what characteristics of the microcircuit activity are plainly evident in order to establish top-down hypothesis and experimental designs to understand the role of each neuron class during microcircuit activity (Carrillo-Reid et al., 2008).

MSNs seldom fire in physiological conditions (without a motor behavior) (Crutcher and DeLong, 1984; Kimura, 1992; Carrillo-Reid et al., 2008; Liang et al., 2008; Vautrelle, 2009; Jaidar et al., 2010), due to their intrinsic inward rectifying K^+ currents and strong depolarization-activated K^+-currents (see above and Bargas et al., 1989; Galarraga et al., 1994; Nisenbaum and Wilson, 1995; Bargas et al., 1999; Tepper et al., 2004). Since MSNs are majority, this characteristic makes the striatum to be classified as a quasi-"silent" nucleus; very different from the neurons of other BG nuclei which exhibit firing all the time (e.g., Nakanishi et al., 1987; Kita and Kitai, 1991; Ibáñez-Sandoval et al., 2007). Either activity from the cortex, thalamus, or addition of NMDA in vitro, activates the striatal microcircuits so that groups of MSNs begin to fire in a persistent or recurrent way (Vergara et al., 2003; Mahon et al., 2006; Vautrelle, 2009).

Firing in MSNs is characterized by prolonged membrane potential transitions from a hyperpolarized "down"-state to a depolarized "up"-state where bursts of action potentials are displayed (Wilson and Kawaguchi, 1996; Vergara et al., 2003; Vautrelle, 2009). In vitro, this firing pattern occurs without overt stimulation and is due to an acquired conditional bistability (Vergara et al., 2003; Carrillo-Reid et al., 2008). Because burst firing can also be recorded using calcium-imaging that allow the recording of dozens of cells simultaneously (Cossart et al., 2003), the use of this technique resulted useful to observe how burst firing can extend to neighboring neurons, and how this firing generates network dynamics, that is, to a cell assembly type of processing (Hebb, 1949).

3. The Cell Assembly hypothesis

Cell Assemblies (CAs) have been posited as the building blocks or structures capable to give support and store neuronal representations, or coding, of perceptual, cognitive, and motor

processes (Grinvald et al., 2003; Harris, 2005). However, although Hebbian and non-Hebbian types of learning have been formalized and used in artificial neuronal networks under different paradigms (Bowles, 2006), the demonstration of the existence of these structures in living circuits has not been trivial and they are mostly assumed to exist using indirect evidence, such as the correlation of the firing generated by a single, or a small group of neurons, with field or multiunitary population recordings (e.g., Sakurai, 1996; Costa et al., 2006; Zold et al., 2009), or with population activity as revealed by voltage dyes (Grinvald et al., 2003; Grinvald, 2005). Numerous evidences of correlated firing in neurons, using these techniques, are available. However, an inconvenience for cell physiology is that these techniques do not achieve single cell resolution. That is, these techniques cannot identify the elements that participate in a given activity of the microcircuit. If they cannot be identified, a role for them cannot be found or assigned. On the other hand, speculations about how a circuit may function, based on cell-focused studies, are abundant and utterly speculative. Between these two extremes: system and cellular neurophysiology, respectively, there is very little work. To fill the gap we need to make a proper description of network dynamics at the cellular level while recording many cells simultaneous with single cell resolution. In the following section we will describe how this is achieved as well as some properties of the striatal microcircuit that reflect cell assembly organization and dynamics. At the same time, we will describe how these properties change in a Parkinsonian microcircuit.

4. Recurrent bursting

The first property is recurrent burst firing. Striatal neurons fire in bursts of action potentials riding on top of depolarizing plateau potentials called "up-states". This firing mode has been shown in vivo and in vitro (Wilson, 1993; Stern et al., 1997; Vergara et al., 2003). Plateau potentials underlying bursts of spikes can arise from intrinsic nonlinear properties leading to bistability (Hounsgaard and Kiehn, 1989; Hsiao et al., 1998; Kiehn, 2006), from temporal summation of excitatory and inhibitory synaptic events (Sanchez-Vives and McCormick, 2000; Yanagawa and Mogi, 2009), or both (Destexhe and Pare, 1999; Tal et al., 2008). It is possible that the same neurons can generate plateau potentials of different origin depending on network situation (Hounsgaard and Kiehn, 1989; Alaburda et al., 2005; Vautrelle, 2009).

Interestingly, recurrent bursts of action potentials on top of sustained depolarizations (up-states or plateau potentials) resemble a basic property of certain microcircuits called Central Pattern Generators (CPGs) (Grillner, 2006). The main difference between CAs and CPGs is that CPGs activity is thought to be "innate", whereas CAs are supposedly to be "acquired" through synaptic plasticity. CPGs can display their electrical behavior in the absence of afferent inputs, and in isolated tissue maintained vitro, as long as an "excitatory drive" turns them on. In the case of fictive locomotion and swimming, a physiological excitatory drive can be generated pharmacologically: by the addition of micromolar NMDA into the bath saline, a maneuver that induces conditional bistability, plateau potentials and recurrent regular bursting (Grillner et al., 1981; Guertin and Hounsgaard, 1998).

In the striatal microcircuit robust recurrent bursting is induced by the same pharmacological manipulation in vivo (Herrling et al., 1983) and in vitro (Vergara et al., 2003) obtaining an electrophysiological patterned output from spiny neurons; similar to that previously recorded in both CPGs or suspected CAs. Furthermore, unilateral NMDA administration induces contralateral turning behavior directly relating recurrent burst firing in medium

spiny neurons with a rhythmic and regular motor behavior (Ossowska, 1995). Then, we can say that the striatal bursting activity under these conditions codes for movement (e.g., Hikosaka et al., 2006).

What happens when the DA is absent? A "logical" common mistake is to think that if a Parkinsonian patient or animal cannot generate movements then, the striatal microcircuit should even be more "silent" that in control conditions. However, it has been shown, *in vitro* and *in vivo*, exactly the opposite: after DA depletion the spontaneous firing and synaptic activity of striatal neurons becomes more active and noisy (Galarraga et al., 1987; Tang et al., 2001; Tseng et al., 2001; Liang et al., 2008). That is, a more robust neuronal activity and bursting can be recorded in the DA-depleted striatum.

5. Correlated firing

The next property observed during CAs physiological behavior, and which can be observed in the striatal microcircuit, is the synchronous or correlated firing of pools of neurons that here will be called "neuronal aggregates". Synchrony or correlated firing (coherence, phase locking) between these auto-associated clusters of neurons make up network states as described in many circuits (e.g., Petersen and Sakmann, 2000; Doupe et al., 2004; Carrillo-Reid et al., 2008; Li et al., 2010). In some cases, the time scale of synchronization is fast: that of synaptic and action potentials duration (Diesmann et al., 1999; Leger et al., 2005; Robbe et al., 2006). However, in most physiological conditions, a great variability in the responses of neurons at the action potential time scale is found (Calvin and Stevens, 1968; Shadlen and Newsome, 1994; Grinvald et al., 2003; Kostal et al., 2007). Thus, synchronicity in the action potential time scale is hard to record in most central nervous system circuits (Shadlen and Newsome, 1994; Arieli et al., 1996) and simulations of that activity change with minimal perturbations (Izhikevich and Edelman, 2008).

Notwithstanding, recurrent burst firing of individual neurons has been found to be synchronized and correlated among several members of a neuronal aggregate (Carrillo-Reid et al., 2008), and also in population recordings of network conditions in which a given neuron participates: its "preferred condition" (Grinvald et al., 2003). Moreover, up-states and bursting have been found to be a reflection of an attractor-like network dynamics (Cossart et al., 2003) capable to recruit connected neurons into a preferred aggregate. Connections, internal to the aggregate, can in part explain the maintenance of bursts shared by the elements of the group (Lambe and Aghajanian, 2007). That is, the up-state is a product or reflection of the correlated firing of a group of interconnected neurons.

In the striatum, correlated firing has been inferred by recording local field potentials correlated with neuronal firing (Murer et al., 2002; Berke et al., 2004; Costa et al., 2006; Mahon et al., 2006; Walters et al., 2007; Zold et al., 2009). Also, the use of calcium imaging techniques, which records bursting behavior of several cells simultaneously, reveals spontaneous peaks of burst synchronization and correlated firing after the application of NMDA (Carrillo-Reid et al., 2008) (See Figure). That is, recurrent bursting recorded in single neurons (Vergara et al., 2003) has been demonstrated to be shared by sets of neurons that spontaneously synchronize their bursts in a particular condition (Carrillo-Reid et al., 2008). During Parkinsonism caused by DA-depletion, the recording of pathological bursting activity exhibit an increase in the number of synchrony peaks (Jaidar et al., 2010). Synchronizing events emerge spontaneously and regularly during recordings. Up-states are the manifestation of a network phenomenon linking neurons that sometimes are located far

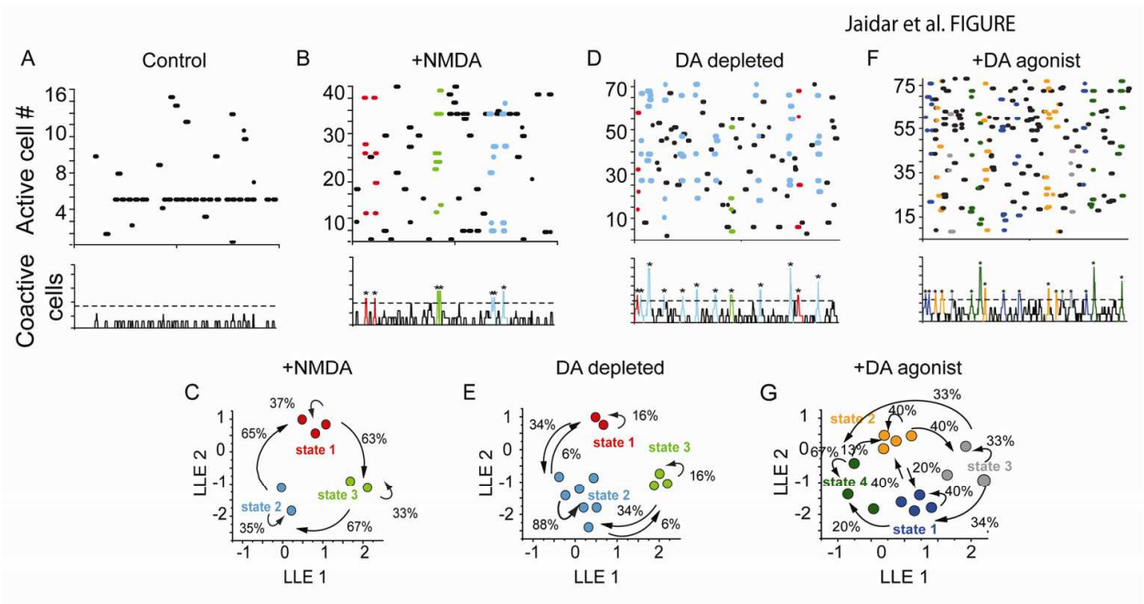

Fig. 1. Following the striatal microcircuit with calcium imaging.

A. Top: A raster plot showing the activity of a striatal slice in control conditions. It exhibits a few active neurons (y-axis = number of active neurons; files, x-axis = time = 3 min recording). No active neurons synchronized their bursting significantly with other neurons. Bottom: histogram representing activity displayed in the raster plot on top (sum of columns).

B. Top: After adding 8 µM NMDA to the bath saline more neurons become active (> 40). Colored dots shows peaks of significant spontaneous synchronization. Bottom: activity histogram shows the spontaneous peaks of synchronization (colored with asterisks) ($P<0.05$ dashed horizontal line).

C. Locally linear embedding (LLE) was used to reduce dimensions of the peaks of synchronization and to project the vectors in a two dimensional space. Column vectors representing similar neurons are represented by clusters of neighboring circles of the same color (network states). Note that neuronal aggregates follow a sequence when displaying their activity, that is, the microcircuit shows its dynamics as an activity cycle or phase sequence. This sequence of network states is robust and may repeat itself several times during about two hours of recording time (only one representative epoch = 3 min is shown).

D. Top: After dopamine depletion (DA-depletion) a striatal slice exhibits more active neurons than with NMDA (> 70). No NMDA is added to DA-depleted slices. That is, DA absence induces that more neurons in the microcircuit become active. Bottom: nevertheless, the same peak of synchrony repeats itself almost all the time during recording. That is, microcircuit dynamics is greatly lost. DA was lowered using the 6-OHDA model of Parkinsonism. The toxin was injected into the substantia nigra pars compacta and the experiments were done after observing turning behavior in lesioned animals.

E: LLE obtained from a DA-depleted slice shows that one network state becomes dominant impeding normal dynamics.

F: When a dopamine receptor agonist (1 µM SKF-81296) is administered in a slice with DA-depletion, diverse peaks of synchrony with high probability of occurrence return. However, the number of active neurons is still high.

G: LLE shows that microcircuit dynamics tends to be restored because the dominant network state is dissolved (see: Carrillo-Reid et al., 2008; Carrillo-Reid et al., 2009; Jaidar et al., 2010).

way from each other (Stern et al., 1997; Carrillo-Reid et al., 2008). Strikingly, in the striatal parkinsonian microcircuit all active neurons synchronize their bursts with one another (Jaidar et al., 2010). No matter what is the predominant component of an up-state: intrinsic, synaptic or both, the important feature is that up-states work as "windows" for synchronization and correlated activity (Yuste et al., 2005), while action potentials within the up-states need not be synchronized (Wickens and Wilson, 1998). A signature of a CAs is that its inputs do not determine all its outputs all the time, in a deterministic way. On the contrary, the spike trains are variable due to the simultaneous integration of inputs within internal circuitry states (Arieli et al., 1996; Grinvald et al., 2003; Harris, 2005).

As stated by the modified Hebbian learning theory, sets of neurons display synchronous or correlated firing because LTP has strengthened the connections among them: "neurons that fire together wire together", whereas LTD has weakened some synapses due to their uncorrelated firing leading to the separation of different neuronal aggregates. Thus, connections within a neuronal ensemble are non-random (Kozloski et al., 2001; Song et al., 2005; Planert et al., 2010). There are preferred pathways for the flow of activity (Markram et al., 1997; Ikegaya et al., 2004; Song et al., 2005) even if anatomically they seem intermingled (Grinvald et al., 2003; Harris, 2005; Song et al., 2005). In conclusion, recurrent bursting elicited in striatal neurons can be seen as the product of correlated firing among neurons belonging to groups or ensembles. The time window for synchronization is the up-state and the product of the ensemble is the same up-state shared by the neurons of the ensemble. Most probably, neurons sharing up-states do in fact maintain these plateau potentials along time due to their strong interconnections (Flores-Barrera et al., 2010).

6. Microcircuit dynamics as sequences of network states

In what follows, a peak of synchronized activity generated by the members of a neuron aggregate or cluster will be called a network state. Therefore, what is recorded using calcium imaging is sequences of network states. That is, different neuronal aggregates with correlated firing, alternate the activity among them following determined sequences (Figure). These sequences result in particular trajectories, sometimes following Hamiltonian or Eulerian rules (Carrillo-Reid et al., 2009). In the case of CPGs, it is clear that what flows through the circuit is the correlated activity of neuron pools that activate in a rhythmic, alternating and recurrent way, making up sequences of activity called "activity cycles" (Grillner, 2003). Activity cycles code for repetitive behaviors such as locomotion, deglutition, swimming, scratching and so on. Activity cycles can go on spontaneously even when the physiological stimulus is no longer active, such as in vitro "ficitive locomotion" (Guertin and Hounsgaard, 1998).

But recursive activity of this sort has also been postulated for CAs where they are called "phase sequences" by DO Hebb (1949), a term coined for chains of neuronal aggregates activated in sequence, each one displaying a network state (Harris, 2005).

In the striatum, the trajectories followed by active CAs may change as a result of the presence of particular modulatory neurotransmitters (Carrillo-Reid et al., 2008; Carrillo-Reid et al., 2009a). This quality allows the striatal circuit to generate diverse phase sequences that probably code for different behaviors while using the same neuronal aggregates.

Interestingly, in the absence of DA, phase sequences are lost. Almost all active neurons participate in the same, repetitive, network state, that apparently is not coding for a useful command or motor program (Jaidar et al., 2010). The normal dynamics of the microcircuit is

gone (Figure). Addition of DA agonists under DA depleted states is capable to modify this state of affairs and partially restore a phase sequence (Jaidar et al., 2010).
To conclude, the striatal microcircuit generates phase sequences, activity trajectories, or cycles, that are lost during DA-depletion but that can be partially restored with DA receptor agonists. Because these methods allow the visualization of these phenomena with single cell resolution, they may be used to test anti-parkinsonian drugs and to search into the details of microcircuitry processing.

7. Final remarks

Over the last century two main visions of neuronal circuits have been generated from experimental data: First, the theory of Central Pattern Generators (CPGs) and, second, the theory of Hebbian Cell Assemblies. What we would like to stress here is that the time has come for a re-synthesis of both into a new microcircuit hypothesis, while new experimental evidence arrives. For instance, their requirements are very much the same. And since they were proposed somewhat independently, we have to conclude that biological evidence that put them forward is robust. Imaging technology used in conjunction with targeted recordings will allow the discerning of their operational rules in control and in pathological situations (Cossart et al., 2003; Grinvald et al., 2003; Carrillo-Reid et al., 2008 ; 2009a; Jaidar et al., 2010). It perhaps will be possible to record, compare and describe diverse pathological microcircuits. These microcircuits could then be challenged with therapeutic manipulations of potential value.

8. References

Alaburda A, Russo R, MacAulay N, Hounsgaard J (2005) Periodic high-conductance states in spinal neurons during scratch-like network activity in adult turtles. J Neurosci 25:6316-6321.

Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 13:266-271.

Arieli A, Sterkin A, Grinvald A, Aertsen A (1996) Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. Science 273:1868-1871.

Bargas J, Galarraga E, Aceves J (1988) Electrotonic properties of neostriatal neurons are modulated by extracellular potassium. Exp Brain Res 72:390-398.

Bargas J, Galarraga E, Aceves J (1989) An early outward conductance modulates the firing latency and frequency of neostriatal neurons of the rat brain. Exp Brain Res 75:146-156.

Bargas J, Ayala CX, Vilchis C, Pineda JC, Galarraga E (1999) Ca^{2+}-activated outward currents in neostriatal neurons. Neurosci 88:479-488.

Berke JD, Okatan M, Skurski J, Eichenbaum HB (2004) Oscillatory entrainment of striatal neurons in freely moving rats. Neuron 43:883-896.

Bjorklund A, Dunnett SB (2007) Dopamine neuron systems in the brain: an update. Trends Neurosci 30:194-202.

Blandini F, Nappi G, Tassorelli C, Martignoni E (2000) Functional changes of the basal ganglia circuitry in Parkinson's disease. Prog Neurobiol 62:63-88.

Bowles R (2006) Investigating the Storage Capacity of a Network with Cell Assemblies. In. UK: Middlesex University.

Brown P (2007) Abnormal oscillatory synchronisation in the motor system leads to impaired movement. Curr Opin Neurobiol 17:656-664.

Calvin WH, Stevens CF (1968) Synaptic noise and other sources of randomness in motoneuron interspike intervals. J Neurophysiol 31:574-587.

Carrillo-Reid L, Tecuapetla F, Ibanez-Sandoval O, Hernandez-Cruz A, Galarraga E, Bargas J (2009) Activation of the cholinergic system endows compositional properties to striatal cell assemblies. J Neurophysiol 101:737-749.

Carrillo-Reid L, Tecuapetla F, Tapia D, Hernandez-Cruz A, Galarraga E, Drucker-Colin R, Bargas J (2008) Encoding network states by striatal cell assemblies. J Neurophysiol 99:1435-1450.

Cossart R, Aronov D, Yuste R (2003) Attractor dynamics of network UP states in the neocortex. Nature 423:283-288.

Costa RM, Lin SC, Sotnikova TD, Cyr M, Gainetdinov RR, Caron MG, Nicolelis MA (2006) Rapid alterations in corticostriatal ensemble coordination during acute dopamine-dependent motor dysfunction. Neuron 52:359-369.

Crutcher MD, DeLong MR (1984) Single cell studies of the primate putamen. II. Relations to direction of movement and pattern of muscular activity. Exp Brain Res 53:244-258.

Destexhe A, Pare D (1999) Impact of network activity on the integrative properties of neocortical pyramidal neurons in vivo. J Neurophysiol 81:1531-1547.

Diesmann M, Gewaltig MO, Aertsen A (1999) Stable propagation of synchronous spiking in cortical neural networks. Nature 402:529-533.

Doupe AJ, Solis MM, Kimpo R, Boettiger CA (2004) Cellular, circuit, and synaptic mechanisms in song learning. Ann N Y Acad Sci 1016:495-523.

Flores-Barrera E, Vizcarra-Chacon BJ, Tapia D, Bargas J, Galarraga E (2010) Different corticostriatal integration in spiny projection neurons from direct and indirect pathways. Front Syst Neurosci 4:15.

Fuentes R, Petersson P, Siesser WB, Caron MG, Nicolelis MA (2009) Spinal cord stimulation restores locomotion in animal models of Parkinson's disease. Science 323:1578-1582.

Galarraga E, Bargas J, Martinez-Fong D, Aceves J (1987) Spontaneous synaptic potentials in dopamine-denervated neostriatal neurons. Neurosci Lett 81:351-355.

Galarraga E, Bargas J, Sierra A, Aceves J (1989) The role of calcium in the repetitive firing of neostriatal neurons. Exp Brain Res 75:157-168.

Galarraga E, Pacheco-Cano MT, Flores-Hernández JV, Bargas J (1994) Subthreshold rectification in neostriatal spiny projection neurons. Exp Brain Res 100:239-249.

Galvan A, Wichmann T (2008) Pathophysiology of parkinsonism. Clin Neurophysiol 119:1459-1474.

Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ, Jr., Sibley DR (1990) D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250:1429-1432.

Grillner S (2003) The motor infrastructure: from ion channels to neuronal networks. Nat Rev Neurosci 4:573-586.

Grillner S (2006) Biological pattern generation: the cellular and computational logic of networks in motion. Neuron 52:751-766.

Grillner S, McClellan A, Sigvardt K, Wallen P, Wilen M (1981) Activation of NMDA-receptors elicits "fictive locomotion" in lamprey spinal cord in vitro. Acta Physiol Scand 113:549-551.

Grinvald A (2005) Imaging input and output dynamics of neocortical networks in vivo: exciting times ahead. Proc Natl Acad Sci U S A 102:14125-14126.

Grinvald A, Arieli A, Tsodyks M, Kenet T (2003) Neuronal assemblies: single cortical neurons are obedient members of a huge orchestra. Biopolymers 68:422-436.

Guertin PA, Hounsgaard J (1998) NMDA-Induced intrinsic voltage oscillations depend on L-type calcium channels in spinal motoneurons of adult turtles. J Neurophysiol 80:3380-3382.

Hammond C, Bergman H, Brown P (2007) Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci 30:357-364.

Harris KD (2005) Neural signatures of cell assembly organization. Nature Rev Neurosci 6:399-407.

Hebb DO (1949) The organization of behavior. New York: Wiley.

Herrling PL, Morris R, Salt TE (1983) Effects of excitatory amino acids and their antagonists on membrane and action potentials of cat caudate neurones. J Physiol 339:207-222.

Hikosaka O, Nakamura K, Nakahara H (2006) Basal ganglia orient eyes to reward. J Neurophysiol 95:567-584.

Hounsgaard J, Kiehn O (1989) Serotonin-induced bistability of turtle motoneurones caused by a nifedipine-sensitive calcium plateau potential. J Physiol 414:265-282.

Hsiao CF, Del Negro CA, Trueblood PR, Chandler SH (1998) Ionic basis for serotonin-induced bistable membrane properties in guinea pig trigeminal motoneurons. J Neurophysiol 79:2847-2856.

Ibáñez-Sandoval O, Tecuapetla F, Unal B, Shah F, Koós T, Tepper JM (2010) Electrophysiological and morphological characteristics and synaptic connectivity of tyrosine hydroxylase-expressing neurons in adult mouse striatum. J Neurosci 30:6999-7016.

Ibáñez-Sandoval O, Carrillo-Reid L, Galarraga E, Tapia D, Mendoza E, Gomora JC, Aceves J, Bargas J (2007) Bursting in substantia nigra pars reticulata neurons in vitro: possible relevance for Parkinson disease. J Neurophysiol 98:2311-2323.

Ikegaya Y, Aaron G, Cossart R, Aronov D, Lampl I, Ferster D, Yuste R (2004) Synfire chains and cortical songs: temporal modules of cortical activity. Science 304:559-564.

Izhikevich EM, Edelman GM (2008) Large-scale model of mammalian thalamocortical systems. Proc Natl Acad Sci U S A 105:3593-3598.

Jaidar O, Carrillo-Reid L, Hernandez A, Drucker-Colin R, Bargas J, Hernandez-Cruz A (2010) Dynamics of the Parkinsonian striatal microcircuit: entrainment into a dominant network state. J Neurosci 30:11326-11336.

Kawaguchi Y, Wilson CJ, Augood SJ, Emson PC (1995) Striatal interneurones: chemical, physiological and morphological characterization. Trends Neurosci 18:527-535.

Kiehn O (2006) Locomotor circuits in the mammalian spinal cord. Annu Rev Neurosci 29:279-306.

Kimura M (1992) Behavioral modulation of sensory responses of primate putamen neurons. Brain Res 578:204-214.

Kita H, Kitai ST (1991) Intracellular study of rat globus pallidus neurons: membrane properties and responses to neostriatal, subthalamic and nigral stimulation. Brain Res 564:296-305.

Kostal L, Lansky P, Rospars JP (2007) Neuronal coding and spiking randomness. Eur J Neurosci 26:2693-2701.

Kozloski J, Hamzei-Sichani F, Yuste R (2001) Stereotyped position of local synaptic targets in neocortex. Science 293:868-872.

Kozlov A, Huss M, Lansner A, Kotaleski JH, Grillner S (2009) Simple cellular and network control principles govern complex patterns of motor behavior. Proc Natl Acad Sci U S A 106:20027-20032.

Kreitzer AC (2009) Physiology and pharmacology of striatal neurons. Annu Rev Neurosci 32:127-147.

Lambe EK, Aghajanian GK (2007) Prefrontal cortical network activity: Opposite effects of psychedelic hallucinogens and D1/D5 dopamine receptor activation. Neuroscience 145:900-910.

Leger JF, Stern EA, Aertsen A, Heck D (2005) Synaptic integration in rat frontal cortex shaped by network activity. J Neurophysiol 93:281-293.

Li X, Ouyang G, Usami A, Ikegaya Y, Sik A (2010) Scale-free topology of the CA3 hippocampal network: a novel method to analyze functional neuronal assemblies. Biophys J 98:1733-1741.

Liang L, DeLong MR, Papa SM (2008) Inversion of dopamine responses in striatal medium spiny neurons and involuntary movements. J Neurosci 28:7537-7547.

Magill PJ, Bolam JP, Bevan MD (2001) Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. Neuroscience 106:313-330.

Mahon S, Vautrelle N, Pezard L, Slaght SJ, Deniau JM, Chouvet G, Charpier S (2006) Distinct patterns of striatal medium spiny neuron activity during the natural sleep-wake cycle. J Neurosci 26:12587-12595.

Markram H, Lubke J, Frotscher M, Roth A, Sakmann B (1997) Physiology and anatomy of synaptic connections between thick tufted pyramidal neurones in the developing rat neocortex. J Physiol 500 (Pt 2):409-440.

Middleton FA, Strick PL (2002) Basal-ganglia 'projections' to the prefrontal cortex of the primate. Cereb Cortex 12:926-935.

Murer MG, Tseng KY, Kasanetz F, Belluscio M, Riquelme LA (2002) Brain oscillations, medium spiny neurons, and dopamine. Cell Mol Neurobiol 22:611-632.

Nakanishi H, Kita H, Kitai ST (1987) Electrical membrane properties of rat subthalamic neurons in an in vitro slice preparation. Brain Res 437:35-44.

Ni ZG, Bouali-Benazzouz R, Gao DM, Benabid AL, Benazzouz A (2001) Time-course of changes in firing rates and firing patterns of subthalamic nucleus neuronal activity after 6-OHDA-induced dopamine depletion in rats. Brain Res 899:142-147.

Nisenbaum ES, Wilson CJ (1995) Potassium currents responsible for inward and outward rectification in rat neostriatal spiny projection neurons. J Neurosci 15:4449-4463.

Ossowska K (1995) Interaction between striatal excitatory amino acid and gamma-aminobutyric acid (GABA) receptors in the turning behaviour of rats. Neurosci Lett 202:57-60.

Parr-Brownlie LC, Poloskey SL, Bergstrom DA, Walters JR (2009) Parafascicular thalamic nucleus activity in a rat model of Parkinson's disease. Exp Neurol 217:269-281.

Petersen CC, Sakmann B (2000) The excitatory neuronal network of rat layer 4 barrel cortex. J Neurosci 20:7579-7586.

Pineda JC, Galarraga E, Bargas J, Cristancho JM, Aceves J (1992) Charybdotoxin and apamin sensitivity of the calcium-dependent repolarization and the afterhyperpolarization in neostriatal neurons. J Neurophysiol 68:287-294.

Planert H, Szydlowski SN, Hjorth JJ, Grillner S, Silberberg G (2010) Dynamics of synaptic transmission between fast-spiking interneurons and striatal projection neurons of the direct and indirect pathways. J Neurosci 30:3499-3507.

Reyes A, Galarraga E, Flores-Hernández J, Tapia D, Bargas J (1998) Passive properties of neostriatal neurons during potassium conductance blockade. Exp Brain Res 120:70-84.

Robbe D, Montgomery SM, Thome A, Rueda-Orozco PE, McNaughton BL, Buzsaki G (2006) Cannabinoids reveal importance of spike timing coordination in hippocampal function. Nat Neurosci 9:1526-1533.

Rommelfanger KS, Wichmann T (2010) Extrastriatal dopaminergic circuits of the basal ganglia. Front Neuroanat 4:139.

Sakurai Y (1996) Hippocampal and neocortical cell assemblies encode memory processes for different types of stimuli in the rat. J Neurosci 16:2809-2819.

Sanchez-Vives MV, McCormick DA (2000) Cellular and network mechanisms of rhythmic recurrent activity in neocortex. Nat Neurosci 3:1027-1034.

Shadlen MN, Newsome WT (1994) Noise, neural codes and cortical organization. Curr Opin Neurobiol 4:569-579.

Shen W, Hamilton SE, Nathanson NM, Surmeier DJ (2005) Cholinergic suppression of KCNQ channel currents enhances excitability of striatal medium spiny neurons. J Neurosci 25:7449-7458.

Smith Y, Bevan MD, Shink E, Bolam JP (1998) Microcircuitry of the direct and indirect pathways of the basal ganglia. Neuroscience 86:353-387.

Smith Y, Bennett BD, Bolam JP, Parent A, Sadikot AF (1994) Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. J Comp Neurol 344:1-19.

Song S, Sjostrom PJ, Reigl M, Nelson S, Chklovskii DB (2005) Highly nonrandom features of synaptic connectivity in local cortical circuits. PLoS Biol 3:e68.

Stern EA, Kincaid AE, Wilson CJ (1997) Spontaneous subthreshold membrane potential fluctuations and action potential variability of rat corticostriatal and striatal neurons in vivo. J Neurophysiol 77:1697-1715.

Surmeier DJ, Bargas J, Kitai ST (1988) Voltage-clamp analysis of a transient potassium current in rat neostriatal neurons. Brain Res 473:187-192.

Tal Z, Chorev E, Yarom Y (2008) State-dependent modification of complex spike waveforms in the cerebellar cortex. Cerebellum 7:577-582.

Tang K, Low MJ, Grandy DK, Lovinger DM (2001) Dopamine-dependent synaptic plasticity in striatum during in vivo development. Proc Natl Acad Sci U S A 98:1255-1260.

Tepper JM, Koos T, Wilson CJ (2004) GABAergic microcircuits in the neostriatum. Trends Neurosci 27:662-669.

Tepper JM, Tecuapetla F, Koos T, Ibanez-Sandoval O (2010) Heterogeneity and diversity of striatal GABAergic interneurons. Front Neuroanat 4:150.

Tseng KY, Kasanetz F, Kargieman L, Riquelme LA, Murer MG (2001) Cortical slow oscillatory activity is reflected in the membrane potential and spike trains of striatal neurons in rats with chronic nigrostriatal lesions. J Neurosci 21:6430-6439.

Vautrelle N, Carrillo-Reid, L., Bargas, J. (2009) Diversity of up-state voltage transitions during different network states. In: Cortico-Subcortical Dynamics in Parkinson Disease (Tseng KY, ed), pp 73-85. New York: Humana/Springer.

Vergara R, Rick C, Hernandez-Lopez S, Laville JA, Guzman JN, Galarraga E, Surmeier DJ, Bargas J (2003) Spontaneous voltage oscillations in striatal projection neurons in a rat corticostriatal slice. J Physiol 553:169-182.

Walters JR, Bergstrom DA (2009) Basal ganglia network synchronization in animal models of Parkinson's disease. In: Cortico-Subcortical Dynamics in Parkinson Disease (Tseng KY, ed), pp 117-142. New York: Humana/Springer.

Walters JR, Hu D, Itoga CA, Parr-Brownlie LC, Bergstrom DA (2007) Phase relationships support a role for coordinated activity in the indirect pathway in organizing slow oscillations in basal ganglia output after loss of dopamine. Neuroscience 144:762-776.

Wickens JR, Wilson CJ (1998) Regulation of action-potential firing in spiny neurons of the rat neostriatum in vivo. J Neurophysiol 79:2358-2364.

Wilson CJ (1993) The generation of natural firing patterns in neostriatal neurons. Prog Brain Res 99:277-297.

Wilson CJ, Kawaguchi Y (1996) The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. J Neurosci 16:2397-2410.

Wilson CJ, Chang HT, Kitai ST (1990) Firing patterns and synaptic potentials of identified giant aspiny interneurons in the rat neostriatum. J Neurosci 10:508-519.

Wilson CL, Cash D, Galley K, Chapman H, Lacey MG, Stanford IM (2006) Subthalamic nucleus neurones in slices from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mice show irregular, dopamine-reversible firing pattern changes, but without synchronous activity. Neuroscience 143:565-572.

Yanagawa T, Mogi K (2009) Analysis of ongoing dynamics in neural networks. Neurosci Res 64:177-184.

Yuste R, MacLean JN, Smith J, Lansner A (2005) The cortex as a central pattern generator. Nat Rev Neurosci 6:477-483.

Zold CL, Belluscio M, Kasanetz F, Pomata PE, Riquelme LA, Gonon F, Murer MG (2009) Converging into a unified model of Parkinson's disease pathophysiology. In: Cortico-Subcortical Dynamics in Parkinson Disease (Tseng KY, ed), pp 143-156. New York: Humana/Springer.

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Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

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